ORGANIC CHEMISTRY



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Organic Chemistry

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CHAPTER OVERVIEW

1: STRUCTURE AND BONDING

CHAPTER OBJECTIVES

This chapter provides a review of material covered in a standard freshman general-chemistry course through a discussion of the following topics:

- the differences between organic and inorganic chemistry.
- the shapes and significance of atomic orbitals.
- electron configurations.
- ionic and covalent bonding.
- molecular orbital theory.
- hybridization.
- the structure and geometry of the compounds methane, ethane, ethylene and acetylene.

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1.0: INTRODUCTION TO ORGANIC CHEMISTRY

OBJECTIVES

After completing this section, you should be able to

1. Define organic chemistry as the study of carbon-containing compounds.
2. Explain why the results of the experiments carried out by Chevreul and Wöhler contributed to the demise of the "vital force" theory.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- organic chemistry

All living things on earth are formed mostly of carbon compounds. The prevalence of carbon compounds in living things has led to the epithet "carbon-based" life. The truth is we know of no other kind of life. Early chemists regarded substances isolated from *organisms* (plants and animals) as a different type of matter that could not be synthesized artificially, and these substances were thus known as *organic compounds*.



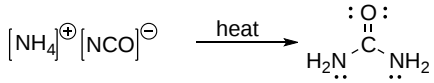
Figure **1.0.1**: All organic compounds contain carbon and most are formed by living things, although they are also formed by geological and artificial processes. (credit left: modification of work by Jon Sullivan; credit left middle: modification of work by Deb Tremper; credit right middle: modification of work by "annszyp"/Wikimedia Commons; credit right: modification of work by George Shuklin)

Jöns Jacob Berzelius, a physician by trade, first coined the term "organic chemistry" in 1806 for the study of compounds derived from biological sources. Up through the early 19th century, naturalists and scientists observed critical differences between compounds that were derived from living things and those that were not.



Berzelius

In 1828, Friedrich Wöhler (widely regarded as a pioneer in organic chemistry) successfully completed an organic synthesis by heating ammonium cyanate and synthesizing of the biological compound urea (a component of urine in many animals) in what is now called "the Wöhler synthesis." Until this discovery it was widely believed by chemists that organic substances could only be formed under the influence of the "vital force" in the bodies of animals and plants. Wöhler's synthesis dramatically proved that view to be false.



ammonium cyanate **urea**

Urea synthesis was a critical discovery for biochemists because it showed that a compound known to be produced in nature only by biological organisms could be produced in a laboratory under controlled conditions from inanimate matter. This "in vitro" synthesis of organic matter disproved the common theory (vitalism) about the *vis vitalis*, a transcendent "life force" needed for producing organic compounds.

The ability to manipulate organic compounds includes fermentation to create wine and the making of soap, both of which have been a part of society so long their discovery has been lost in antiquity. Evidence has shown the Babylonians, as early as 2800 BC, were creating soap by mixing animal fat with wood ashes. It wasn't until the 19th century that the chemical nature of the creation of soap was discovered by Eugène Chevreul. In a reaction now call saponification, fats are heated in the presence of a strong base (KOH or NaOH) to produce fatty acid salts and glycerol. The fatty acid salts are the soap which improve water's ability to dissolve grease.

$$\text{animal fat} \xrightarrow[H_2O]{NaOH} \text{soap} + \text{glycerol}$$

Although originally defined as the chemistry of biological molecules, **organic chemistry** has since been redefined to refer specifically to carbon compounds — even those with non-biological origin. Some carbon molecules are not considered organic, with carbon dioxide being the most well known and most common inorganic carbon compound, but such molecules are the exception and not the rule. Organic chemistry focuses on carbon compounds and following movement of the electrons in carbon chains and rings, and also how electrons are shared with other carbon atoms and heteroatoms. Organic chemistry is primarily concerned with the properties of covalent bonds and non-metallic elements, though ions and metals do play critical roles in some reactions.

Why is carbon so special? The answer to this question involves carbon's special ability to bond with itself, which will be discussed in this chapter. Carbon is unique in its ability to form a wide variety of compounds from simple to complex. There are literally millions of organic compounds known to science from methane, which contains one carbon atom, to DNA which contains millions of carbons. More importantly, organic chemistry gives us the ability to make and alter the structure of organic compounds, which is the main topic in this book. The applications of organic chemistry are myriad, and include all sorts of plastics, dyes, flavorings, scents, detergents, explosives, fuels and many, many other products. Read the ingredient list for almost any kind of food that you eat — or even your shampoo bottle — and you will see the handiwork of organic chemists listed there.



The value to us of organic compounds ensures that organic chemistry is an important discipline within the general field of chemistry. In this chapter, we discuss why the element carbon gives rise to a vast number and variety of compounds, how those compounds are classified, and the role of organic compounds in representative biological and industrial settings. The field of organic chemistry is probably the most active and important field of chemistry at the moment, due to its extreme applicability to both biochemistry (especially in the pharmaceutical industry) and petrochemistry (especially in the energy industry). Organic chemistry has a relatively recent history, but it will have an enormously important future, affecting the lives of everyone around the world for many, many years to come

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1.1: ATOMIC STRUCTURE - THE NUCLEUS

OBJECTIVE

After completing this section, you should be able to describe the basic structure of the atom.

KEY TERMS

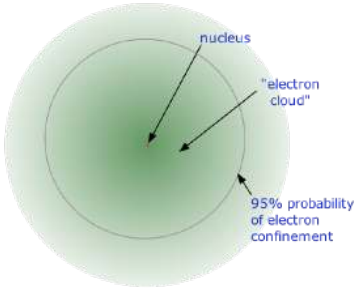
Make certain that you can define, and use in context, the key terms below.

- atomic number
- atomic weight
- electron
- mass number
- neutron
- proton

THE NUCLEAR ATOM

The precise physical nature of atoms finally emerged from a series of elegant experiments carried out between 1895 and 1915. The most notable of these achievements was Ernest Rutherford's famous 1911 alpha-ray scattering experiment, which established that:

- Almost all of the *mass* of an atom is contained within a tiny (and therefore extremely dense) *nucleus* which carries a positive electric charge whose value identifies each element and is known as the *atomic number* of the element.
- Almost all of the *volume* of an atom consists of empty space in which *electrons*, the fundamental carriers of negative electric charge, reside. The extremely small mass of the electron ($1/1840^{th}$ the mass of the hydrogen nucleus) causes it to behave as a quantum particle, which means that its location at any moment cannot be specified; the best we can do is describe its behavior in terms of the probability of its manifesting itself at any point in space. It is common (but somewhat misleading) to describe the volume of space in which the electrons of an atom have a significant probability of being found as the *electron cloud*. The latter has no definite outer boundary, so neither does the atom. The radius of an atom must be defined arbitrarily, such as the boundary in which the electron can be found with 95% probability. Atomic radii are typically 30-300 pm.



The nucleus is itself composed of two kinds of particles. *Protons* are the carriers of positive electric charge in the nucleus; the proton charge is exactly the same as the electron charge, but of opposite sign. This means that in any [electrically neutral] atom, the number of protons in the nucleus (often referred to as the *nuclear charge*) is balanced by the same number of electrons outside the nucleus. The other nuclear particle is the *neutron*. As its name implies, this particle carries no electrical charge. Its mass is almost the same as that of the proton. Most nuclei contain roughly equal numbers of neutrons and protons, so we can say that these two particles together account for almost all the mass of the atom.

> *Because the electrons of an atom are in contact with the outside world, it is possible for one or more electrons to be lost, or some new ones to be added. The resulting electrically-charged atom is called an ion.*

ATOMIC NUMBER (Z)

What single parameter uniquely characterizes the atom of a given element? It is not the atom's relative mass, as we will see in the section on isotopes below. It is, rather, the number of protons in the nucleus, which we call the *atomic number* and denote by the symbol *Z*. Each

proton carries an electric charge of +1, so the atomic number also specifies the electric charge of the nucleus. In the neutral atom, the *Z protons* within the nucleus are balanced by *Z electrons* outside it.



Atomic numbers were first worked out in 1913 by Henry Moseley, a young member of Rutherford's research group in Manchester.

Moseley searched for a measurable property of each element that increases linearly with atomic number. He found this in a class of X-rays emitted by an element when it is bombarded with electrons. The frequencies of these X-rays are unique to each element, and they increase uniformly in successive elements. Moseley found that the square roots of these frequencies give a straight line when plotted against Z; this enabled him to sort the elements in order of increasing atomic number.

You can think of the atomic number as a kind of serial number of an element, commencing at 1 for hydrogen and increasing by one for each successive element. The chemical name of the element and its symbol are uniquely tied to the atomic number; thus the symbol "Sr" stands for strontium, whose atoms all have $Z = 38$.

MASS NUMBER (A)

The *mass number* equals the sum of the numbers of protons and the number of neutrons in the nucleus. It is sometimes represented by the symbol $\boldsymbol{A}$, so

$$\boldsymbol{A = Z + N}$$

in which $\boldsymbol{Z}$ is the atomic number and $\boldsymbol{N}$ is the *neutron number*.

ELEMENTS

To date, about 115 different elements have been discovered; by definition, each is chemically unique. To understand why they are unique, you need to understand the structure of the atom (the fundamental, individual particle of an element) and the characteristics of its components. Atoms consist of electrons, protons, and neutrons. Although this is an oversimplification that ignores the other subatomic particles that have been discovered, it is sufficient for discussion of chemical principles. Some properties of these subatomic particles are summarized in Table **1.1.1**, which illustrates three important points:

1. Electrons and protons have electrical charges that are identical in magnitude but opposite in sign. Relative charges of −1 and +1 are assigned to the electron and proton, respectively.
2. Neutrons have approximately the same mass as protons but no charge. They are electrically neutral.
3. The mass of a proton or a neutron is about 1836 times greater than the mass of an electron. Protons and neutrons constitute the bulk of the mass of atoms.

The discovery of the electron and the proton was crucial to the development of the modern model of the atom and provides an excellent case study in the application of the scientific method. In fact, the elucidation of the atom's structure is one of the greatest detective stories in the history of science.

Table **1.1.1**: Properties of Subatomic Particles*

Particle	Mass (g)	Atomic Mass (amu)	Electrical Charge (coulombs)	Relative Charge
electron	$\boldsymbol{9.109 \times 10^{-28}}$	0.0005486	-1.602×10^{-19}	−1
proton	$\boldsymbol{1.673 \times 10^{-24}}$	1.007276	$+1.602 \times 10^{-19}$	+1
neutron	$\boldsymbol{1.675 \times 10^{-24}}$	1.008665	0	0

In most cases, the symbols for the elements are derived directly from each element's name, such as C for carbon, U for uranium, Ca for calcium, and Po for polonium. Elements have also been named for their properties [such as radium (Ra) for its radioactivity], for the native country of the scientist(s) who discovered them [polonium (Po) for Poland], for eminent scientists [curium (Cm) for the Curies], for gods and goddesses [selenium (Se) for the Greek goddess of the moon, Selene], and for other poetic or historical reasons. Some of the symbols

used for elements that have been known since antiquity are derived from historical names that are no longer in use; only the symbols remain to indicate their origin. Examples are Fe for iron, from the Latin *ferrum*; Na for sodium, from the Latin *natrium*; and W for tungsten, from the German *wolfram*. Examples are in Table **1.1.2**.

Table **1.1.2**: Element Symbols Based on Names No Longer in Use

Element	Symbol	Derivation	Meaning
antimony	Sb	stibium	Latin for “mark”
copper	Cu	cuprum	from Cyprium, Latin name for the island of Cyprus, the major source of copper ore in the Roman Empire
gold	Au	aurum	Latin for “gold”
iron	Fe	ferrum	Latin for “iron”
lead	Pb	plumbum	Latin for “heavy”
mercury	Hg	hydrargyrum	Latin for “liquid silver”
potassium	K	kalium	from the Arabic al-qili, “alkali”
silver	Ag	argentum	Latin for “silver”
sodium	Na	natrium	Latin for “sodium”
tin	Sn	stannum	Latin for “tin”
tungsten	W	wolfram	German for “wolf stone” because it interfered with the smelting of tin and was thought to devour the tin

Recall that the nuclei of most atoms contain neutrons as well as protons. Unlike protons, the number of neutrons is not absolutely fixed for most elements. Atoms that have the same number of protons, and hence the same atomic number, but different numbers of neutrons are called isotopes. All isotopes of an element have the same number of protons and electrons, which means they exhibit the same chemistry. The isotopes of an element differ only in their atomic mass, which is given by the mass number (A), the sum of the numbers of protons and neutrons.

CARBON ISOTOPES

The element carbon (C) has an atomic number of 6, which means that all neutral carbon atoms contain 6 protons and 6 electrons. In a typical sample of carbon-containing material, 98.89% of the carbon atoms also contain 6 neutrons, so each has a mass number of 12. An isotope of any element can be uniquely represented as ${}^{A}_{Z}X$, where X is the atomic symbol of the element. The isotope of carbon that has 6 neutrons is therefore ${}^{12}_{6}C$. The subscript indicating the atomic number is actually redundant because the atomic symbol already uniquely specifies Z. Consequently, ${}^{12}_{6}C$ is more often written as ^{12}C, which is read as “carbon-12.” Nevertheless, the value of Z is commonly included in the notation for nuclear reactions because these reactions involve changes in Z.

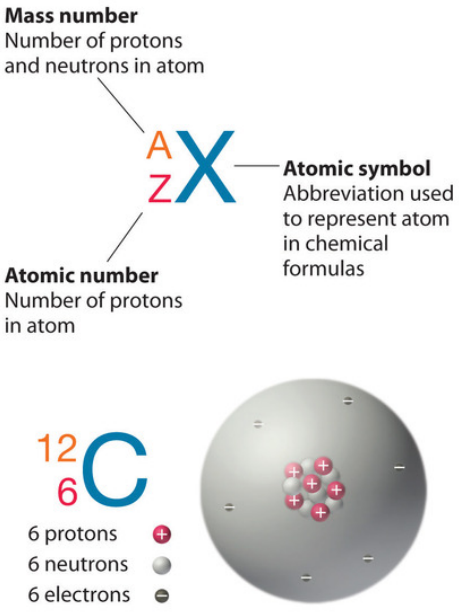


Figure **1.1.2**: Formalism used for identifying specific nuclide (any particular kind of nucleus)

In addition to ${}^{12}C$, a typical sample of carbon contains 1.11% ${}^{13}_{6}C$ (^{13}C), with 7 neutrons and 6 protons, and a trace of ${}^{14}_{6}C$ (^{14}C), with 8 neutrons and 6 protons. The nucleus of ^{14}C is not stable, however, but undergoes a slow radioactive decay that is the basis of the carbon-14

dating technique used in archaeology. Many elements other than carbon have more than one stable isotope; tin, for example, has 10 isotopes. The properties of some common isotopes are in Table **1.1.3**.

Table **1.1.3**: Properties of Selected Isotopes

Element	Symbol	Atomic Mass (amu)	Isotope Mass Number	Isotope Masses (amu)	Percent Abundances (%)
hydrogen	H	1.0079	1	1.007825	99.9855
			2	2.014102	0.0115
boron	B	10.81	10	10.012937	19.91
			11	11.009305	80.09
carbon	C	12.011	12	12 (defined)	99.89
			13	13.003355	1.11
oxygen	O	15.9994	16	15.994915	99.757
			17	16.999132	0.0378
			18	17.999161	0.205
iron	Fe	55.845	54	53.939611	5.82
			56	55.934938	91.66
			57	56.935394	2.19
			58	57.933276	0.33
uranium	U	238.03	234	234.040952	0.0054
			235	235.043930	0.7204
			238	238.050788	99.274

Sources of isotope data: G. Audi et al., Nuclear Physics A 729 (2003): 337–676; J. C. Kotz and K. F. Purcell, Chemistry and Chemical Reactivity, 2nd ed., 1991.

EXAMPLE 1.1.1

An element with three stable isotopes has 82 protons. The separate isotopes contain 124, 125, and 126 neutrons. Identify the element and write symbols for the isotopes.

Given: number of protons and neutrons

Asked for: element and atomic symbol

Strategy:

A. Refer to the periodic table and use the number of protons to identify the element.
B. Calculate the mass number of each isotope by adding together the numbers of protons and neutrons.
C. Give the symbol of each isotope with the mass number as the superscript and the number of protons as the subscript, both written to the left of the symbol of the element.

Solution:

A The element with 82 protons (atomic number of 82) is lead: Pb.

B For the first isotope, A = 82 protons + 124 neutrons = 206. Similarly, A = 82 + 125 = 207 and A = 82 + 126 = 208 for the second and third isotopes, respectively. The symbols for these isotopes are $^{206}_{82}Pb$, $^{207}_{82}Pb$, and $^{208}_{82}Pb$, which are usually abbreviated as ^{206}Pb, ^{207}Pb, and ^{208}Pb.

EXERCISE 1.1.1

Identify the element with 35 protons and write the symbols for its isotopes with 44 and 46 neutrons.

Answer

$^{79}_{35}Br$ and $^{81}_{35}Br$ or, more commonly, ^{79}Br and ^{81}Br.

SUMMARY

The atom consists of discrete particles that govern its chemical and physical behavior. Each atom of an element contains the same number of protons, which is the **atomic number** (*Z*). Neutral atoms have the same number of electrons and protons. Atoms of an element that contain different numbers of neutrons are called **isotopes**. Each isotope of a given element has the same atomic number but a different **mass number** (*A*), which is the sum of the numbers of protons and neutrons. The relative masses of atoms are reported using the **atomic mass unit** (**amu**), which is defined as one-twelfth of the mass of one atom of carbon-12, with 6 protons, 6 neutrons, and 6 electrons.

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1.2: ATOMIC STRUCTURE - ORBITALS

OBJECTIVES

After completing this section, you should be able to

1. describe the physical significance of an orbital.
2. list the atomic orbitals from 1*s* to 3*d* in order of increasing energy.
3. sketch the shapes of *s* and *p* orbitals.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- nodal plane
- node
- orbital
- quantum mechanics
- wave function

ATOMIC ORBITALS

An orbital is the quantum mechanical refinement of Bohr's orbit. In contrast to his concept of a simple circular orbit with a fixed radius, orbitals are mathematically derived regions of space with different *probabilities* of having an electron. One way of representing electron probability distributions is Ψ^2. Because Ψ^2 gives the probability of finding an electron in a given volume of space (such as a cubic picometer), a plot of Ψ^2 versus distance from the nucleus (r) is a plot of the **probability density**. For example, the 1*s* orbital is spherically symmetrical, so the probability of finding a 1*s* electron at any given point depends *only* on its distance from the nucleus. The probability density is greatest at $r = 0$ (at the nucleus) and decreases steadily with increasing distance. At very large values of *r*, the electron probability density is very small but *not* zero.

We can calculate the **radial probability** (the probability of finding a 1*s* electron at a distance *r* from the nucleus) by adding together the probabilities of an electron being at all points on a series of *x* spherical shells of radius r_1, r_2, r_3,…, r_{x-1}, r_x. In effect, we are dividing the atom into very thin concentric shells, much like the layers of an onion (part (a) in Figure **1.2.1**), and calculating the probability of finding an electron on each spherical shell. Recall that the electron probability density is greatest at $r = 0$ (part (b) in Figure **1.2.1**), so the density of dots is greatest for the smallest spherical shells in part (a) in Figure **1.2.1**. In contrast, the surface area of each spherical shell is equal to $4\pi r^2$, which increases very rapidly with increasing *r* (part (c) in Figure **1.2.1**). Because the surface area of the spherical shells increases more rapidly with increasing *r* than the electron probability density decreases, the plot of radial probability has a maximum at a particular distance (part (d) in Figure **1.2.1**). Most important, when *r* is very small, the surface area of a spherical shell is so small that the *total* probability of finding an electron close to the nucleus is very low; at the nucleus, the electron probability vanishes (part (d) in Figure **1.2.1**).

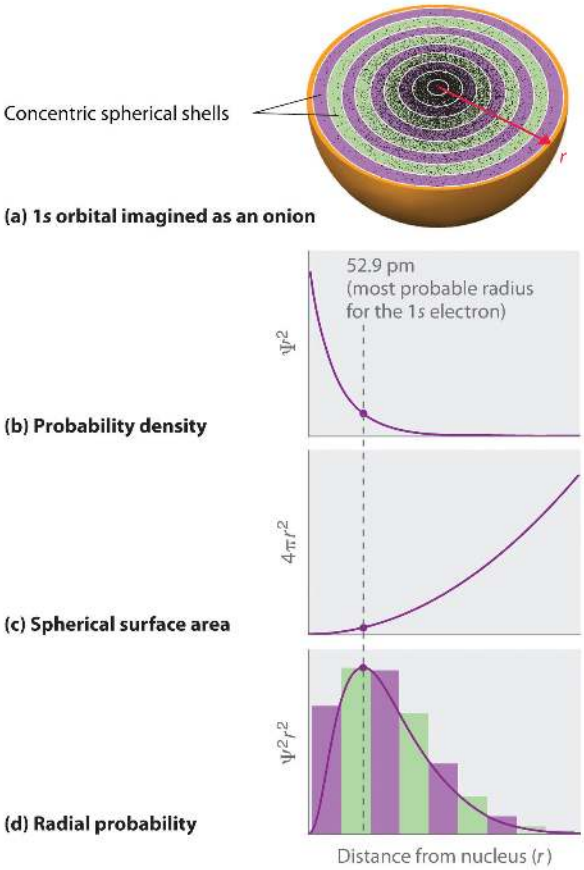


Figure **1.2.1**: Most Probable Radius for the Electron in the Ground State of the Hydrogen Atom. (a) Imagine dividing the atom's total volume into very thin concentric shells as shown in the onion drawing. (b) A plot of electron probability density Ψ^2 versus r shows that the electron probability density is greatest at $r = 0$ and falls off smoothly with increasing r. The density of the dots is therefore greatest in the innermost shells of the onion. (c) The surface area of each shell, given by $4\pi r^2$, increases rapidly with increasing r. (d) If we count the number of dots in each spherical shell, we obtain the total probability of finding the electron at a given value of r. Because the surface area of each shell increases more rapidly with increasing r than the electron probability density decreases, a plot of electron probability versus r (the *radial probability*) shows a peak. This peak corresponds to the most probable radius for the electron, 52.9 pm, which is exactly the radius predicted by Bohr's model of the hydrogen atom. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

For the hydrogen atom, the peak in the radial probability plot occurs at $r = 0.529$ Å (52.9 pm), which is exactly the radius calculated by Bohr for the $n = 1$ orbit. Thus the *most probable radius* obtained from quantum mechanics is identical to the radius calculated by classical mechanics. In Bohr's model, however, the electron was assumed to be at this distance 100% of the time, whereas in the quantum mechanical Schrödinger model, it is at this distance only some of the time. The difference between the two models is attributable to the wavelike behavior of the electron and the Heisenberg uncertainty principle.

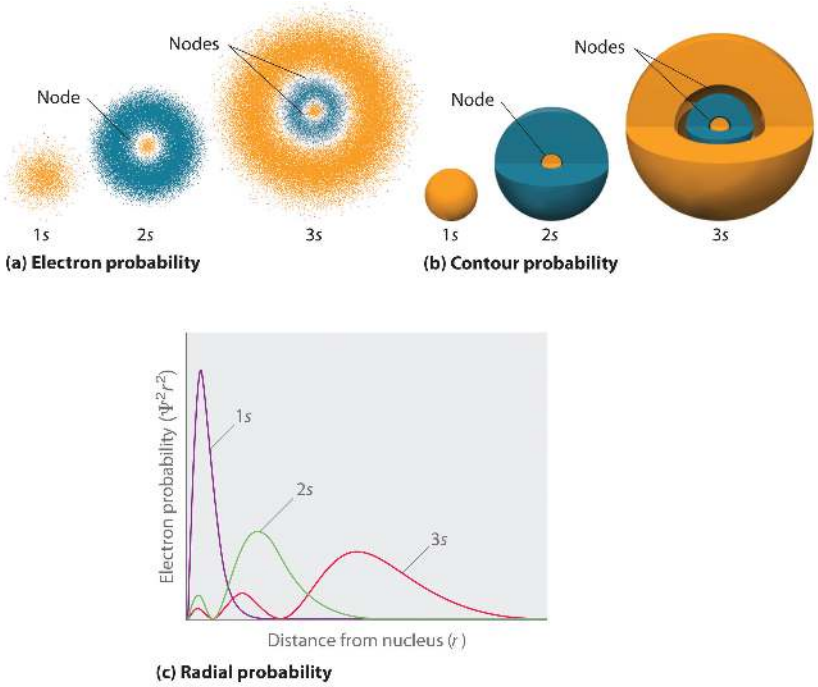


Figure **1.2.2**: Probability Densities for the 1*s*, 2*s*, and 3*s* Orbitals of the Hydrogen Atom. (a) The electron probability density in any plane that contains the nucleus is shown. Note the presence of circular regions, or nodes, where the probability density is zero. (b) Contour surfaces enclose 90% of the electron probability, which illustrates the different sizes of the 1*s*, 2*s*, and 3*s* orbitals. The cutaway drawings give partial views of the internal spherical nodes. The orange color corresponds to regions of space where the phase of the wave function is positive, and the blue color corresponds to regions of space where the phase of the wave function is negative. (c) In these plots of electron probability as a function of distance from the nucleus (*r*) in all directions (radial probability), the most probable radius increases as *n* increases, but the 2*s* and 3*s* orbitals have regions of significant electron probability at small values of *r*. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

Figure **1.2.2** compares the electron probability densities for the hydrogen 1*s*, 2*s*, and 3*s* orbitals. Note that all three are spherically symmetrical. For the 2*s* and 3*s* orbitals, however (and for all other *s* orbitals as well), the electron probability density does not fall off smoothly with increasing *r*. Instead, a series of minima and maxima are observed in the radial probability plots (part (c) in Figure **1.2.2**). The minima correspond to spherical nodes (regions of zero electron probability), which alternate with spherical regions of nonzero electron probability.

S ORBITALS

Three things happen to *s* orbitals as *n* increases (Figure **1.2.2**):

1. They become larger, extending farther from the nucleus.
2. They contain more nodes. This is similar to a standing wave that has regions of significant amplitude separated by nodes, points with zero amplitude.
3. For a given atom, the *s* orbitals also become higher in energy as *n* increases because of their increased distance from the nucleus.

Orbitals are generally drawn as three-dimensional surfaces that enclose 90% of the electron density, as was shown for the hydrogen 1*s*, 2*s*, and 3*s* orbitals in part (b) in Figure **1.2.2**. Although such drawings show the relative sizes of the orbitals, they do not normally show the spherical nodes in the 2*s* and 3*s* orbitals because the spherical nodes lie inside the 90% surface. Fortunately, the positions of the spherical nodes are not important for chemical bonding.

P ORBITALS

Only *s* orbitals are spherically symmetrical. As the value of *l* increases, the number of orbitals in a given subshell increases, and the shapes of the orbitals become more complex. Because the 2*p* subshell has $l = 1$, with three values of m_l (−1, 0, and +1), there are three 2*p* orbitals.

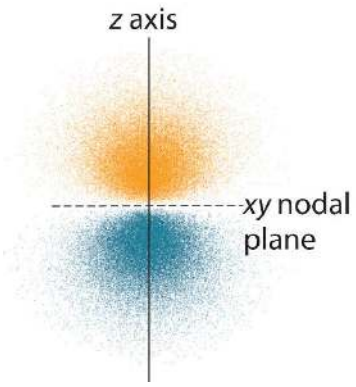


Figure **1.2.2**, the colors correspond to regions of space where the phase of the wave function is positive (orange) and negative (blue). (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

The electron probability distribution for one of the hydrogen 2*p* orbitals is shown in Figure **1.2.3**. Because this orbital has two lobes of electron density arranged along the *z* axis, with an electron density of zero in the *xy* plane (i.e., the *xy* plane is a nodal plane), it is a $2p_z$ orbital. As shown in Figure **1.2.4**, the other two 2*p* orbitals have identical shapes, but they lie along the *x* axis ($2p_x$) and *y* axis ($2p_y$), respectively. Note that each *p* orbital has just one nodal plane. In each case, the phase of the wave function for each of the 2*p* orbitals is positive for the lobe that points along the positive axis and negative for the lobe that points along the negative axis. It is important to emphasize that these signs correspond to the *phase* of the wave that describes the electron motion, *not* to positive or negative charges.

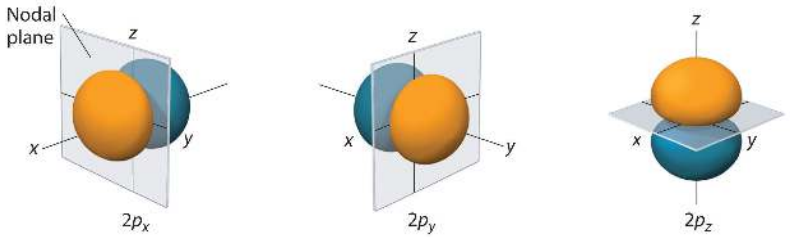


Figure **1.2.4** The Three Equivalent 2*p* Orbitals of the Hydrogen Atom. (CC BY-NC-SA 3.0; Anonymous via LibreTexts)

The surfaces shown enclose 90% of the total electron probability for the $2p_x$, $2p_y$, and $2p_z$ orbitals. Each orbital is oriented along the axis indicated by the subscript and a nodal plane that is perpendicular to that axis bisects each 2*p* orbital. The phase of the wave function is positive (orange) in the region of space where *x*, *y*, or *z* is positive and negative (blue) where *x*, *y*, or *z* is negative.

Just as with the *s* orbitals, the size and complexity of the *p* orbitals for any atom increase as the principal quantum number *n* increases. The shapes of the 90% probability surfaces of the 3*p*, 4*p*, and higher-energy *p* orbitals are, however, essentially the same as those shown in Figure **1.2.4**.

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

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1.3: ATOMIC STRUCTURE - ELECTRON CONFIGURATIONS

OBJECTIVE

After completing this section, you should be able to write the ground-state electron configuration for each of the elements up to and including atomic number 36.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- ground-state electronic configuration
- Hund's rule
- Pauli exclusion principle
- aufbau principle

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

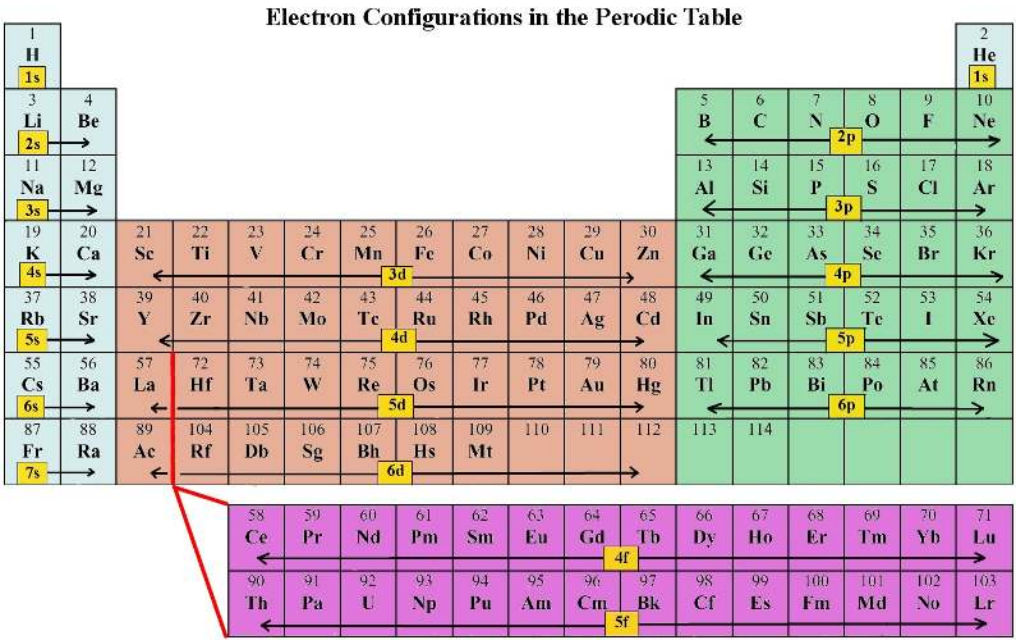


Figure **1.3.1**: The Periodic Table. (CC BY-SA-NC; Sarah Faizi via LibreTexts)

ELECTRON CONFIGURATIONS

The electron configuration of an atom is the representation of the arrangement of electrons distributed among the orbital shells and subshells. Commonly, the electron configuration is used to describe the orbitals of an atom in its ground state, but it can also be used to represent an atom that has ionized into a cation or anion by compensating with the loss of or gain of electrons in their subsequent orbitals. Many of the physical and chemical properties of elements can be correlated to their unique electron configurations. The valence electrons, electrons in the outermost shell, are the determining factor for the unique chemistry of the element.

Before assigning the electrons of an atom into orbitals, one must become familiar with the basic concepts of electron configurations. Every element on the periodic table consists of atoms, which are composed of protons, neutrons, and electrons. Electrons exhibit a negative charge and are found around the nucleus of the atom in electron orbitals, defined as the volume of space in which the electron can be found within

95% probability. The four different types of orbitals (s,p,d, and f) have different shapes, and one orbital can hold a maximum of two electrons. The p, d, and f orbitals have different sublevels, thus can hold more electrons.

As stated, the electron configuration of each element is unique to its position on the periodic table. The energy level is determined by the period and the number of electrons is given by the atomic number of the element. Orbitals on different energy levels are similar to each other, but they occupy different areas in space. The 1s orbital and 2s orbital both have the characteristics of an s orbital (radial nodes, spherical volume probabilities, can only hold two electrons, etc.) but, as they are found in different energy levels, they occupy different spaces around the nucleus. Each orbital can be represented by specific blocks on the periodic table. The s-block is the region of the alkali metals including helium (Groups 1 & 2), the d-block are the transition metals (Groups 3 to 12), the p-block are the main group elements from Groups 13 to 18, and the f-block are the lanthanides and actinides series.

Using the periodic table to determine the electron configurations of atoms is key, but also keep in mind that there are certain rules to follow when assigning electrons to different orbitals. The periodic table is an incredibly helpful tool in writing electron configurations. For more information on how electron configurations and the periodic table are linked, visit the Connecting Electrons to the Periodic Table module.

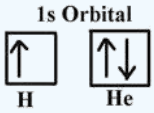
RULES FOR ASSIGNING ELECTRON ORBITALS

PAULI EXCLUSION PRINCIPLE

The Pauli exclusion principle states that no two electrons can have the same four quantum numbers. The first three (n, l, and m_l) may be the same, but the fourth quantum number must be different. A single orbital can hold a maximum of two electrons, which **must** have opposing spins; otherwise they would have the same four quantum numbers, which is forbidden. One electron is spin up (m_s = +1/2) and the other would spin down (m_s = -1/2). This tells us that each subshell has double the electrons per orbital. The s subshell has 1 orbital that can hold up to 2 electrons, the p subshell has 3 orbitals that can hold up to 6 electrons, the d subshell has 5 orbitals that hold up to 10 electrons, and the f subshell has 7 orbitals with 14 electrons.

✔ EXAMPLE 1: HYDROGEN AND HELIUM

The first three quantum numbers of an electron are n=1, l=0, m_l=0. Only two electrons can correspond to these, which would be either m_s = -1/2 or m_s = +1/2. As we already know from our studies of quantum numbers and electron orbitals, we can conclude that these four quantum numbers refer to the 1s subshell. If only one of the m_s values are given then we would have $1s^1$ (denoting hydrogen) if both are given we would have $1s^2$ (denoting helium). Visually, this is be represented as:



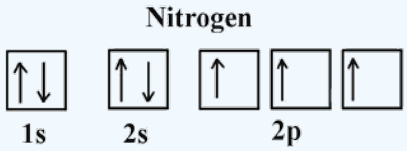
As shown, the 1s subshell can hold only two electrons and, when filled, the electrons have opposite spins.

HUND'S RULE

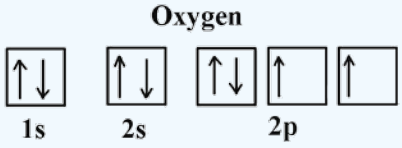
When assigning electrons in orbitals, each electron will first fill all the orbitals with similar energy (also referred to as degenerate) before pairing with another electron in a half-filled orbital. Atoms at ground states tend to have as many unpaired electrons as possible. When visualizing this processes, think about how electrons are exhibiting the same behavior as the same poles on a magnet would if they came into contact; as the negatively charged electrons fill orbitals they first try to get as far as possible from each other before having to pair up.

✔ EXAMPLE 2: OXYGEN AND NITROGEN

If we look at the correct electron configuration of the Nitrogen (Z = 7) atom, a very important element in the biology of plants: $1s^2\ 2s^2\ 2p^3$



We can clearly see that p orbitals are half-filled as there are three electrons and three p orbitals. This is because Hund's Rule states that the three electrons in the 2p subshell will fill all the empty orbitals first before filling orbitals with electrons in them. If we look at the element after nitrogen in the same period, oxygen (Z = 8) its electron configuration is: $1s^2\ 2s^2\ 2p^4$ (for an atom).



Oxygen has one more electron than nitrogen and as the orbitals are all half filled the electron must pair up.

OCCUPATION OF ORBITALS

Electrons fill orbitals in a way to minimize the energy of the atom. Therefore, the electrons in an atom fill the principal energy levels in order of increasing energy (the electrons are getting farther from the nucleus). The relative energy of the orbitals is shown in Figure **1.3.2**

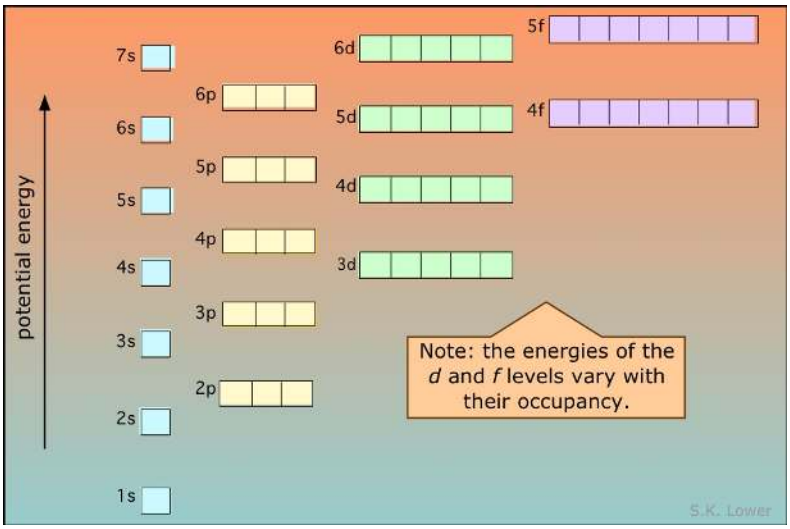


Figure **1.3.2**: The relative potential energy of atomic orbitals. (CC BY-NC; Stephen Lower)

The order of levels filled is then:

1s, 2s, 2p, 3s, 3p, 4s, 3d, 4p, 5s, 4d, 5p, 6s, 4f, 5d, 6p, 7s, 5f, 6d, and 7p

The general order in which orbitals are filled is depicted in Figure **1.3.3**. Subshells corresponding to each value of *n* are written from left to right on successive horizontal lines, where each row represents a row in the periodic table. The order in which the orbitals are filled is indicated by the diagonal lines running from the upper right to the lower left. Accordingly, the 4*s* orbital is filled prior to the 3*d* orbital because of shielding and penetration effects. Consequently, the electron configuration of potassium, which begins the fourth period, is $[Ar]4s^1$, and the configuration of calcium is $[Ar]4s^2$. Five 3*d* orbitals are filled by the next 10 elements, the transition metals, followed by three 4*p* orbitals. Notice that the last member of this row is the noble gas krypton ($Z = 36$), $[Ar]4s^23d^{10}4p^6 = [Kr]$, which has filled 4*s*, 3*d*, and 4*p* orbitals. The fifth row of the periodic table is essentially the same as the fourth, except that the 5*s*, 4*d*, and 5*p* orbitals are filled sequentially.

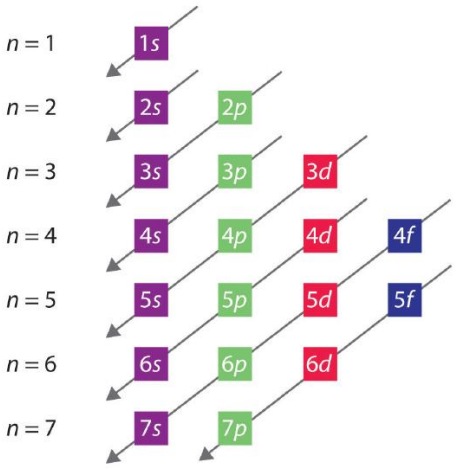


Figure **1.3.3**: Predicting the Order in Which Orbitals Are Filled in Multielectron Atoms. If you write the subshells for each value of the principal quantum number on successive lines, the observed order in which they are filled is indicated by a series of diagonal lines running from the upper right to the lower left.

THE AUFBAU PROCESS

Aufbau comes from the German word "aufbauen" meaning "to build." When writing electron configurations, orbitals are built up from atom to atom. When writing the electron configuration for an atom, orbitals are filled in order of increasing atomic number. However, there are some exceptions to this rule.

✔ EXAMPLE 3: 3RD ROW ELEMENTS

Following the pattern across a period from B (Z=5) to Ne (Z=10), the number of electrons increases and the subshells are filled. This example focuses on the p subshell, which fills from boron to neon.

- B (Z=5) configuration: $1s^2\ 2s^2\ 2p^1$
- C (Z=6) configuration:$1s^2\ 2s^2\ 2p^2$
- N (Z=7) configuration:$1s^2\ 2s^2\ 2p^3$
- O (Z=8) configuration:$1s^2\ 2s^2\ 2p^4$
- F (Z=9) configuration:$1s^2\ 2s^2\ 2p^5$
- Ne (Z=10) configuration:$1s^2\ 2s^2\ 2p^6$

THE NUMBER OF VALENCE ELECTRONS

The number of valence electrons of an element can be determined by the periodic table group (vertical column) in which the element is categorized. With the exception of groups 3–12 (the transition metals), the units digit of the group number identifies how many valence electrons are associated with a neutral atom of an element listed under that particular column. For example in group 16, the units digit is 6 and elements in this group have 6 valence electrons.

Table **1.3.1**: Valence electrons derived from periodic table group

Periodic table group	Valence electrons
Group 1: alkali metals	1
Group 2: alkaline earth metals	2
Groups 3-12: transition metals	2* (The 4s shell is complete and cannot hold any more electrons)
Group 13: boron group	3
Group 14: carbon group	4
Group 15: pnictogens	5
Group 16: chalcogens	6
Group 17: halogens	7
Group 18: noble gases	8**

** The general method for counting valence electrons is generally not useful for transition metals. Instead the modified **d electron count method** is used.*

** *Except for helium, which has only two valence electrons.*

The electron configuration of an element is the arrangement of its electrons in its atomic orbitals. By knowing the electron configuration of an element, we can predict and explain a great deal of its chemistry.

EXAMPLE 1.3.1

Draw an orbital diagram and use it to derive the electron configuration of phosphorus, $Z = 15$. What is its valence electron configuration?

Given: atomic number

Asked for: orbital diagram and valence electron configuration for phosphorus

Strategy:

A. Locate the nearest noble gas preceding phosphorus in the periodic table. Then subtract its number of electrons from those in phosphorus to obtain the number of valence electrons in phosphorus.

B. Referring to Figure 1.3.1, draw an orbital diagram to represent those valence orbitals. Following Hund's rule, place the valence electrons in the available orbitals, beginning with the orbital that is lowest in energy. Write the electron configuration from your orbital diagram.

C. Ignore the inner orbitals (those that correspond to the electron configuration of the nearest noble gas) and write the valence electron configuration for phosphorus.

Solution:

A Because phosphorus is in the third row of the periodic table, we know that it has a [Ne] closed shell with 10 electrons. We begin by subtracting 10 electrons from the 15 in phosphorus.

B The additional five electrons are placed in the next available orbitals, which Figure 1.2.5 tells us are the 3*s* and 3*p* orbitals:

P: [Ne] 3*p* ___ ___ ___
3*s* ___

Because the 3*s* orbital is lower in energy than the 3*p* orbitals, we fill it first:

P: [Ne] 3*p* ___ ___ ___
3*s* ⇅

Hund's rule tells us that the remaining three electrons will occupy the degenerate 3*p* orbitals separately but with their spins aligned:

P: [Ne] 3*p* ↑ ↑ ↑
3*s* ⇅

The electron configuration is $[Ne]3s^23p^3$.

C We obtain the valence electron configuration by ignoring the inner orbitals, which for phosphorus means that we ignore the [Ne] closed shell. This gives a valence-electron configuration of $3s^23p^3$.

EXERCISE 1.3.1

Draw an orbital diagram and use it to derive the electron configuration of chlorine, $Z = 17$. What is its valence electron configuration?

Answer

$[Ne]3s^23p^5$; $3s^23p^5$

The sixth row of the periodic table will be different from the preceding two because the 4*f* orbitals, which can hold 14 electrons, are filled between the 6*s* and the 5*d* orbitals. The elements that contain 4*f* orbitals in their valence shell are the lanthanides. When the 6*p* orbitals are finally filled, we have reached the next (and last known) noble gas, radon ($Z = 86$), $[Xe]6s^24f^{14}5d^{10}6p^6 = [Rn]$. In the last row, the 5*f* orbitals are filled between the 7*s* and the 6*d* orbitals, which gives the 14 actinide elements. Because the large number of protons makes their nuclei unstable, all the actinides are radioactive.

EXAMPLE 1.3.2

Write the electron configuration of mercury (Z = 80), showing all the inner orbitals.

Given: atomic number

Asked for: complete electron configuration

Strategy:

Using the orbital diagram in Figure **1.3.3** and the periodic table as a guide, fill the orbitals until all 80 electrons have been placed.

Solution:

By placing the electrons in orbitals following the order shown in Figure **1.3.3** and using the periodic table as a guide, we obtain

$1s^2$	row 1	2 electrons
$2s^22p^6$	row 2	8 electrons
$3s^23p^6$	row 3	8 electrons
$4s^23d^{10}4p^6$	row 4	18 electrons
$5s^24d^{10}5p^6$	row 5	18 electrons
	row 1–5	54 electrons

After filling the first five rows, we still have 80 − 54 = 26 more electrons to accommodate. According to Figure 1.3.1, we need to fill the 6*s* (2 electrons), 4*f* (14 electrons), and 5*d* (10 electrons) orbitals. The result is mercury's electron configuration:

$$1s^22s^22p^63s^23p^64s^23d^{10}4p^65s^24d^{10}5p^66s^24f^{14}5d^{10} = \text{Hg} = [\text{Xe}]6s^24f^{14}5d^{10}$$

with a filled 5*d* subshell, a $6s^24f^{14}5d^{10}$ valence shell configuration, and a total of 80 electrons. (You should always check to be sure that the total number of electrons equals the atomic number.)

SUMMARY

Based on the Pauli principle and a knowledge of orbital energies obtained using hydrogen-like orbitals, it is possible to construct the periodic table by filling up the available orbitals beginning with the lowest-energy orbitals (the **aufbau principle**), which gives rise to a particular arrangement of electrons for each element (its **electron configuration**). **Hund's rule** says that the lowest-energy arrangement of electrons is the one that places them in degenerate orbitals with their spins parallel. For chemical purposes, the most important electrons are those in the outermost principal shell, the **valence electrons**.

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1.4: DEVELOPMENT OF CHEMICAL BONDING THEORY

OBJECTIVES

After completing this section, you should be able to

1. draw Lewis Dot Symbols for main group elements and ions.
2. describe the three-dimensional nature of molecules.
3. sketch a tetrahedral molecule, CX_4, using the “wedge-and-broken-line” method of representation.
4. make a ball-and-stick model of a simple tetrahedral molecule such as methane, CH_4.
5. draw Lewis Dot Structures for 2 electron group molecules.
6. draw Lewis Dot Structures for 3 electron group molecules.
7. draw Lewis Dot Structures for 4 electron group molecules.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bond strength
- covalent bond
- ionic bond
- Lewis structure
- lone-pair electron
- non-bonding electron

Study Notes

To draw Lewis structures successfully, you need to know the number of valence electrons present in each of the atoms involved. Memorize the number of valence electrons possessed by each of the elements commonly encountered in organic chemistry: C, H, O, N, S, P and the halogens.

When drawing any organic structure, you must remember that a neutral carbon atom will almost always have four bonds. Similarly, hydrogen always has one bond; neutral oxygen atoms have two bonds; and neutral nitrogen atoms have three bonds. By committing these simple rules to memory, you can avoid making unnecessary mistakes later in the course.

The “wedge-and-broken-line” type of representation, which helps to convey the three-dimensional nature of organic compounds, will be used throughout the course.

BONDING OVERVIEW

Why are some substances chemically bonded molecules and others are an association of ions? The answer to this question depends upon the electronic structures of the atoms and nature of the chemical forces within the compounds. Although there are no sharply defined boundaries, chemical bonds are typically classified into three main types: ionic bonds, covalent bonds, and metallic bonds. In this chapter, each type of bond and the general properties found in typical substances in which the bond type occurs will be discussed.

1. Ionic bonds results from ***electrostatic forces that exist between ions of opposite charge***. These bonds typically involve a metal with a nonmetal
2. Covalent bonds ***result from the sharing of electrons between two atoms***. The bonds typically involve one nonmetallic element with another
3. Metallic bonds are found in solid metals (copper, iron, aluminum) with each metal atom bonded to several neighboring metal atoms and the bonding electrons are free to move throughout the 3-dimensional structure.

Each bond classification is discussed in detail in subsequent sections of the chapter. Let's look at the preferred arrangements of electrons in atoms when they form chemical compounds.

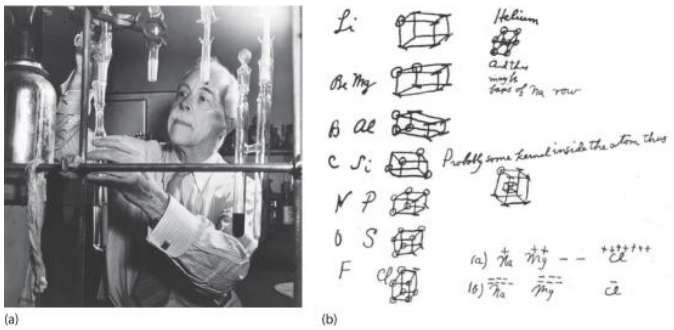


Figure 1.4.1: G. N. Lewis and the Octet Rule. (a) Lewis is working in the laboratory. (b) In Lewis's original sketch for the octet rule, he initially placed the electrons at the corners of a cube rather than placing them as we do now.

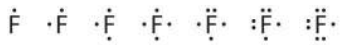
LEWIS SYMBOLS

At the beginning of the 20th century, the American chemist G. N. Lewis (1875–1946) devised a system of symbols—now called Lewis electron dot symbols, often shortened to *Lewis dot symbols*—that can be used for predicting the number of bonds formed by most elements in their compounds. Each Lewis dot symbol consists of the chemical symbol for an element surrounded by dots that represent its valence electrons.

LEWIS DOT SYMBOLS:

- provide a convenient representation of valence electrons
- allows you to keep track of valence electrons during bond formation
- consists of the chemical symbol for the element plus a dot for each valence electron

To write an element's Lewis dot symbol, we place dots representing its valence electrons, one at a time, around the element's chemical symbol. Up to four dots are placed above, below, to the left, and to the right of the symbol (in any order, as long as elements with four or fewer valence electrons have no more than one dot in each position). The next dots, for elements with more than four valence electrons, are again distributed one at a time, each paired with one of the first four. Fluorine, for example, with the electron configuration $[He]2s^22p^5$, has seven valence electrons, so its Lewis dot symbol is constructed as follows:



Group	1	2	13	14	15	16	17	18
Electron Configuration	$[He]2s^1$	$[He]2s^2$	$[He]2s^22p^1$	$[He]2s^22p^2$	$[He]2s^22p^3$	$[He]2s^22p^4$	$[He]2s^22p^5$	$[He]2s^22p^6$
Lewis Dot Symbol	Li ·	·Be·	· B ·	· C ·	· N ·	: O ·	: F ·	:Ne:

Figure **1.4.2**: Lewis Dot Symbols for the Elements in Period 2

Lewis used the unpaired dots to predict the number of bonds that an element will form in a compound. Consider the symbol for nitrogen in Figure **1.4.2**. The Lewis dot symbol explains why nitrogen, with three unpaired valence electrons, tends to form compounds in which it shares the unpaired electrons to form three bonds. Boron, which also has three unpaired valence electrons in its Lewis dot symbol, also tends to form compounds with three bonds, whereas carbon, with four unpaired valence electrons in its Lewis dot symbol, tends to share all of its unpaired valence electrons by forming compounds in which it has four bonds. Lewis symbols are a tool to help draw structures. We will see why bonding in molecular compounds follow Lewis' theory in the next section.

Elements in the same group have the same number of valence electrons and similar Lewis symbols. For example, the electron configuration for atomic sulfur is $[Ne]3s^23p^4$, thus there are ***six*** valence electrons. Its Lewis symbol would therefore be similar to oxygen and look like:



THE OCTET RULE

Lewis's major contribution to bonding theory was to recognize that atoms tend to lose, gain, or share electrons to reach a total of eight valence electrons, called an *octet*. This so-called octet rule explains the stoichiometry of most compounds in the *s* and *p* blocks of the

periodic table. We now know from quantum mechanics that the number eight corresponds to one *ns* and three *np* valence orbitals, which together can accommodate a total of eight electrons. Remarkably, though, Lewis's insight was made nearly a decade before Rutherford proposed the nuclear model of the atom. Common exceptions to the octet rule are helium, whose $1s^2$ electron configuration gives it a full $n = 1$ shell, and hydrogen, which tends to gain or share its one electron to achieve the electron configuration of helium.

Lewis's idea of an octet explains why noble gases rarely form compounds. They have the stable s^2p^6 configuration (full octet, no charge), so they have no reason to react and change their configuration. All other elements attempt to gain, lose, or share electrons to achieve a noble gas configuration. This explains why atom combine together to form compounds. By forming bond the makes the atoms more stable and lower in energy. Making bonds releases energy and represents a driving force for the formation of compounds.

Atoms often gain, lose, or share electrons to achieve the same number of electrons as the noble gas closest to them in the periodic table.

LEWIS STRUCTURES

Lewis structures represent how Lewis symbols gain, lose, or share electrons to obtain an octet by forming compounds.

LEWIS STRUCTURES OF IONIC COMPOUNDS

Whenever there is a metal present in the structure of an organic compound, there is a high likelihood that at least one ionic bond is present. Ionic bonds are represented differently in Lewis structures than covalent bonds. Great care should be taken whenever drawing the Lewis structure of an organic compounds which contains and ionic bond. Ionic bonds typically are formed when a metal and a nonmetal are part of a compound. Some atoms achieve an octet by fully gaining or losing electrons to form ions. Ionic bonds form through the eletrostatic attraction of the created ions. The formula for table salt is NaCl. It is the result of Na^+ ions and Cl^- ions bonding together. If sodium metal and chlorine gas mix under the right conditions, they will form salt. The sodium loses an electron, and the chlorine gains that electron. In the process, a great amount of light and heat is released. The resulting salt is mostly unreactive — it is stable. It will not undergo any explosive reactions, unlike the sodium and chlorine that it is made of. Why? Referring to the octet rule, atoms attempt to get a noble gas electron configuration, which is eight valence electrons. Sodium ($1s^2 2s^2 2p^6 3s^1$) has one valence electron, so giving it up would result in the same electron configuration as neon ($1s^2 2s^2 2p^6$). Chlorine ($1s^2 2s^2 2p^6 3s^2 3p^7$)has seven valence electrons, so if it takes one it will have eight (an octet). Chlorine has the electron configuration of argon ($1s^2 2s^2 2p^6 3s^2 3p^8$) when it gains an electron.

The Lewis structure of an ionic compound show the movement of electrons. For NaCl, sodium is in group 1 and has one valence electron and chlorine is in group 17 and has seven valence electrons. Sodium loses its sole valence electron thereby becomes positively charged. Chlorine gains this electron, gaining a full octet, and a negative charge. After the gain/loss of an electron the new Lewis structures of Na^+ and Cl^- are written next to each other representing the ionic bond in NaCl.

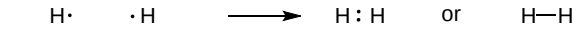
Examples of Lewis Structures of Ionic Compounds

Metal		Nonmetal		Ionic Compound
$Na\cdot$	+	$:\ddot{Cl}\cdot$	⟶	$Na^+[:\ddot{Cl}:]^-$
sodium atom		chlorine atom		sodium chloride (sodium ion and chloride ion)
$\cdot Mg\cdot$	+	$:\ddot{O}\cdot$	⟶	$Mg^{2+}[:\ddot{O}:]^{2-}$
magnesium atom		oxygen atom		magnesium oxide (magnesium ion and oxide ion)
$\cdot Ca\cdot$	+	$2:\ddot{F}\cdot$	⟶	$Ca^{2+}[:\ddot{F}:]^-_2$
calcium atom		fluorine atoms		calcium fluoride (calcium ion and two fluoride ions)

COVALENT BONDS AND THE LEWIS STRUCTURES OF MOLECULAR COMPOUNDS

While alkali metals (such as sodium and potassium), alkaline earth metals (such as magnesium and calcium), and halogens (such as fluorine and chlorine) often form ions in order to achieve a full octet, the principle elements of organic chemistry - carbon, hydrogen, nitrogen, and oxygen - instead tend to fill their octet by *sharing* electrons with other atoms, forming covalent bonds. Consider the simplest case of hydrogen gas. An isolated hydrogen atom has only one electron, located in the 1*s* orbital. If two hydrogen atoms come close enough so that their respective 1*s* orbitals overlap, the two electrons can be shared between the two nuclei, and a covalently bonded H_2 molecule is formed.

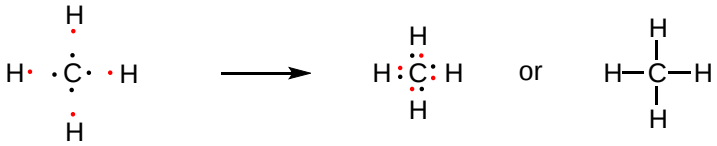
In the Lewis structure of H_2, each pair of electrons that is shared between two atoms is drawn as a single line, designating a single covalent bond.



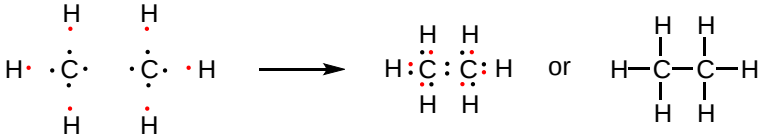
two hydrogen atoms — a hydrogen molecule (H_2)

Hydrogen represents a special case, because a hydrogen atom cannot fulfill the octet rule; it needs only two electrons to have a full shell. This is often called the 'doublet rule' for hydrogen.

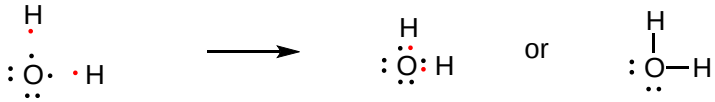
One of the simplest organic molecules is methane with the molecular formula CH_4. Methane is the 'natural gas' burned in home furnaces and hot water heaters, as well as in electrical power generating plants. To illustrate the covalent bonding in methane using a Lewis structure, we first must recognize that, although a carbon atom has a total of six electrons it's Lewis symbol has four unpaired electrons. Following Lewis' theory the carbon atom wants to form four covalent bonds to fill its octet. In a methane molecule, the central carbon atom shares its four valence electrons with four hydrogen atoms, thus forming four bonds and fulfilling the octet rule (for the carbon) and the 'doublet rule' (for each of the hydrogens).



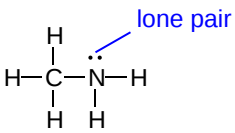
The next relatively simple organic molecule to consider is ethane, which has the molecular formula C_2H_6. If we draw each atom's Lewis symbol separately, we can see that the octet/doublet rule can be fulfilled for all of them by forming one carbon-carbon bond and six carbon-hydrogen bonds.



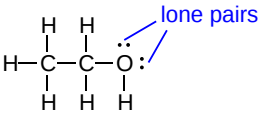
The same approach can be used for molecules in which there is no carbon atom. In a water molecule, the Lewis symbol of the oxygen atom has two unpaired electrons. These are paired with the single electron in the Lewis symbols of the hydrogens' two O-H covalent bonds. The remaining four non-bonding electrons on oxygen called 'lone pairs'.



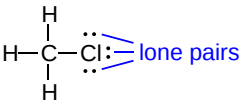
Since the lone pair electrons are often NOT shown in chemical structures, it is important to see mentally add the lone pairs. In the beginning, it can be helpful to physically add the lone pair electrons.



methylamine



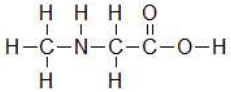
ethanol



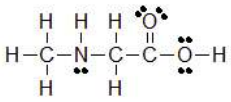
chloromethane

EXERCISE

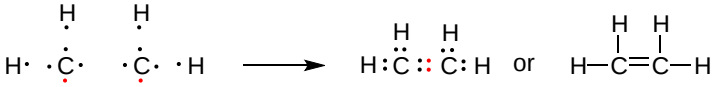
For the following structure, please fill in all of the missing lone pair electrons.



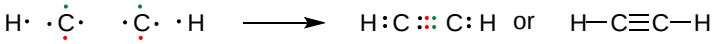
ANSWER



When two or more electrons are shared between atoms a multiple covalent bond is formed. The molecular formula for ethene (also known as ethylene, a compound found in fruits, such as apples, that signals them to ripen) is C_2H_4. Arranging Lewis symbols of the atoms, you can see that the octet/doublet rule can be fulfilled for all atoms only if the two carbons share *two* pairs of electrons between them. Ethene contains a carbon/carbon double bond.



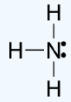
Following this pattern, the triple bond in ethyne molecular formula C_2H_2, (also known as acetylene, the fuel used in welding torches), is formed when the two carbon atoms share *three* pairs of electrons between them.



? EXERCISE 1.4.1

Draw the Lewis structure for ammonia, NH_3.

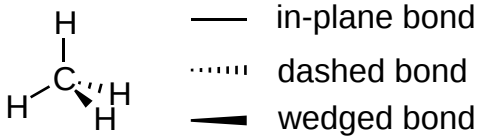
Answer



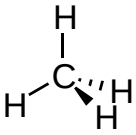
ammonia

MOLECULAR SHAPE

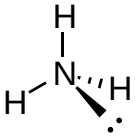
A stick and wedge drawing of methane shows the tetrahedral angles...(The wedge is coming out of the paper and the dashed line is going behind the paper. The solid lines are in the plane of the paper.)



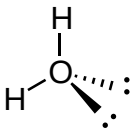
The following examples make use of this notation, and also illustrate the importance of including non-bonding valence shell electron pairs when viewing such configurations.



Methane



Ammonia



Water

Bonding configurations are readily predicted by valence-shell electron-pair repulsion theory, commonly referred to as **VSEPR** in most introductory chemistry texts. This simple model is based on the fact that electrons repel each other, and that it is reasonable to expect that the bonds and non-bonding valence electron pairs associated with a given atom will prefer to be as far apart as possible. The bonding configurations of carbon are easy to remember, since there are only three categories.

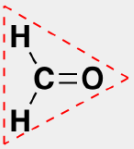
Configuration	Bonding Partners	Bond Angles	Example
Tetrahedral	4	109.5º	
Trigonal Planar	3	120º	
Linear	2	180º	

Figure 1.4.3

In the three examples shown above, the central atom (carbon) does not have any non-bonding valence electrons; consequently the configuration may be estimated from the number of bonding partners alone. However, for molecules of water and ammonia, the non-bonding electrons must be included in the calculation. In each case there are four regions of electron density associated with the valence shell so that a tetrahedral bond angle is expected. The measured bond angles of these compounds (H_2O 104.5º & NH_3 107.3º) show that they are closer to being tetrahedral than trigonal planar or linear. Of course, it is the configuration of atoms (not electrons) that defines the the shape of a molecule, and in this sense ammonia is said to be pyramidal (not tetrahedral). The compound boron trifluoride, BF_3, does not have non-bonding valence electrons and the configuration of its atoms is trigonal. Nice treatments of VSEPR theory have been provided by Oxford and Purdue. The best way to study the three-dimensional shapes of molecules is by using molecular models. Many kinds of model kits are available to students and professional chemists.

TWO ELECTRON GROUPS

Our first example is a molecule with two bonded atoms and no lone pairs of electrons, .

AX_2: BEH_2

1. The central atom, beryllium, contributes two valence electrons, and each hydrogen atom contributes one. The Lewis electron structure is



Figure 1.4.4: Lewis Structure for BeH_2

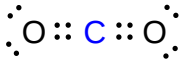
2. There are two electron groups around the central atom. We see from Figure 1.4.3 that the arrangement that minimizes repulsions places the groups 180° apart.

3. Both groups around the central atom are bonding pairs (BP). Thus BeH_2 is designated as AX_2.

4. From Figure 1.4.3 we see that with two bonding pairs, the molecular geometry that minimizes repulsions in BeH_2 is *linear*.

AX_2: CO_2

1. The central atom, carbon, contributes four valence electrons, and each oxygen atom contributes six. The Lewis electron structure is



2. The carbon atom forms two double bonds. Each double bond is a group, so there are two electron groups around the central atom. Like BeH_2, the arrangement that minimizes repulsions places the groups 180° apart.

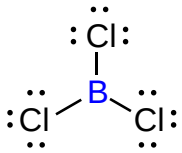
3. Once again, both groups around the central atom are bonding pairs (BP), so CO_2 is designated as AX_2.

4. VSEPR only recognizes groups around the *central* atom. Thus the lone pairs on the oxygen atoms do not influence the molecular geometry. With two bonding pairs on the central atom and no lone pairs, the molecular geometry of CO_2 is linear (Figure 1.4.3).

THREE ELECTRON GROUPS

AX_3: BCL_3

1. The central atom, boron, contributes three valence electrons, and each chlorine atom contributes seven valence electrons. The Lewis electron structure is



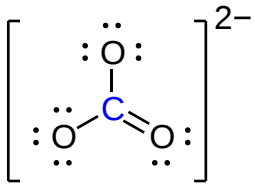
2. There are three electron groups around the central atom. To minimize repulsions, the groups are placed 120° apart (Figure 1.4.3).

3. All electron groups are bonding pairs (BP), so the structure is designated as AX_3.

4. From Figure 1.4.3 we see that with three bonding pairs around the central atom, the molecular geometry of BCl_3 is *trigonal planar*.

AX_3: CO_3^{2-}

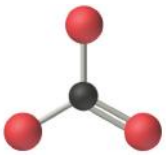
1. The central atom, carbon, has four valence electrons, and each oxygen atom has six valence electrons. As you learned previously, the Lewis electron structure of one of three resonance forms is represented as



2. The structure of CO_3^{2-} is a resonance hybrid. It has three identical bonds, each with a bond order of 4/3. We minimize repulsions by placing the three groups 120° apart (Figure 1.4.3).

3. All electron groups are bonding pairs (BP). With three bonding groups around the central atom, the structure is designated as AX_3.

4. We see from Figure 1.4.3 that the molecular geometry of CO_3^{2-} is trigonal planar.

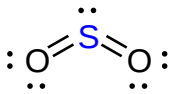


Molecular geometry
(trigonal planar)

In our next example we encounter the effects of lone pairs and multiple bonds on molecular geometry for the first time.

- ### AX_2E: SO_2

  1. The central atom, sulfur, has 6 valence electrons, as does each oxygen atom. With 18 valence electrons, the Lewis electron structure is shown below.



  2. There are three electron groups around the central atom, two double bonds and one lone pair. We initially place the groups in a trigonal planar arrangement to minimize repulsions (Figure 1.4.3).

  3. There are two bonding pairs and one lone pair, so the structure is designated as AX_2E. This designation has a total of three electron pairs, two X and one E. Because a lone pair is not shared by two nuclei, it occupies more space near the central atom than a bonding pair (Figure 1.4.4). Thus bonding pairs and lone pairs repel each other electrostatically in the order BP–BP < LP–BP < LP–LP. In SO_2, we have one BP–BP interaction and two LP–BP interactions.

  4. The molecular geometry is described only by the positions of the nuclei, *not* by the positions of the lone pairs. Thus with two nuclei and one lone pair the shape is *bent*, or *V shaped*, which can be viewed as a trigonal planar arrangement with a missing vertex (Figures 1.4.2.1 and 1.4.3).

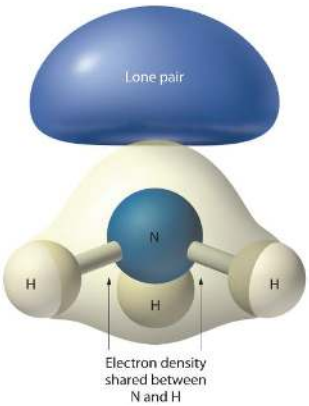
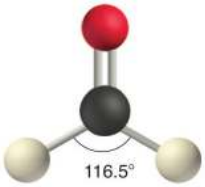


Figure 1.4.4: The Difference in the Space Occupied by a Lone Pair of Electrons and by a Bonding Pair

As with SO_2, this composite model of electron distribution and negative electrostatic potential in ammonia shows that a lone pair of electrons occupies a larger region of space around the nitrogen atom than does a bonding pair of electrons that is shared with a hydrogen atom.

Like lone pairs of electrons, multiple bonds occupy more space around the central atom than a single bond, which can cause other bond angles to be somewhat smaller than expected. This is because a multiple bond has a higher electron density than a single bond, so its electrons occupy more space than those of a single bond. For example, in a molecule such as CH_2O (AX_3), whose structure is shown below, the double bond repels the single bonds more strongly than the single bonds repel each other. This causes a deviation from ideal geometry (an H–C–H bond angle of 116.5° rather than 120°).

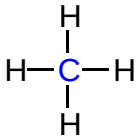


FOUR ELECTRON GROUPS

One of the limitations of Lewis structures is that they depict molecules and ions in only two dimensions. With four electron groups, we must learn to show molecules and ions in three dimensions.

AX_4: CH_4

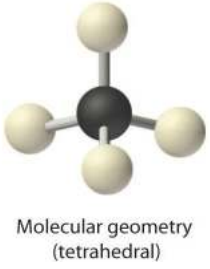
1. The central atom, carbon, contributes four valence electrons, and each hydrogen atom has one valence electron, so the full Lewis electron structure is



2. There are four electron groups around the central atom. As shown in Figure 1.4.2, repulsions are minimized by placing the groups in the corners of a tetrahedron with bond angles of 109.5°.

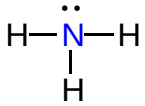
3. All electron groups are bonding pairs, so the structure is designated as AX_4.

4. With four bonding pairs, the molecular geometry of methane is *tetrahedral* (Figure 1.4.3).



AX_3E: NH_3

1. In ammonia, the central atom, nitrogen, has five valence electrons and each hydrogen donates one valence electron, producing the Lewis electron structure



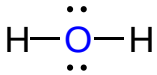
2. There are four electron groups around nitrogen, three bonding pairs and one lone pair. Repulsions are minimized by directing each hydrogen atom and the lone pair to the corners of a tetrahedron.

3. With three bonding pairs and one lone pair, the structure is designated as AX_3E. This designation has a total of four electron pairs, three X and one E. We expect the LP–BP interactions to cause the bonding pair angles to deviate significantly from the angles of a perfect tetrahedron.

4. There are three nuclei and one lone pair, so the molecular geometry is *trigonal pyramidal*. In essence, this is a tetrahedron with a vertex missing (Figure 1.4.3). However, the H–N–H bond angles are less than the ideal angle of 109.5° because of LP–BP repulsions.

AX_2E_2: H_2O

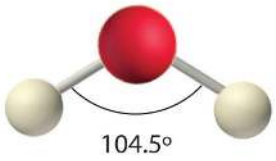
1. Oxygen has six valence electrons and each hydrogen has one valence electron, producing the Lewis electron structure



2. There are four groups around the central oxygen atom, two bonding pairs and two lone pairs. Repulsions are minimized by directing the bonding pairs and the lone pairs to the corners of a tetrahedron Figure 1.4.3.

3. With two bonding pairs and two lone pairs, the structure is designated as AX_2E_2 with a total of four electron pairs. Due to LP–LP, LP–BP, and BP–BP interactions, we expect a significant deviation from idealized tetrahedral angles.

4. With two hydrogen atoms and two lone pairs of electrons, the structure has significant lone pair interactions. There are two nuclei about the central atom, so the molecular shape is *bent*, or *V shaped*, with an H–O–H angle that is even less than the H–N–H angles in NH_3, as we would expect because of the presence of two lone pairs of electrons on the central atom rather than one.. This molecular shape is essentially a tetrahedron with two missing vertices.



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1.5: DESCRIBING CHEMICAL BONDS - VALENCE BOND THEORY

OBJECTIVES

After completing this section, you should be able to

1. explain how covalent bonds are formed as a result of the ability of atoms to share electrons.
2. describe the formation of covalent bonds in terms of the overlapping of atomic orbitals.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bond strength
- covalent bond
- bond length
- sigma (σ) bond
- pi (π) bond
- valence bond theory

VALENCE BOND THEORY

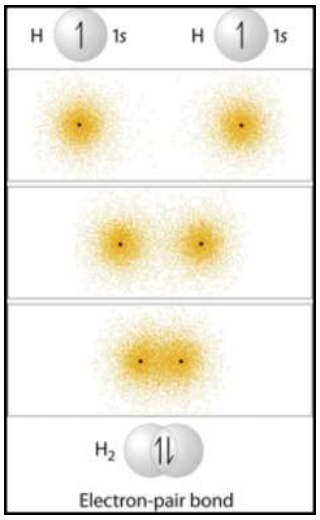
As we have been discussing how to use Lewis structures to depict the bonding in organic compounds, we have been very vague so far in our language about the actual nature of the chemical bonds themselves. We know that a covalent bond involves the 'sharing' of a pair of electrons between two atoms – but how does this happen, and how does it lead to the formation of a bond holding the two atoms together? Two main models have been developed to described how covalent bonds are formed: valence bond theory and molecularly orbital theory.

Valence bond theory is most often used to describe bonding in organic molecules. In this model, covalent bonds are considered to form from the overlap of two atomic orbitals on different atoms, each orbital containing a single electron. The electrons become paired in the orbital overlap bonding the atoms together.

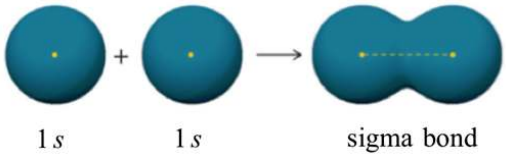
The simplest example valence bond theory can be demonstrated by the H_2 molecule. We can see from the periodic table that each hydrogen atom has a single valence electron. If 2 hydrogen atoms come together to form a bond, then each hydrogen atom effectively has a share in both electrons and thus each resembles the noble gas helium and is more stable. The 2 electrons shared in the orbital overlap are represented by a single dash between the atoms.



Valence bond theory describes a chemical bond as the overlap of atomic orbitals. In the case of the hydrogen molecule, the 1s orbital of one hydrogen atom overlaps with the 1s orbital of the second hydrogen atom to form a molecular orbital called a sigma bond which contains two electrons of opposite spin. The mutual attraction between this negatively charged electron pair and the two atoms' positively charged nuclei serves to physically link the two atoms through a force we define as a covalent bond. The strength of a covalent bond depends on the extent of overlap of the orbitals involved. Orbitals that overlap extensively form bonds that are stronger than those that have less overlap.



ne more characteristic of the covalent bond in H_2 is important to consider at this point. The two overlapping 1*s* orbitals can be visualized as two spherical balloons being pressed together. This means that the bond has **cylindrical symmetry**: if we were to take a cross-sectional plane of the bond at any point, it would form a circle. This type of bond is referred to as a **σ(sigma) bond**.



The energy of the system depends on how much the orbitals overlap. The energy diagram below illustrates how the sum of the energies of two hydrogen atoms (the colored curve) changes as they approach each other. When the atoms are far apart there is no overlap, and by convention we set the sum of the energies at zero. As the atoms move together, their orbitals begin to overlap. Each electron begins to feel the attraction of the nucleus in the other atom. In addition, the electrons begin to repel each other, as do the nuclei. While the atoms are still widely separated, the attractions are slightly stronger than the repulsions, and the energy of the system decreases. (A bond begins to form.) As the atoms move closer together, the overlap increases, so the attraction of the nuclei for the electrons continues to increase (as do the repulsions among electrons and between the nuclei). At some specific distance between the atoms, which varies depending on the atoms involved, the energy reaches its lowest (most stable) value. This optimum distance between the two bonded nuclei is called the the bond lengths between the two atoms. The bond is stable because at this point, the attractive and repulsive forces combine to create the lowest possible energy configuration.

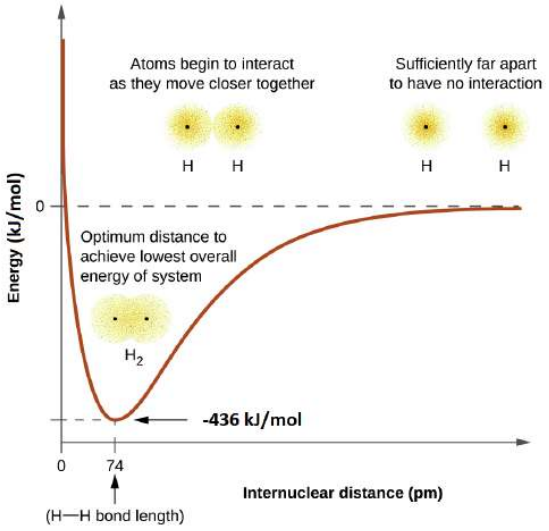


Figure **1.5.2**: A Plot of Potential Energy versus Internuclear Distance for the Interaction between Two Gaseous Hydrogen **Atoms**

This optimal internuclear distance is the **bond length**. For the H_2 molecule, the distance is 74 pm (picometers, 10^{-12} meters). Likewise, the difference in potential energy between the lowest energy state (at the optimal internuclear distance) and the state where the two atoms are completely separated is called the **bond dissociation energy,** or, more simply**, bond strength**. For the hydrogen molecule, the H-H bond strength is equal to about 435 kJ/mol. This means it would take 435 kJ to break one mole of H-H bonds.

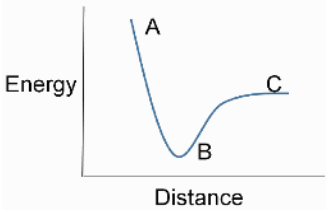
Every covalent bond in a given molecule has a characteristic length and strength. In general, the length of a typical carbon-carbon single bond in an organic molecule is about 150 pm, while carbon-carbon double bonds are about 130 pm, carbon-oxygen double bonds are about 120 pm, and carbon-hydrogen bonds are in the range of 100 to 110 pm. The strength of covalent bonds in organic molecules ranges from about 234 kJ/mol for a carbon-iodine bond (in thyroid hormone, for example), about 410 kJ/mole for a typical carbon-hydrogen bond, and up to over 800 kJ/mole for a carbon-carbon triple bond.

Table: Representative Bond Energies and Lengths

Bond	Length (pm)	Energy (kJ/mol)	Bond	Length (pm)	Energy (kJ/mol)
H-H	74	436	C-O	140.1	358
H-C	106.8	413	C=O	119.7	745
H-N	101.5	391	C≡O	113.7	1072
H-O	97.5	467	H-Cl	127.5	431
C-C	150.6	347	H-Br	141.4	366
C=C	133.5	614	H-I	160.9	298
C≡C	120.8	839	O-O	148	146
C-N	142.1	305	O=O	120.8	498
C=N	130.0	615	F-F	141.2	159
C≡N	116.1	891	Cl-Cl	198.8	243

EXERCISES

1) For the following energy diagram for energy vs. intermolecular distance is for a fluorine molecule (F_2). Please describe the importance for points A, B, & C on the graph.



SOLUTIONS

1)

A - Repulsive Forces are present, nuclei are too close to one another.

B - Optimal distance between the two orbitals to have a bond (the bond length)

C - Cannot form a bond, the orbitals are too far apart.

EXERCISES

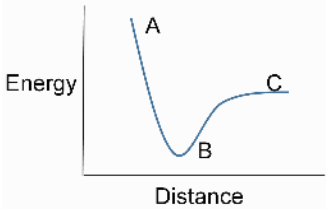
QUESTIONS

Q1.5.1

Draw an energy diagram for energy vs. intermolecular distance for a fluorine molecule (F_2) and describe the regions of the graph.

SOLUTIONS

S1.5.1



A - Repulsive Forces are present, p-orbitals are too close together

B - Optimal distance between the two p-orbitals to have a bond (the bond length)

C - Cannot form a bond, orbitals are too far away

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1.6: SP³ HYBRID ORBITALS AND THE STRUCTURE OF METHANE

OBJECTIVE

After completing this section, you should be able to describe the structure of methane in terms of the sp^3 hybridization of the central carbon atom.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

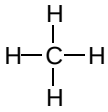
- bond angle
- hybridization
- sp^3 hybrid

STUDY NOTES

The tetrahedral shape is a very important one in organic chemistry, as it is the basic shape of all compounds in which a carbon atom is bonded to four other atoms. Note that the tetrahedral bond angle of **H – C – H** is 109.5°.

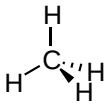
VALENCE BOND THEORY

Valence bond theory's use of overlapping atomic orbitals to explain how chemical bonds form works well in simple diatomic molecules such as H_2. However, when molecules with more than two atoms form stable bonds, we require a more detailed model. A good example is methane (CH_4). According to valence bond theory, the structure of a covalent species can be depicted using a Lewis structure.



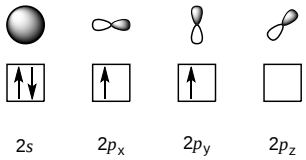
1

Experimentally, it has been shown that the four carbon-hydrogen bonds in the methane molecule are identical, meaning they have the same bond energy and the same bond length. Also, VSEPR theory suggests that the geometry at the carbon atom in the methane molecule is tetrahedral **(2)**, and there exists a large body of both theoretical and experimental evidence supporting this prediction.



2

According to valence bond theory, to form a covalent bond forms when an unpaired electron in one atom overlaps with an unpaired electron in a different atom. Now, consider the the electron configuration of the four valence electrons in carbon.



There is a serious mismatch between the electron configuration of carbon ($1s^2 2s^2 2p^2$) and the predicted structure of methane. The modern structure shows that there are only 2 unpaired electrons to share with hydrogens, instead of the 4 needed to create methane. Also, the p_x and p_y orbitals are at 90° to each other. They would form perpendicular bonds instead of the tetrahedral 109.5° bond angle predicted by VSEPR and experimental data. Lastly, there are two different orbitals, 2*s* and 2*p*, which would create different types of C-H bonds. As noted earlier, experimentally, the four carbon-hydrogen bonds in the methane molecule are identical.

HYBRID ORBITALS

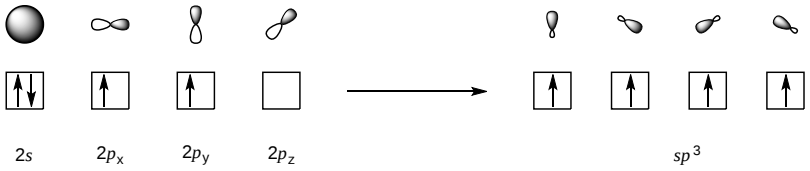
An answer to the problems posed above was offered in 1931 by Linus Pauling. He showed mathematically that an *s* orbital and three *p* orbitals on an atom can combine to form four equivalent hybrid atomic orbitals.

IMPORTANT IDEALS IN UNDERSTANDING HYBRIDIZATION

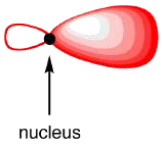
1. Hybrid orbitals do not exist in isolated atoms. They are formed only in covalently bonded atoms.
2. Hybrid orbitals have shapes and orientations that are very different from those of the atomic orbitals in isolated atoms.
3. A set of hybrid orbitals is generated by combining atomic orbitals. The number of hybrid orbitals in a set is equal to the number of atomic orbitals that were combined to produce the set.
4. All orbitals in a set of hybrid orbitals are equivalent in shape and energy.
5. The type of hybrid orbitals formed in a bonded atom create the molecular geometry as predicted by the VSEPR theory.
6. Hybrid orbitals overlap to form σ bonds.
7. Lone pair electrons are often contained in hybrid orbitals

SP^3 HYBRIDIZATION IN METHANE

In order to explain this observation, valence bond theory relies on a concept called **orbital hybridization**. In this picture, the four valence orbitals of the carbon (one 2*s* and three 2*p* orbitals) combine mathematically (remember: orbitals are described by equations) to form four equivalent **hybrid orbitals**, which are named ***sp*^{3} orbitals** because they are formed from mixing one *s* and three *p* orbitals. In the new electron configuration, each of the four valence electrons on the carbon occupies a single sp^3 orbital creating four unpaired electrons.



The shape of an sp^3 hybridized orbital is a combination of *s* and *p* atomic orbitals.



Each sp^3-hybridized orbital bears an electron, and electrons repel each other. To minimize the repulsion between electrons, the four sp^3-hybridized orbitals arrange themselves around the carbon nucleus so that they are as far away as possible from each other, resulting in the tetrahedral arrangement predicted by VSPER. The carbon atom in methane is called an "sp^3-hybridized carbon atom." The larger lobes of the sp^3 hybrids are directed towards the four corners of a tetrahedron, meaning that the angle between any two orbitals is 109.5°.

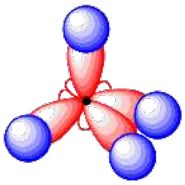


5

BONDING IN METHANE

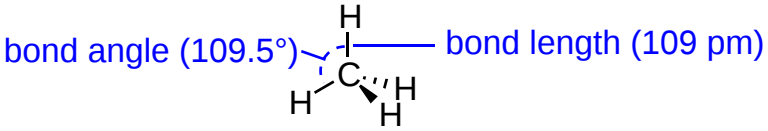
Each C-H bond in methane, then, can be described as an overlap between a half-filled 1*s* orbital in four hydrogen atoms and the larger lobe of one of the four half-filled sp^3 hybrid orbitals form a four equivalent sigma (σ) bond. This orbital overlap is often described using the notation: sp^3(C)-1*s*(H). The formation of sp^3 hybrid orbitals successfully explains the tetrahedral structure of methane and the equivalency of the the four C-H bonds.

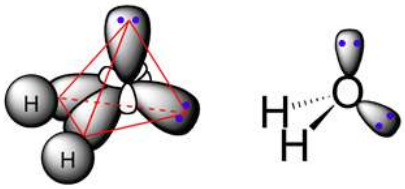
What remains is an explanation of why the sp^3 hybrid orbitals form. When the *s* and 3 *p* orbitals in carbon hybridize the resulting sp^3 hybrid orbital is unsymmetrical with one lobe larger than the other. This means the larger lobe can overlap more effectively with orbitals from other bonds making them stronger. Hybridizing allows for the carbon to form stronger bonds than it would with unhybridized *s* or *p* orbitals.



6

The four carbon-hydrogen bonds in methane are equivalent and all have a bond length of 109 pm (1.09 x 10-10 m), bond strength of of 429 kJ/mol. All of the H-C-H bond angles are 109.5°.



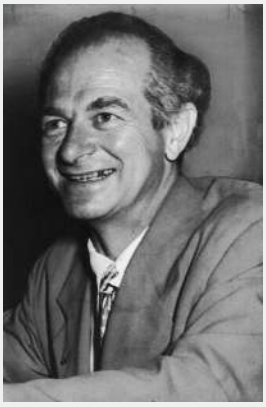


LOOKING CLOSER: LINUS PAULING

Arguably the most influential chemist of the 20th century, Linus Pauling (1901–1994) is the only person to have won two individual (that is, unshared) Nobel Prizes. In the 1930s, Pauling used new mathematical theories to enunciate some fundamental principles of the chemical bond. His 1939 book *The Nature of the Chemical Bond* is one of the most significant books ever published in chemistry.

Pauling's big contribution to chemistry was valence bond theory, which combined his knowledge of quantum mechanical theory with his knowledge of basic chemical facts, like bond lengths and and bond strengths and shapes of molecules. Valence bond theory, like Lewis's bonding theory, provides a simple model that is useful for predicting and understanding the structures of molecules, especially for organic chemistry. .

By 1935, Pauling's interest turned to biological molecules, and he was awarded the 1954 Nobel Prize in Chemistry for his work on protein structure. (He was very close to discovering the double helix structure of DNA when James Watson and James Crick announced their own discovery of its structure in 1953.) He was later awarded the 1962 Nobel Peace Prize for his efforts to ban the testing of nuclear weapons.



Linus Pauling was one of the most influential chemists of the 20th century.

In his later years, Pauling became convinced that large doses of vitamin C would prevent disease, including the common cold. Most clinical research failed to show a connection, but Pauling continued to take large doses daily. He died in 1994, having spent a lifetime establishing a scientific legacy that few will ever equal

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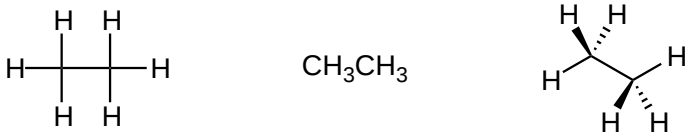
1.7: SP³ HYBRID ORBITALS AND THE STRUCTURE OF ETHANE

OBJECTIVE

After completing this section, you should be able to describe the structure of ethane in terms of the sp^3 hybridization of the two carbon atoms present in the molecule ethane.

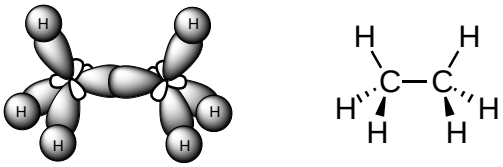
BONDING IN ETHANE

The simplest molecule with a carbon-carbon bond is ethane, C_2H_6.

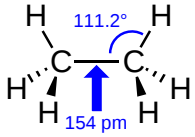


Representations of Ethane

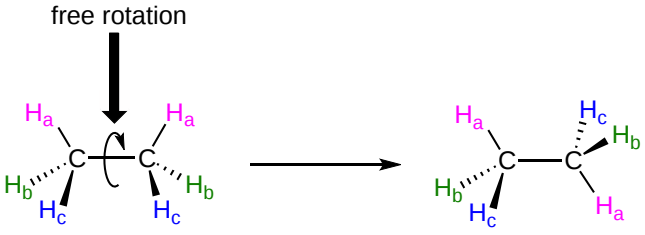
In ethane (CH_3CH_3), both carbons are sp^3-hybridized, meaning that both have four bonds with tetrahedral geometry. An sp^3 orbital of one carbon atom overlaps end to end with an sp^3 orbital of the second carbon atom to form a carbon-carbon σ bond. This orbital overlap is often described using the notation: sp^3(C)-sp^3(C). Each of the remaining sp^3 hybrid orbitals overlaps with the ***S*** orbital of a hydrogen atom to form carbon–hydrogen σ bonds.



The σ carbon-carbon bond has a bond length of 154 pm, and a bond strength of 377 kJ/mol. The carbon-hydrogen σ bonds are slightly weaker, 421 kJ/mol, than those of methane. The C-C-H bond angles in ethane are 111.2° which is close to the what is expected for tetrahedral molecules.



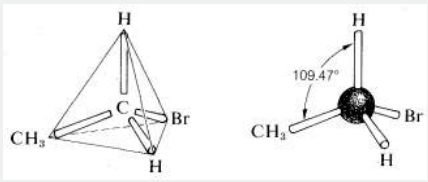
The orientation of the two CH3 groups is not fixed relative to each other. Because they are formed from the end-on-end overlap of two orbitals, *sigma bonds are free to rotate*. This means, in the case of ethane molecule, that the two methyl (CH_3) groups can be pictured as two wheels on a hub, each one able to rotate freely with respect to the other. In Section 3.7 we will learn more about the implications of rotational freedom in sigma bonds, when we discuss the 'conformation' of organic molecules

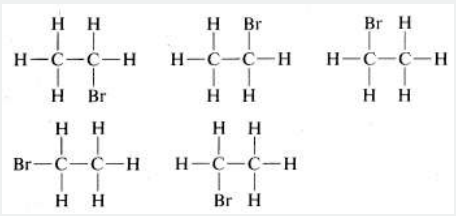


HOW DID THEY KNOW?

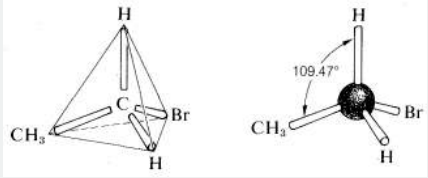
The tetrahedral geometry of carbon was predicted as far back as 1874. But how did they know? A question came up when looking at ethane with a bromine substituent (C_2H_5Br). When looking at the possible structures of the compound C_2H_5Br there are several possible structural formulas.here was a serious problem as to whether these formulas represent the same or different compounds. All that was known in the early days was that every purified sample of C_2H_5Br, no matter how prepared, had a boiling point of 38 °C and density of 1.460 gml^{-1}. Furthermore, all looked the same, all smelled the same, and all underwent the same chemical reactions. There

was no evidence that C_2H_5Br was a mixture or that more than one compound of this formula could be prepared. One might conclude, therefore, that all of the structural formulas above represent a single substance but how? A brilliant solution to the problem came when J. H. van 't Hoff proposed that all four bonds of carbon are equivalent and directed to the corners of a regular tetrahedron. If we redraw the structures for C_2H_5Br with both carbons having tetrahedral geometry, we see that there is only one possible arrangement. This theory hints at the idea of free rotation around sigma bonds which will be discussed later.





There was a serious problem as to whether these formulas represent the same or different compounds. All that was known in the early days was that every purified sample of C_2H_5Br, no matter how prepared, had a boiling point of 38 ºC and density of 1.460 gml^{-1}. Furthermore, all looked the same, all smelled the same, and all underwent the same chemical reactions. There was no evidence that C_2H_5Br was a mixture or that more than one compound of this formula could be prepared. One might conclude, therefore, that all of the structural formulas above represent a single substance but how? A brilliant solution to the problem came when J. H. van 't Hoff proposed that all four bonds of carbon are equivalent and directed to the corners of a regular tetrahedron. If we redraw the structures for C_2H_5Br with both carbons having tetrahedral geometry, we see that there is only one possible arrangement. This theory hints at the idea of free rotation around sigma bonds which will be discussed later.



EXERCISE

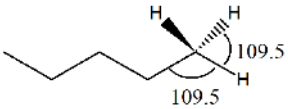
QUESTIONS

Q1.7.1

Draw pentane, $CH_3CH_2CH_2CH_2CH_3$, predict the bond angles within this molecule.

SOLUTIONS

S1.7.1



All the bond angles will be the same size.

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1.8: SP² HYBRID ORBITALS AND THE STRUCTURE OF ETHYLENE

OBJECTIVES

After completing this section, you should be able to

1. account for the formation of carbon-carbon double bonds using the concept of sp^2 hybridization.
2. describe a carbon-carbon double bond as consisting of one σ bond and one π bond.
3. explain the difference between a σ bond and a π bond in terms of the way in which *p* orbitals overlap.

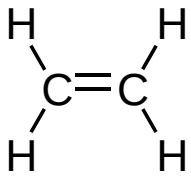
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

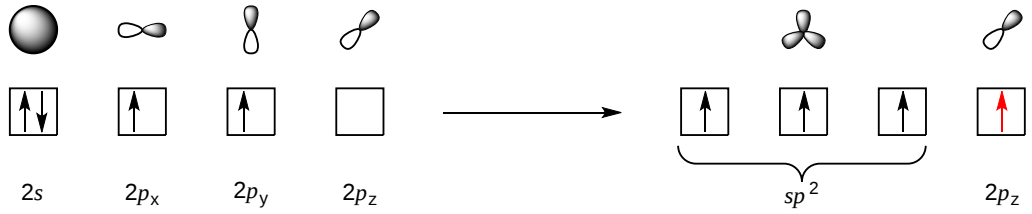
- pi (π) bond
- sp^2 hybrid

BONDING IN ETHYLENE

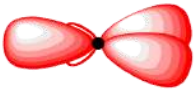
Thus far valence bond theory has been able to describe the bonding in molecules containing only single bonds. However, when molecules contain double or triple bonds the model requires more details. Ethylene (commonly knows as ethene), CH_2CH_2, is the simplest molecule which contains a carbon carbon double bond. The Lewis structure of ethylene indicates that there are one carbon-carbon double bond and four carbon-hydrogen single bonds. Experimentally, the four carbon-hydrogen bonds in the ethylene molecule have been shown to be identical. Because each carbon is surrounded by three electron groups, VSEPR theory says the molecule should have a trigonal planar geometry. Although each carbon has fulfilled its tetravalent requirement, one bond appears different. Clearly, a different type of orbital overlap is involved.



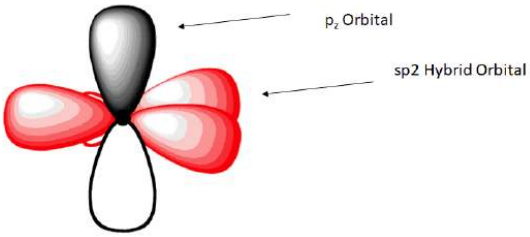
The sigma bonds formed in ethene is by the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$ – combine to form three sp^2 hybrids, leaving the $2p_z$ orbital unhybridized. Three of the four valence electrons on each carbon are distributed to the three sp^2 hybrid orbitals, while the remaining electron goes into the unhybridized p_z orbital. Each carbon in ethene is said to be a "sp^2-hybridized carbon." The electron configuration of the sp^2 hybridized carbon shows that there are four unpaired electrons to form bonds. However, the unpaired electrons are contained in two different types of orbitals so it is to be expected that two different types of bonds will form.



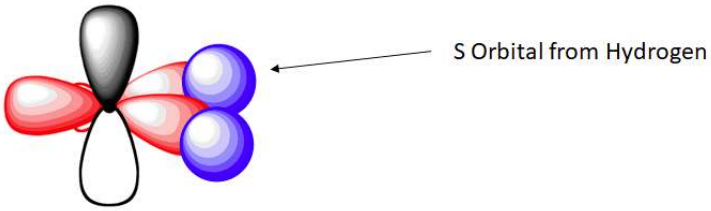
The shape of the sp^2-hybridized orbital has be mathematically shown to to be roughly the same as that of the sp^3-hybridized orbital. To minimize the repulsion between electrons, the three sp^2-hybridized orbitals are arranged with a trigonal planar geometry. Each orbital lobe is pointing to the three corners of an equilateral triangle, with angles of 120° between them. Again, geometry and hybrization can be tied together. Atoms surrounded by three electron groups can be said to have a trigonal planar geometry and sp^2 hybridization.



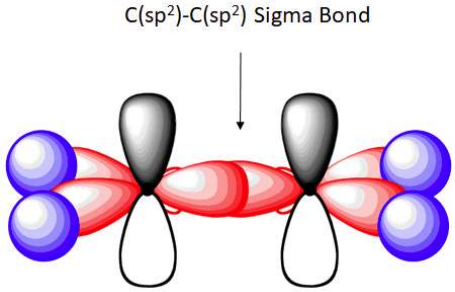
The unhybridized $2p_z$ orbital is *perpendicular* to the plane of the trigonal planar sp^2 hybrid orbtals.



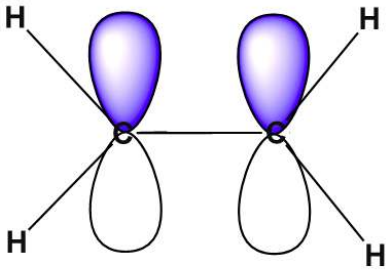
In the ethylene molecule, each carbon atom is bonded to two hydrogen atoms. Thus, overlap two sp^2-hybridized orbitals with the 1s orbitals of two hydrogen atoms for the C-H sigma bonds in ethylene (sp^2(C)-1s(H). Consequently, consistent with the observations, the four carbon-hydrogen bonds in ethylene are identical.



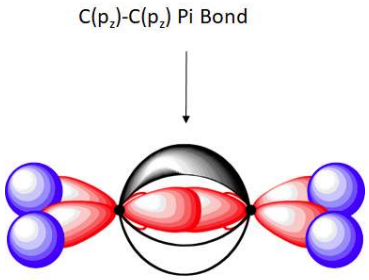
The C-C sigma bond in ethylene is formed by the overlap of an sp^2 hybrid orbital from each carbon.



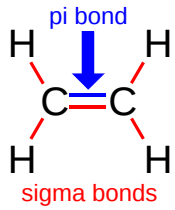
The overlap of hybrid orbitals or a hybrid orbital and a 1s orbtial from hydrogen creates the sigma bond framework of the ethylene molecule. However the unhybridized p_z orbital on each carbon remains.



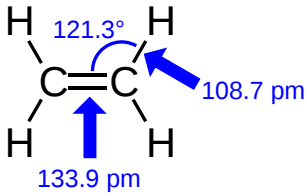
The unhybridized pz orbitals on each carbon overlap to a π bond (pi). The orbital overlap is commonly written as p_z(C)-1p_z(C). In general multiple bonds in molecular compound are formed by the overlap of unhybridized p orbitals. It should be noted that the carbon-carbon double bond in ethlene is made up of two different types of bond, a sigma and a pi.



Overall, ethylene is said to contain five sigma bonds and one pi bond. Pi bonds tend to be weaker than sigma bonds because the side-by-side overlap the p orbitals give a less effective orbital overlap when compared to the end-to-end orbital overlap of a sigma bond. This makes the pi much easier to break which is one of the most important ideas in organic chemistry reactions as we will see in Chapter 7 and subsequent chapters.

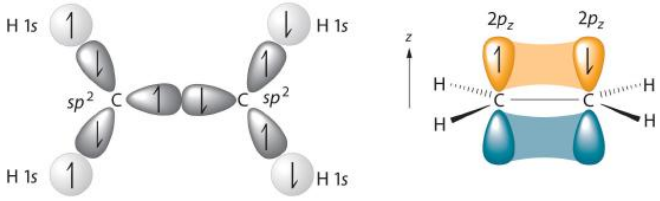


An ethylene molecule is said to be made up of five sigma bonds and one pi bond. The three sp^2 hybrid orbitals on each carbon orient to create the basic trigonal planer geometry. The H-C-C bond angle in ethylene is 121.3º which is very close to the 120º predicted by VSEPR. The four C-H sigma bonds in ethylene . The carbon-carbon double bond in ethylene is both shorter (133.9 pm) and almost twice as strong (728 kJ/mol) than the carbon- carbon single bond in ethylene (154 pm & 377 kJ/mol). Each of the four carbon-hydrogen bond in ethylene are equivalent has have a length of 108.7 pm



RIGIDITY IN ETHENE

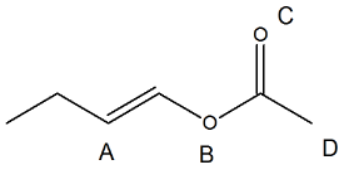
Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. If free rotation were to occur the p-orbitals would have to go through a phase where they are 90° from each other, which would break the pi bond because there would be no overlap. Since the pi bond is essential to the structure of ethene it must not break, so there can be not free rotation about the carbon-carbon sigma bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane.



(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

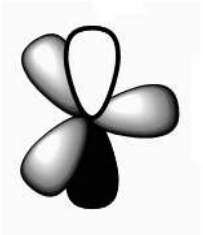
EXERCISE

1) Consider the following molecule:



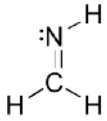
At each atom, what is the hybridization and the bond angle and the bond angle predicted by VSPER?

2) Please identify the types of orbitals shown in the following diagram:



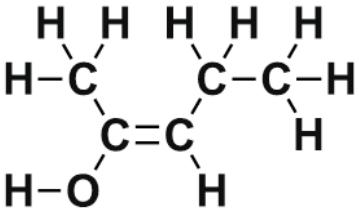
3)

a: Describe the orbitals which overlap to the carbon-nitrogen sigma bond and pie bond in the molecule below:



b: What kind of orbital holds the nitrogen lone pair?

4) For the following molecule please indicate with atoms are being held in the same plane by the carbon-carbon double bond:



SOLUTIONS

1)

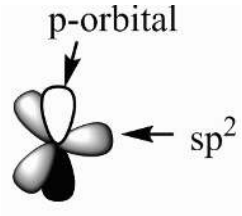
A - sp^2, 120°

B - sp^3, 109°

C - sp^2, 120° (with the lone pairs present)

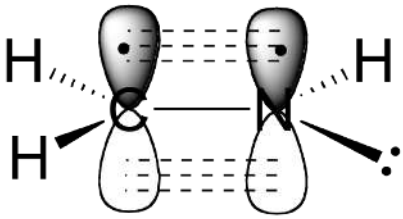
D - sp^3, 109°

2)



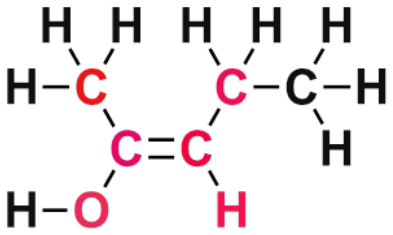
3)

a) The carbon and nitrogen atoms are both sp^2 hybridized. The carbon-nitrogen double bond is composed of a sigma bond formed from two sp^2 orbitals, and a pi bond formed from the side-by-side overlap of two unhybridized *2p* orbitals.



b) As shown in the figure above, the nitrogen lone pair electrons occupy one of the three sp^2 hybrid orbitals.

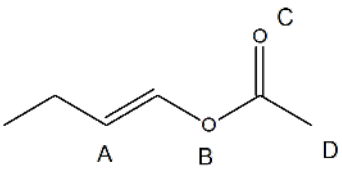
4)



QUESTIONS

Q1.8.1

Consider the following molecule:



At each atom, what is the hybridization and the bond angle? At atom A draw the molecular orbital.

SOLUTIONS

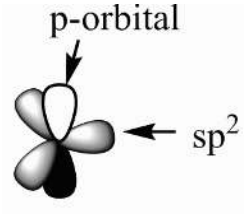
S1.8.1

A - sp^2, 120°

B - sp^3, 109°

C - sp^2, 120° (with the lone pairs present)

D - sp^3, 109°



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1.9: SP HYBRID ORBITALS AND THE STRUCTURE OF ACETYLENE

OBJECTIVES

After completing this section, you should be able to

1. use the concept of *sp* hybridization to account for the formation of carbon-carbon triple bonds, and describe a carbon-carbon triple bond as consisting of one σ bond and two π bonds.
2. list the approximate bond lengths associated with typical carbon-carbon single bonds, double bonds and triple bonds. [You may need to review Sections 1.7 and 1.8.]
3. list the approximate bond angles associated with sp^3-, sp^2- and *sp*-hybridized carbon atoms and predict the bond angles to be expected in given organic compounds. [If necessary, review Sections 1.6, 1.7 and 1.8.]
4. account for the differences in bond length, bond strength and bond angles found in compounds containing sp^3-, sp^2- and sp-hybridized carbon atoms, such as ethane, ethylene and acetylene.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

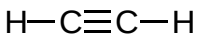
- *sp* hybrid orbital

STUDY NOTES

The bond angles associated with sp^3-, sp^2- and *sp*-hybridized carbon atoms are approximately 109.5°, 120° and 180°, respectively.

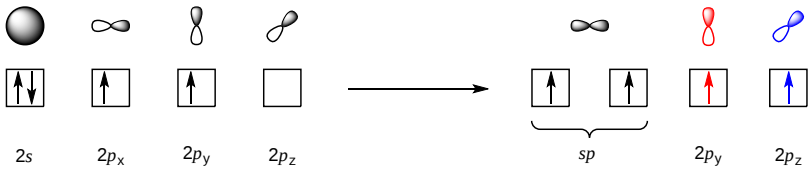
BONDING IN ACETYLENE

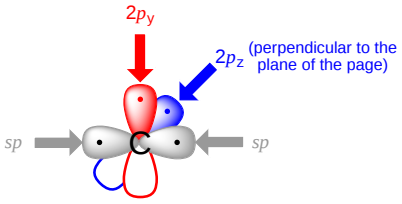
Finally, the hybrid orbital concept applies well to triple-bonded groups, such as alkynes and nitriles. Consider, for example, the structure of ethyne (another common name is acetylene), the simplest alkyne.



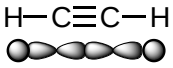
ethyne
(acetylene)

This molecule is linear: all four atoms lie in a straight line. The carbon-carbon triple bond is only 1.20Å long. In the hybrid orbital picture of acetylene, both carbons are ***sp*-hybridized**. In an *sp*-hybridized carbon, the 2*s* orbital combines with the $2p_x$ orbital to form two *sp* hybrid orbitals that are oriented at an angle of 180°with respect to each other (eg. along the x axis). The $2p_y$ and $2p_z$ orbitals remain non-hybridized, and are oriented perpendicularly along the y and z axes, respectively.

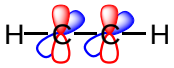




The C-C sigma bond is formed by the overlap of one *sp* orbital from each of the carbons, while the two C-H sigma bonds are formed by the overlap of the second *sp* orbital on each carbon with a 1*s* orbital on a hydrogen. Each carbon atom still has two half-filled $2p_y$ and $2p_z$ orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two perpendicular pairs of *p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds).

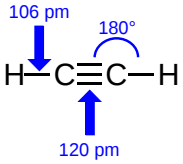


sigma bonding in ethylene



pi bonding in ethylene

Acetylene is said to have three sigma bonds and two pi bonds. The carbon-carbon triple bond in acetylene is the shortest (120 pm) and the strongest (965 kJ/mol) of the carbon-carbon bond types. Because each carbon in acetylene has two electron groups, VSEPR predicts a linear geometry and and H-C-C bond angle of 180º.

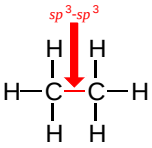


Comparison of C-C bonds Ethane, Ethylene, and Acetylene

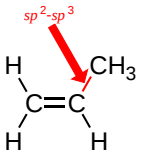
Molecule	Bond	Bond Strength (kJ/mol)	Bond Length (pm)
Ethane, CH_3CH_3	(sp^3) C-C (sp^3)	376	154
Ethylene, $H_2C{=}CH_2$	(sp^2) C=C (sp^2)	728	134
Acetylene, HC≡CH	(sp) C≡C (sp)	965	120

Notice that as the bond order increases the bond length decreases and the bond strength increases.

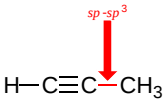
The hybrid orbital concept nicely explains another experimental observation: single bonds adjacent to double and triple bonds are progressively shorter and stronger than 'normal' single bonds, such as the one in a simple alkane. The carbon-carbon bond in ethane (structure A below) results from the overlap of two sp^3 orbitals.



A



B



C

In propene (B), however, the carbon-carbon single bond is the result of overlap between an sp^2 orbital and an sp^3 orbital, while in propyne (C) the carbon-carbon single bond is the result of overlap between an sp orbital and an sp^3 orbital. These are all single bonds, but the single bond in molecule C is shorter and stronger than the one in B, which is in turn shorter and stronger than the one in A.

The explanation here is relatively straightforward. An sp orbital is composed of one *s* orbital and one *p* orbital, and thus it has 50% *s* character and 50% *p* character. sp^2 orbitals, by comparison, have 33% *s* character and 67% *p* character, while sp^3 orbitals have 25% *s* character and 75% *p* character. Because of their spherical shape, 2*s* orbitals are smaller, and hold electrons closer and 'tighter' to the nucleus, compared to 2*p* orbitals. Consequently, bonds involving sp + sp^3 overlap (as in alkyne C) are shorter and stronger than bonds involving sp^2 + sp^3 overlap (as in alkene B). Bonds involving sp^3-sp^3overlap (as in alkane A) are the longest and weakest of the group, because of the 75% '*p*' character of the hybrids.

HYBRIDIZATION SUMMARY

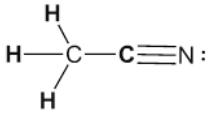
- A single bond is a sigma bond.
- A double bond is made up of a sigma bond and a pi bond.
- A triple bond is made up of a sigma bond and two pi bonds.
- Sigma bonds are made by the overlap of two hybrid orbitals or the overlap of a hybrid orbital and a s orbital from hydrogen.
- Pi bonds are made by the overlap of two unhybridized p orbitals.
- Lone pair electrons are usually contained in hybrid orbitals.

The hybrid orbitals used (and hence the hybridization) depends on how many electron groups are around the atom in question. An electron group can mean either a bonded atom or a lone pair. Molecular geometry is also decided by the number of electron groups so it is directly linked to hybridization.

# of Electron Groups	Hybrid Orbital Used	Example	Basic Geometry	Basic Bond Angle
2	sp		Linear	180°
3	sp^2		Trigonal Planar	120°
4	sp^3		Tetrahedral	109.5°

EXERCISES

1) For the molecule acetonitrile:



Acetonitrile

a) How many sigma and pi bonds does it have?

b) What orbitals overlap to form the C-H sigma bonds?

c) What orbitals overlap to form the C-C sigma bond?

d) What orbitals overlap to form the C-N sigma bond?

e) What orbitals overlap to the form the C-N pi bonds?

f) What orbital contains the lone pair electrons on nitrogen?

SOLUTIONS

1)

a) 5 sigma and 2 pi

b) An sp^3 hybrid orbital from carbon and an a s orbital from hydrogen.

c) An sp^3 hybrid orbital from one carbon and an a sp^3 orbital from the other carbon.

d) An sp hybrid orbital from carbon and an a sp orbital from nitrogen.

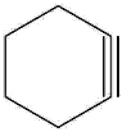
e) An p_y and p_z orbital from carbon and an p_y and p_z orbital from nitrogen.

f) An sp hybrid orbital.

QUESTIONS

Q1.9.1

1-Cyclohexyne is a very strained molecule. By looking at the molecule explain why there is such a intermolecular strain using the knowledge of hybridization and bond angles.



SOLUTIONS

S1.9.1

The alkyne is a sp hybridized orbital. By looking at a sp orbital, we can see that the bond angle is 180°, but in cyclohexane the regular angles would be 109.5°. Therefore the molecule would be strained to force the 180° to be a 109°.

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1.10: HYBRIDIZATION OF NITROGEN, OXYGEN, PHOSPHORUS AND SULFUR

OBJECTIVE

After completing this section, you should be able to apply the concept of hybridization of atoms such as N, O, P and S to explain the structures of simple species containing these atoms.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- lone pair electrons

STUDY NOTES

Nitrogen is frequently found in organic compounds. As with carbon atoms, nitrogen atoms can be sp^3-, sp^2- or *sp*-hybridized.

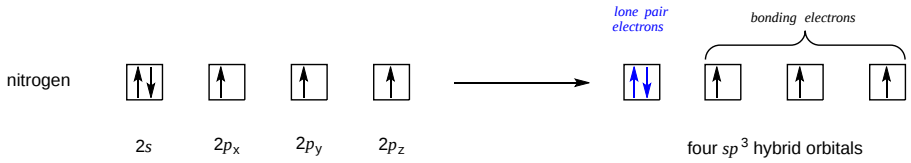
Note that, in this course, the term “lone pair” is used to describe an unshared pair of electrons.

The valence-bond concept of orbital hybridization can be extrapolated to other atoms including nitrogen, oxygen, phosphorus, and sulfur. In other compounds, covalent bonds that are formed can be described using hybrid orbitals.

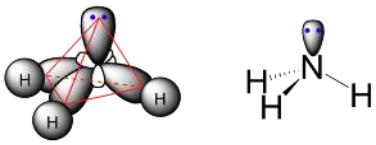
NITROGEN

BONDING IN NH_3

The nitrogen in NH_3 has five valence electrons. After hybridization these five electrons are placed in the four equivalent sp^3 hybrid orbitals. The electron configuration of nitrogen now has one sp^3 hybrid orbital completely filled with two electrons and three sp^3 hybrid orbitals with one unpaired electron each. The two electrons in the filled sp^3 hybrid orbital are considered non-bonding because they are already paired. These electrons will be represented as a lone pair on the structure of NH_3. The three unpaired electrons in the hybrid orbitals are considered bonding and will overlap with the s orbitals in hydrogen to form N-H sigma bonds. Note! This bonding configuration was predicted by the Lewis structure of NH_3.

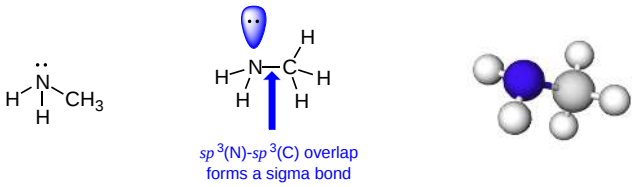


The four sp^3 hybrid orbitals of nitrogen orientate themselves to form a tetrahedral geometry. The three N-H sigma bonds of NH_3 are formed by sp^3(N)-1s(H) orbital overlap. The fourth sp^3 hybrid orbital contains the two electrons of the lone pair and is not directly involved in bonding.



METHYL AMINE

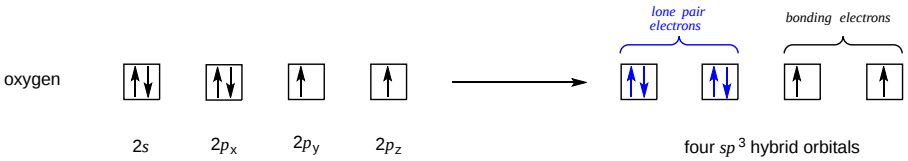
The nitrogen is sp^3 hybridized which means that it has four sp^3 hybrid orbitals. Two of the sp^3 hybridized orbitals overlap with s orbitals from hydrogens to form the two N-H sigma bonds. One of the sp^3 hybridized orbitals overlap with an sp^3 hybridized orbital from carbon to form the C-N sigma bond. The lone pair electrons on the nitrogen are contained in the last sp^3 hybridized orbital. Due to the sp^3 hybridization the nitrogen has a tetrahedral geometry. However, the H-N-H and H-N-C bonds angles are less than the typical 109.5º due to compression by the lone pair electrons.



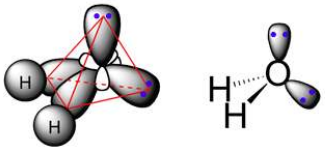
OXYGEN

BONDING IN H_2O

The oxygen in H_2O has six valence electrons. After hybridization these six electrons are placed in the four equivalent sp^3 hybrid orbitals. The electron configuration of oxygen now has two sp^3 hybrid orbitals completely filled with two electrons and two sp^3 hybrid orbitals with one unpaired electron each. The filled sp^3 hybrid orbitals are considered non-bonding because they are already paired. These electrons will be represented as a two sets of lone pair on the structure of H_2O . The two unpaired electrons in the hybrid orbitals are considered bonding and will overlap with the s orbitals in hydrogen to form O-H sigma bonds. Note! This bonding configuration was predicted by the Lewis structure of H_2O.

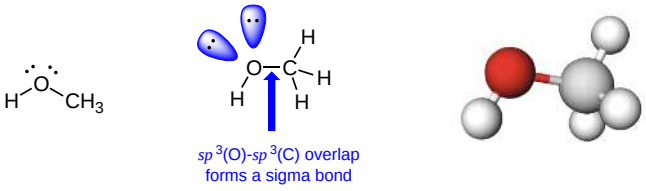


The four sp^3 hybrid orbitals of oxygen orientate themselves to form a tetrahedral geometry. The two O-H sigma bonds of H_2O are formed by sp^3(O)-1s(H) orbital overlap. The two remaining sp^3 hybrid orbitals each contain two electrons in the form of a lone pair.



METHANOL

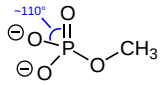
The oxygen is sp^3 hybridized which means that it has four sp^3 hybrid orbitals. One of the sp^3 hybridized orbitals overlap with s orbitals from a hydrogen to form the O-H sigma bonds. One of the sp^3 hybridized orbitals overlap with an sp^3 hybridized orbital from carbon to form the C-O sigma bond. Both the sets of lone pair electrons on the oxygen are contained in the remaining sp^3 hybridized orbital. Due to the sp^3 hybridization the oxygen has a tetrahedral geometry. However, the H-O-C bond angles are less than the typical 109.5º due to compression by the lone pair electrons.

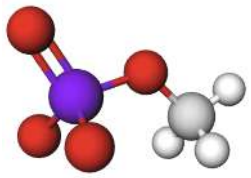


PHOSPHORUS

METHYL PHOSPHATE

The bond pattern of phosphorus is analogous to nitrogen because they are both in period 15. However, phosphorus can have have expanded octets because it is in the n = 3 row. Typically, phosphorus forms five covalent bonds. In biological molecules, phosphorus is usually found in organophosphates. Organophosphates are made up of a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to a carbon. In methyl phosphate, the phosphorus is sp^3 hybridized and the O-P-O bond angle varies from 110° to 112º.

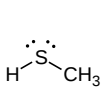


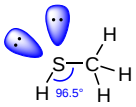


SULFUR

METHANETHIOL & DIMETHYL SULFIDE

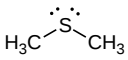
Sulfur has a bonding pattern similar to oxygen because they are both in period 16 of the periodic table. Because sulfur is positioned in the third row of the periodic table it has the ability to form an expanded octet and the ability to form more than the typical number of covalent bonds. In biological system, sulfur is typically found in molecules called thiols or sulfides. In a thiol, the sulfur atom is bonded to one hydrogen and one carbon and is analogous to an alcohol O-H bond. In a sulfide, the sulfur is bonded to two carbons. The simplest example of a thiol is methane thiol (CH_3SH) and the simplest example of a sulfide is dimethyl sulfide [$(CH_3)_3S$]. In both cases the sulfur is sp^3 hybridized, however the sulfur bond angles are much less than the typical tetrahedral 109.5° being 96.6° and 99.1° respectively.

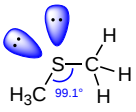


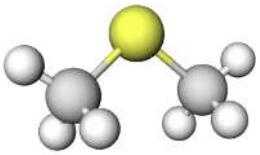




methanethiol





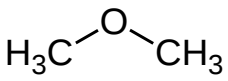


dimethyl sulfide

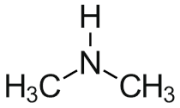
EXERCISES

1) Insert the missing lone pairs of electrons in the following molecules, and tell what hybridization you expect for each of the indicated atoms.

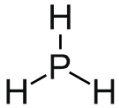
a) The oxygen is dimethyl ether:



b) The nitrogen in dimethyl amine:

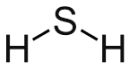


c) The phosphorus in phosphine:



d) The sulfur in hydrogen sulfide:

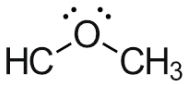
https://chem.libretexts.org/@go/page/31377



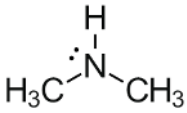
SOLUTIONS

1)

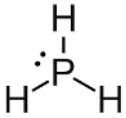
a) sp^3 hybridization



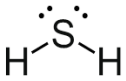
b) sp^3 hybridization



c) sp^3 hybridization



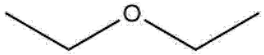
d) sp^3 hybridization



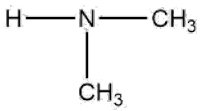
QUESTIONS

Q1.10.1

Identify geometry and lone pairs on each heteroatom of the molecules given.



Diethyl Ether



Dimethylamine

SOLUTIONS

S1.10.1

Diethyl ether would have two lone pairs of electrons and would have a bent geometry around the oxygen.

Dimethyl amine would have one lone pair and would show a pyramidal geometry around the nitrogen.

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1.11: DESCRIBING CHEMICAL BONDS - MOLECULAR ORBITAL THEORY

OBJECTIVES

After completing this section, you should be able to

1. describe the formation of covalent bonds in terms of molecular orbitals.
2. account for differences in bond length and strength in terms of the efficiency with which atomic orbitals overlap.
3. draw simple molecular orbital diagrams (e.g., for the H_2 molecule) showing the formation of bonding and anti-bonding orbitals.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

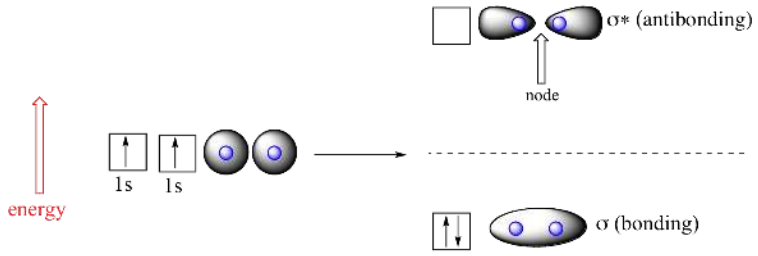
- anti-bonding molecular orbital
- bonding molecular orbital
- molecular orbital (MO) theory

As we have seen, valence bond theory does a remarkably good job of explaining the bonding geometry and properties of many organic compounds. There are some areas, however, where the valence bond theory falls short. It fails to adequately account, for example, for some interesting properties of compounds that contain alternating double and single bonds. In order to understand these properties, we need to think about chemical bonding in a new way, using the ideas of molecular orbital (MO) theory.

ANOTHER LOOK AT THE H_2 MOLECULE: BONDING AND ANTI-BONDING SIGMA MOLECULAR ORBITALS

Let's consider again the simplest possible covalent bond: the one in molecular hydrogen (H_2). When we described the hydrogen molecule using valence bond theory, we said that the two 1*s* orbitals from each atom overlap, allowing the two electrons to be shared and thus forming a covalent bond. In molecular orbital theory, we make a further statement: we say that the two atomic 1*s* orbitals don't just overlap, they actually *combine to form two completely new orbitals*. These two new orbitals, instead of describing the likely location of an electron around a single nucleus, describe the location of an electron pair around two or more nuclei. The bonding in H_2, then, is due to the formation of a new **molecular orbital** (MO), in which a pair of electrons is delocalized around two hydrogen nuclei.

An important principle of quantum mechanical theory is that when orbitals combine, the number of orbitals before the combination takes place must equal the number of new orbitals that result – orbitals don't just disappear! We saw this previously when we discussed hybrid orbitals: one *s* and three *p* orbitals make four sp^3 hybrids. When two atomic 1*s* orbitals combine in the formation of H_2, the result is two molecular orbitals called **sigma (σ) orbitals**. According to MO theory, the first sigma orbital is lower in energy than either of the two isolated atomic 1*s* orbitals – thus this sigma orbital is referred to as a **bonding molecular orbital**. The second, **sigma-star (σ*) orbital** is higher in energy than the two atomic 1*s* orbitals, and is referred to as an **anti-bonding molecular orbital**. In MO theory, a star (*) sign always indicates an anti-bonding orbital.



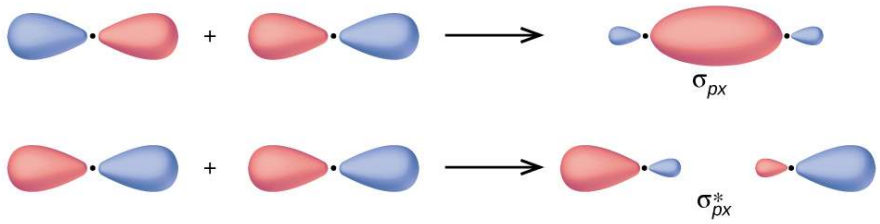
Following the *aufbau* ('building up') principle, we place the two electrons in the H_2 molecule in the lowest energy molecular orbital, which is the (bonding) sigma orbital.

The bonding sigma orbital, which holds both electrons in the ground state of the molecule, is egg-shaped, encompassing the two nuclei, and with the highest likelihood of electrons being in the area between the two nuclei. The high-energy, anti-bonding sigma-star orbital can be visualized as a pair of droplets, with areas of higher electron density near each nucleus and a 'node', (area of zero electron density) midway between the two nuclei.

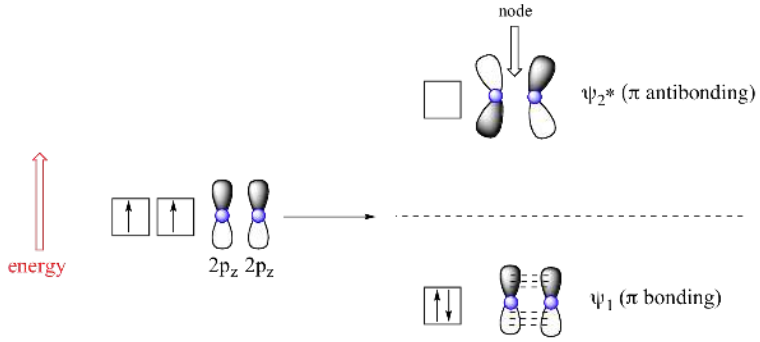
Remember that we are thinking here about electron behavior as *wave behavior*. When two separate waves combine, they can do so with what is called constructive interference, where the two amplitudes reinforce one another, or destructive interference, where the two amplitudes cancel one another out. Bonding MO's are the consequence of constructive interference between two atomic orbitals which results in an attractive interaction and an increase in electron density between the nuclei. Anti-bonding MO's are the consequence of destructive interference which results in a repulsive interaction and a 'canceling out' of electron density between the nuclei (in other words, a node).

MO THEORY AND PI BONDS

In p orbitals, the wave function gives rise to two lobes with opposite phases, analogous to how a two-dimensional wave has both parts above and below the average. We indicate the phases by shading the orbital lobes different colors. When orbital lobes of the same phase overlap, constructive wave interference increases the electron density. When regions of opposite phase overlap, the destructive wave interference decreases electron density and creates nodes. When p orbitals overlap end to end, they create σ and σ* orbitals. If two atoms are located along the x-axis in a Cartesian coordinate system, the two px orbitals overlap end to end and form σp_x (bonding) and $\sigma * p_x$ (antibonding) (read as "sigma-p-x" and "sigma-p-x star," respectively). Just as with s-orbital overlap, the asterisk indicates the orbital with a node between the nuclei, which is a higher-energy, antibonding orbital.



The advantage of MO theory becomes more apparent when we think about pi bonds, especially in those situations where two or more pi bonds are able to interact with one another. Let's first consider the pi bond in ethene from an MO theory standpoint (in this example we will be disregarding the various sigma bonds, and thinking *only* about the pi bond). According to MO theory, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π.



In the bonding Ψ_1 orbital, the two shaded lobes of the $2p_z$ orbitals interact constructively with each other, as do the two unshaded lobes (remember, the shading choice represents mathematical (+) and (-) signs for the wavefunction). Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital.

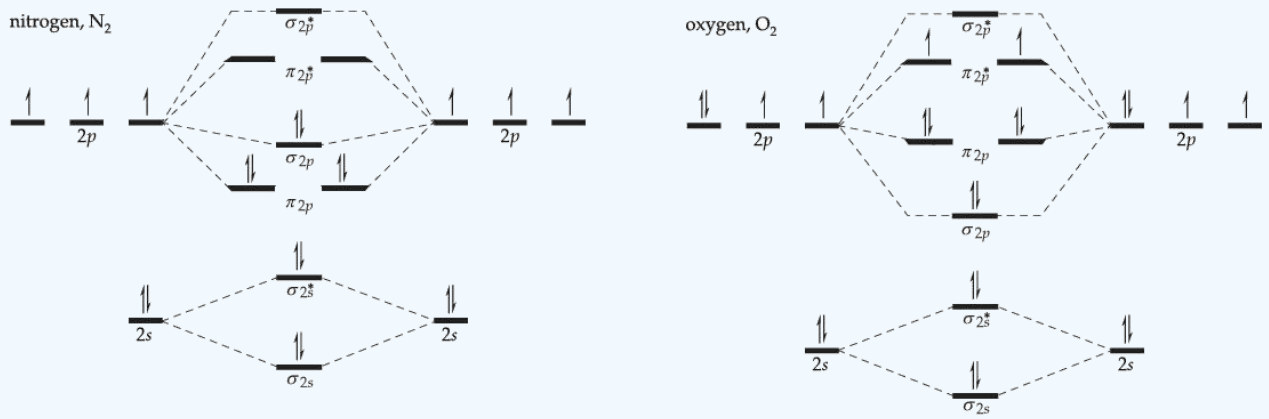
In the higher-energy anti-bonding Ψ_2* orbital, the shaded lobe of one $2p_z$ orbital interacts destructively with the unshaded lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy Ψ_1 orbital when the molecule is in the ground state.

✔ EXAMPLE 1.11.1

Draw a simple molecular orbital diagram for each of the following molecules

a. nitrogen, N_2.
b. oxygen, O_2.

Solution



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1.12: DRAWING CHEMICAL STRUCTURES

OBJECTIVES

After completing this section, you should be able to

1. propose one or more acceptable Kekulé structures (structural formulas) for any given molecular formula
2. write the molecular formula of a compound, given its Kekulé structure.
3. draw the shorthand structure of a compound, given its Kekulé structure.
4. interpret shorthand structures and convert them to Kekulé structures.
5. write the molecular formula of a compound, given its shorthand structure.

STUDY NOTES

When drawing the structure of a neutral organic compound, you will find it helpful to remember that

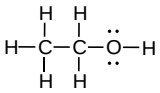
- each carbon atom has four bonds.
- each nitrogen atom has three bonds.
- each oxygen atom has two bonds.
- each hydrogen atom has one bond.

Through general chemistry, you may have already experienced looking at molecular structures using Lewis structures. Because organic chemistry can involve large molecules it would be beneficial if Lewis structures could be abbreviated. The three different ways to draw organic molecules include **Kekulé Formulas**, **Condensed Formulas**, and **Skeletal structures** (also called line-bond structures or line formulas). During this course, you will view molecules written in all three forms. It will be more helpful if you become comfortable going from one style of drawing to another, and look at drawings and understanding what they represent. Developing the ability to convert between different types of formulas requires practice, and in most cases the aid of molecular models. Many kinds of model kits are available to students and professional chemists, and the beginning student is encouraged to obtain one.

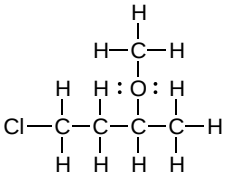
Simplification of structural formulas may be achieved without any loss of the information they convey. Kekule formulas is just organic chemistry's term for Lewis structures you have previously encountered. In **condensed structural formulas**, the bonds to each carbon are omitted, but each distinct structural unit (group) is written with subscript numbers designating multiple substituents, including the hydrogens. **Line formulas** omit the symbols for carbon and hydrogen entirely (unless the hydrogen is bonded to an atom other than carbon). Each straight line segment represents a bond, the ends and intersections of the lines are carbon atoms, and the correct number of hydrogens is calculated from the tetravalency of carbon. Non-bonding valence shell electrons are omitted in these formulas.

KEKULÉ (A.K.A. LEWIS STRUCTURES)

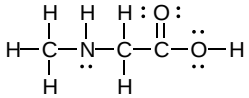
A Kekulé Formula or structural formula displays the atoms of the molecule in the order they are bonded. It also depicts how the atoms are bonded to one another, for example single, double, and triple covalent bond. Covalent bonds are shown using lines. The number of dashes indicate whether the bond is a single, double, or triple covalent bond. All atom labels are shown and all lone pairs are shown.



A



B



C

CONDENSED FORMULA

A condensed formula is made up of the elemental symbols. Condensed structural formulas show the order of atoms like a structural formula but are written in a single line to save space and make it more convenient and faster to write out. The order of the atoms suggests the connectivity in the molecule. Condensed structural formulas are also helpful when showing that a group of atoms is connected to a single atom in a compound. When this happens, parenthesis are used around the group of atoms to show they are together. Also, if more than one of the same substituent is attached to a given atom, it is show with a subscript number. An example is CH_4, which represents four hydrogens

attached to the same carbon. Condensed formulas can be read from either direction and H_3C is the same as CH_3, although the latter is more common.

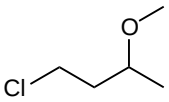
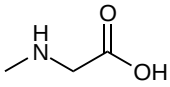
Look at the examples below and match them with their identical molecule under the Kekulé structures and the line formulas.

CH_3CH_2OH	$ClCH_2CH_2CH(OCH_3)CH_3$	CH_3NHCH_2COOH
A	**B**	**C**

Let's look closely at example B. As you go through a condensed formula, you want to focus on the carbons and other elements that aren't hydrogen. The hydrogen's are important, but are usually there to complete octets. Also, notice the $-OCH_3$ is in written in parentheses which tell you that it not part of the main chain of carbons. As you read through a a condensed formula, if you reach an atom that doesn't have a complete octet by the time you reach the next hydrogen, then it's possible that there are double or triple bonds. In example C, the carbon is double bonded to oxygen and single bonded to another oxygen. Notice how COOH means C(=O)-O-H instead of CH_3-C-O-O-H because carbon does not have a complete octet and oxygens.

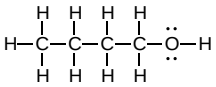
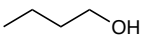
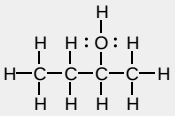
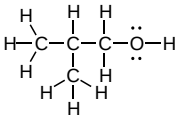
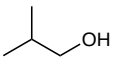
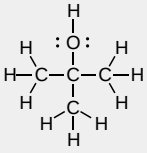
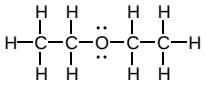
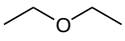
LINE FORMULA

Because organic compounds can be complex at times, line-angle formulas are used to write carbon and hydrogen atoms more efficiently by replacing the letter "C" with lines. A carbon atom is present wherever a line intersects another line. Hydrogen atoms are omitted but are assumed to be present to complete each of carbon's four bonds. Hydrogens that are attached to elements other than carbon are shown. Atom labels for all other elements are shown. Lone pair electrons are usually omitted. They are assumed to be present to complete the octet of non-carbon atoms. Line formulas help show the structure and order of the atoms in a compound.

		
A	**B**	**C**

These molecules correspond to the exact same molecules depicted for Kekulé structures and condensed formulas. Notice how the carbons are no longer drawn in and are replaced by the ends and bends of a lines. In addition, the hydrogens have been omitted, but could be easily drawn in (see practice problems). Although we do not usually draw in the H's that are bonded to carbon, we do draw them in if they are connected to other atoms besides carbon (example is the OH group above in example A) . This is done because it is not always clear if the non-carbon atom is surrounded by lone pairs or hydrogens. Also in example A, notice how the OH is drawn with a bond to the second carbon, but it does not mean that there is a third carbon at the end of that bond/ line.

Table **1.12.1**: Structural Formulas for $C_4H_{10}O$ isomers

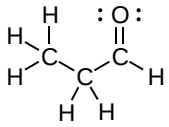
Kekulé Formula	Condensed Formula	Line Formula
	$CH_3(CH_2)_3OH$	
	$CH_3CH_2CH(OH)CH_3$	
	$(CH_3)_2CHCH_2OH$	
	$(CH_3)_3COH$	
	$CH_3CH_2OCH_2CH_3$	

EXAMPLE: CONVERTING BETWEEN STRUCTURAL FORMULAS

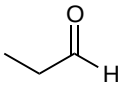
It is helpful to convert compounds into different structural formulas (Kekule, Line, and Condensed) depending on the type of question that is asked. Standardized exams frequently include a high percentage of condensed formulas because it is easier and cheaper to type letters and numbers than to import figures. Initially, it can be difficult writing a Line structure directly from a condensed formula. First, write the Kekule structure from the condensed formula and then draw the Line structure from the Kekule.

a) The condensed formula for propanal is CH_3CH_2CHO. Draw the Kekule structure.

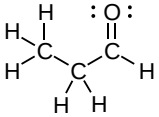
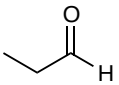
The Kekule structure for propanal is shown below. Remember that every carbon will have four bonds and oxygens octet is filled with lone pairs.



The bond-line structure for propanal is shown below. First, remove hydrogens. The hydrogen attached to the aldehyde group remains because it is part of a functional group. The remove the "C" labels from the structure and keep the lines in place. Lastly, remove any lone pairs.



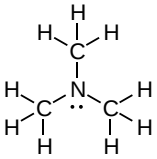
All three structures represent the same compound, propanal.

CH_3CH_2CHO =  = 

b) The following is the line structure of the molecule trimethyl amine.



To convert it to a Kekule structure first identify the carbons in the molecule. The will be at the corners and ends of line without an atom label. Trimethyl amine has three carbons. Next, add hydrogens to the carbons until four bonds are present. Each carbon in trimethyl amine is singly bonded to nitrogen. This means each carbon will need three additional C-H bonds to create its octet. Lastly, add lone pairs to other elements to fill their octets. The nitrogen in trimethyl amine is bonded to three carbons. This means it will require one of lone pair electrons to complete its octet.



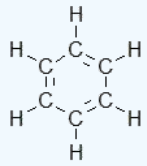
? EXERCISE 1.12.1

How many carbons are in the following drawing? How many hydrogens?



Answer

Remember the octet rule and how many times carbons and hydrogens are able to bond to other atoms.

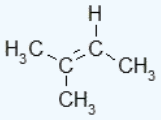


EXERCISE 1.12.2

How many carbons are in the following drawing? How many hydrogens?

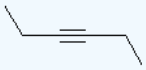


Answer

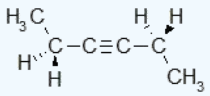


EXERCISE 1.12.3

How many carbons are in the following drawing? How many hydrogens?

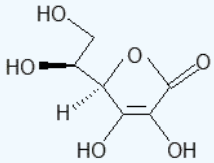


Answer



EXERCISE 1.12.4

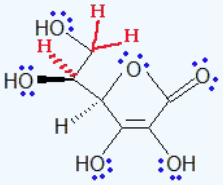
Look at the following molecule of vitamin A and draw in the hidden hydrogens and electron pairs.



Hint: Do all of the carbons have 4 bonds? Do all the oxygens have a full octet?

Answer

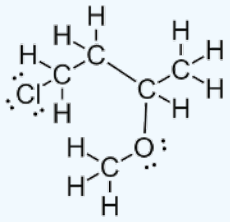
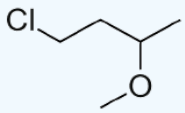
Electron pairs drawn in blue and hydrogens draw in red.



EXERCISE 1.12.5

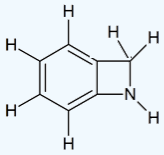
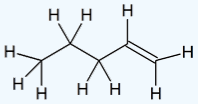
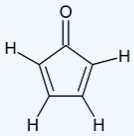
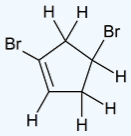
Draw $ClCH_2CH_2CH(OCH_3)CH_3$ in Kekulé and line form.

Answer


and


EXERCISE 1.12.6

Write down the molecular formula for each of the compounds shown here.

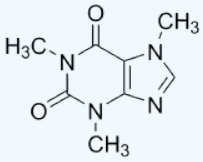

A

B

C

D

Answer

a. C_7H_7N
b. C_5H_{10}
c. C_5H_4O
d. $C_5H_6Br_2$

EXERCISE 1.12.7

Below is the molecule for caffeine. Give the molecular formula for it.



Answer

$C_8H_{10}O_2N_4$

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1.S: STRUCTURE AND BONDING (SUMMARY)

CONCEPTS & VOCABULARY

1.0: Prelude to Structure and Bonding

- Organic compounds contain carbon atoms bonded hydrogen and other carbon atoms.
- Organic chemistry studies the properties and reactions of organic compounds.

1.1: Atomic Structure: The Nucleus

- Atoms are comprised of **protons**, **neutrons** and **electrons**. Protons and neutrons are found in the nucleus of the atom, while electrons are found in the electron cloud around the nucleus. The relative electrical charge of a proton is +1, a neutron has no charge, and an electron's relative charge is -1.
- The number of protons in an atom's nucleus is called the **atomic number, *Z***.
- The **mass number, *A***, is the sum of the number of protons and the number of neutrons in a nucleus.
- The type of element an atom represents is defined by the atomic number, *Z* in the atom. All atoms of one specific element have the same number of protons (Z).
- Atoms that have the same atomic number (Z), but different mass numbers (A) are called **isotopes**.

1.2: Atomic Structure: Orbitals

- An **atomic orbital** is the probability description of where an electron can be found. The four basic types of orbitals are designated as ***s***, ***p***, ***d***, and ***f***.

1.3: Atomic Structure: Electron Configurations

- The order in which electrons are placed in atomic orbitals is called the **electron configuration** and is governed by the ***aufbau* principle**.
- Electrons in the outermost shell of an atom are called **valence electrons**. The number of valence electrons in any atom is related to its position in the periodic table. Elements in the same periodic group have the same number of valence electrons.

1.4: Development of Chemical Bonding Theory

- **Lewis Dot Symbols** are a way of indicating the number of valence electrons in an atom. They are useful for predicting the number and types of covalent bonds within organic molecules.
- The **molecular shape** of molecules is predicted by Valence Shell Electron Pair Repulsion (VSEPR) theory. The shapes of common organic molecules are based on **tetrahedral**, **trigonal planar** or **linear** arrangements of electron groups.

1.5: The Nature of Chemical Bonds: Valence Bond Theory

- **Covalent bonds** form as valence electrons are shared between two atoms.
- **Lewis Structures** and **structural formulas** are common ways of showing the covalent bonding in organic molecules.
- **Formal charge** describes the changes in the number of valence electrons as an atom becomes bonded into a molecule. If the atom has a net loss of valence electrons it will have a positive formal charge. If the atom has a net gain of valence electrons it will have a negative formal charge.
- Atomic orbitals often change as they overlap to form molecular orbitals. This process is known as **orbital hybridization**. The common types of hybrid orbitals in organic molecules are ***sp*^{3}**, ***sp*^{2}**, and ***sp***.

1.6: *sp*^{3} Hybrid Orbitals and the Structure of Methane

- The four identical C-H single bonds in CH_4 form as the result of sigma bond overlap between the sp^3 hybrid orbitals of carbon and the *s* orbital of each hydrogen.

1.7: *sp*^{3} Hybrid Orbitals and the Structure of Ethane

- The C-C bond in C_2H_6 forms as the result of sigma bond overlap between a sp^3 hybrid orbital on each carbon. and the *s* orbital of each hydrogen. The six identical C-H single bonds in form as the result of sigma bond overlap between the sp^3 hybrid orbitals of carbon and the *s* orbital of each hydrogen.

1.8: *sp*^{2} Hybrid Orbitals and the Structure of Ethylene

- The C=C bond in C_2H_4 forms as the result of both a sigma bond overlap between a sp^2 hybrid orbital on each carbon and a pi bond overlap of a *p* orbital on each carbon

1.9 *sp* Hybrid Orbitals and the Structure of Acetylene

- The carbon-carbon triple bond in C_2H_4 forms as the result of one sigma bond overlap between a *sp* hybrid orbital on each carbon and two pi bond overlaps of *p* orbitals on each carbon.

1.10: Hybridization of Nitrogen, Oxygen, Phosphorus and Sulfur

- The atomic orbitals of nitrogen, oxygen, phosphorus and sulfur can hybridize in the same way as those of carbon.

1.11: The Nature of Chemical Bonds: Molecular Orbital Theory

- **Molecular Orbital theory (MO)** is a more advanced bonding model than Valence Bond Theory, in which two atomic orbitals overlap to form *two* molecular orbitals – a bonding MO and an anti-bonding MO.

1.12: Drawing Chemical Structures

- **Kekulé Formulas** or **structural formulas** display the atoms of the molecule in the order they are bonded.
- **Condensed structural formulas** show the order of atoms like a structural formula but are written in a single line to save space.
- **Skeleton formulas** or **Shorthand formulas** or **line-angle formulas** are used to write carbon and hydrogen atoms more efficiently by replacing the letters with lines.
- **Isomers** have the same molecular formula, but different structural formulas

SUMMARY PROBLEMS

? EXERCISE 1.*S*.1

The following molecule is highly reactive and contains a functional group called a ketene. For each numbered atom, list the geometry, bond angle, hybridization, orbitals present, and orbital function. Notes: Ignore the geometry and bond angle for atom #1. For orbitals present, list all of the orbitals at that atom. For orbital function, describe what each orbital is doing (e.g., participating in a sigma bond, containing lone pair electrons, etc.).



Answer

#1 - sp^2 hybridization; 3 sp^2 orbitals and 1 p orbital present; p orbital participates in a pi bond, 1 sp^2 orbital participates in a sigma bond, 2 sp^2 orbitals contain lone pair electrons

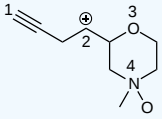
#2 - linear; 180 degrees; sp hybridization; 2 sp orbitals and 2 p orbitals present; p orbitals participate in two pi bonds, s sp^2 orbitals participate in two sigma bonds

#3 - trigonal planar; 120 degrees; sp^2 hybridization; 3 sp^2 orbitals and 1 p orbital present; p orbital participates in a pi bond, 3 sp^2 orbitals participate in three sigma bonds

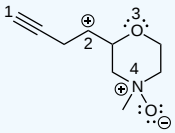
#4 - tetrahedral; 109.5 degrees; sp^3 hybridization; 4 sp^3 orbitals present; 4 sp^3 orbitals participate in four sigma bonds

? EXERCISE 1.*S*.2

First, add lone pair electrons and formal charges to the molecule shown below; its net charge is plus one. (The only formal charge on a carbon atom has already been added for you.) Second, for each numbered atom, list the geometry, bond angle, hybridization, orbitals present, and orbital function. Notes: For orbitals present, list all of the orbitals at that atom. For orbital function, describe what each orbital is doing (e.g., participating in a sigma bond, containing lone pair electrons, etc.).



Answer



#1 - linear; 180 degrees; sp hybridization; 2 sp orbitals and 2 p orbitals present; p orbitals participate in two pi bonds, s sp^2 orbitals participate in two sigma bonds

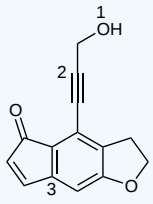
#2 - trigonal planar; 120 degrees; sp^2 hybridization; 3 sp^2 orbitals and 1 p orbital present; p orbital is empty, 3 sp^2 orbitals participate in three sigma bonds

#3 - bent; <109.5 degrees; sp^3 hybridization; 4 sp^3 orbitals present; 2 sp^3 orbitals participate in two sigma bonds, 2 sp^3 orbitals contain two lone pairs

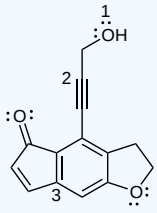
#4 - tetrahedral; 109.5 degrees; sp^3 hybridization; 4 sp^3 orbitals present; 4 sp^3 orbitals participate in four sigma bonds

? EXERCISE 1.S.3

First, add lone pair electrons and formal charges to the molecule shown below. Second, for each numbered atom, list the geometry, bond angle, hybridization, orbitals present, and orbital function. Third, clearly identify on the structure below sigma bonds formed by overlap of the following orbitals: sp-sp^2 (label as "a"), sp-sp^3 (label as "b"), sp^2-sp^2 (label as "c"), sp^2-sp^3 (label as "d"), and sp^3-sp^3 (label as "e"). Notes: For orbitals present, list all of the orbitals at that atom. For orbital function, describe what each orbital is doing (e.g., participating in a sigma bond, containing lone pair electrons, etc.). When identifying particular types of sigma bonds, there will be more than one correct answer for some options.



Answer

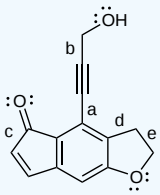


All atoms are neutral in this molecule.

#1 - bent; <109.5 degrees; sp^3 hybridization; 4 sp^3 orbitals present; 2 sp^3 orbitals participate in two sigma bonds, 2 sp^3 orbitals contain two lone pairs

#2 - linear; 180 degrees; sp hybridization; 2 sp orbitals and 2 p orbitals present; p orbitals participate in two pi bonds, s sp^2 orbitals participate in two sigma bonds

#3 - trigonal planar; 120 degrees; sp^2 hybridization; 3 sp^2 orbitals and 1 p orbital present; p orbital participates in a pi bond, 3 sp^2 orbitals participate in three sigma bonds



For a and b, these are the only bonds that are correct. For c, there are several correct options. For d, there is one other option (from the benzene ring to the O in the five-membered ring. For e, there are several correct options.

SKILLS TO MASTER

Skill 1.1 Determine the number of protons, neutrons, and electrons in a nuclide.

Skill 1.2 Write the electron configuration and orbital diagram for an atom.

Skill 1.3 Determine the number of valence electrons in an atom.

Skill 1.4 Draw the molecular formula, Lewis Dot Structure, structural formula, condensed structural formula, shorthand formula and wedge-dash structure of simple organic molecules.

Skill 1.5 Use Lewis Dot structures to predict molecular shape, bond angle, hybridization.

Skill 1.6 Calculate formal charge on an atom in a molecule.

Skill 1.7 Determine the number of sigma and pi bonds in organic molecules.

Skill 1.8 Determine relative bond energy and bond length based on atoms involved in the bond and bond type.

Skill 1.9 Describe and draw the orbital overlap and types of bonding in simple organic molecules like methane, ethane, ethylene and acetylene.

Skill 1.10 Describe the bonding in organic molecules using both the Valence Bond Theory and Molecular Orbital Theory.

MEMORIZATION TASKS (MT)

MT 1.1 Memorize the number of valence electrons in the atoms - C, H, N, O, and the halides.

MT 1.2 Memorize the number of bonds and lone pairs to atoms of carbon, hydrogen, oxygen and nitrogen that result in formal charges of zero.

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CHAPTER OVERVIEW

2: POLAR COVALENT BONDS; ACIDS AND BASES

CHAPTER OBJECTIVES

This chapter provides a review of the more advanced material covered in a standard introductory chemistry course through a discussion of the following topics:

- the use of electronegativity to determine bond polarity, and the application of this knowledge to determine whether a given molecule possesses a dipole moment.
- the drawing and interpretation of organic chemical structures.
- the concept and determination of formal charge.
- resonance and drawing of resonance forms
- the Brønsted-Lowry and Lewis definitions of acids and bases, acidity constants and acid-base reactions.
- intermolecular forces

2.0: Polar Covalent Bonds - Electronegativity
2.1: Polar Covalent Bonds - Dipole Moments
2.2: Formal Charges
2.3: Resonance
2.4: Rules for Resonance Forms
2.5: Drawing Resonance Forms
2.6: Acids and Bases - The Brønsted-Lowry Definition
2.7: Acid and Base Strength
2.8: Predicting Acid-Base Reactions from pKa Values
2.9: Organic Acids and Organic Bases
2.10: Acids and Bases - The Lewis Definition
2.11: Noncovalent Interactions Between Molecules
2.MM: Molecular Models
2.S: Polar Covalent Bonds; Acids and Bases (Summary)

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2.0: POLAR COVALENT BONDS - ELECTRONEGATIVITY

OBJECTIVES

After completing this section, you should be able to

- describe how differences in electronegativity give rise to bond polarity.
- arrange a given series of the elements most often encountered in organic chemistry (C, H, O, N, S, P and the halogens) in order of increasing or decreasing electronegativity, without referring to a table of electronegativities.
- predict the partial positive and partial negative ends of a given bond formed between any two of the elements listed in Objective 2, above, without the use of a table of electronegativities or a periodic table.
- predict the partial positive and partial negative ends of a given bond formed between any two elements not listed in Objective 2, above, using a periodic table.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electronegativity inductive effect
- polar covalent bond

STUDY NOTES

Students often wonder why it is important to be able to tell whether a given bond is polar or not, and why they need to know which atoms carry a partial positive charge and which a partial negative charge. Consider the chloromethane (CH_3Cl) molecule. The carbon atom is shown as carrying a partial positive charge. Now, recall that opposite charges attract. Thus, it seems reasonable that the slightly positive carbon atom in chloromethane should be susceptible to attack by a negatively charged species, such as the hydroxide ion, OH^-. This theory is borne out in practice: hydroxide ions react with chloromethane by attacking the slightly positive carbon atom in the latter. It is often possible to rationalize chemical reactions in this manner, and you will find the knowledge of bond polarity indispensable when you start to write reaction mechanisms.

Note: Because of the small difference in electronegativity between carbon and hydrogen, the **C-H** bond is normally assumed to be nonpolar.

ELECTRONEGATIVITY

Because the tendency of an element to gain or lose electrons is so important in determining its chemistry, various methods have been developed to quantitatively describe this tendency. The most important method uses a measurement called **electronegativity** (represented by the Greek letter *chi*, χ, pronounced “ky” as in “sky”), which is defined as the *relative* ability of an atom to attract electrons to itself *in a chemical compound*. Elements with high electronegativities tend to acquire electrons in chemical reactions and are found in the upper right corner of the periodic table. Elements with low electronegativities tend to lose electrons in chemical reactions and are found in the lower left corner of the periodic table.

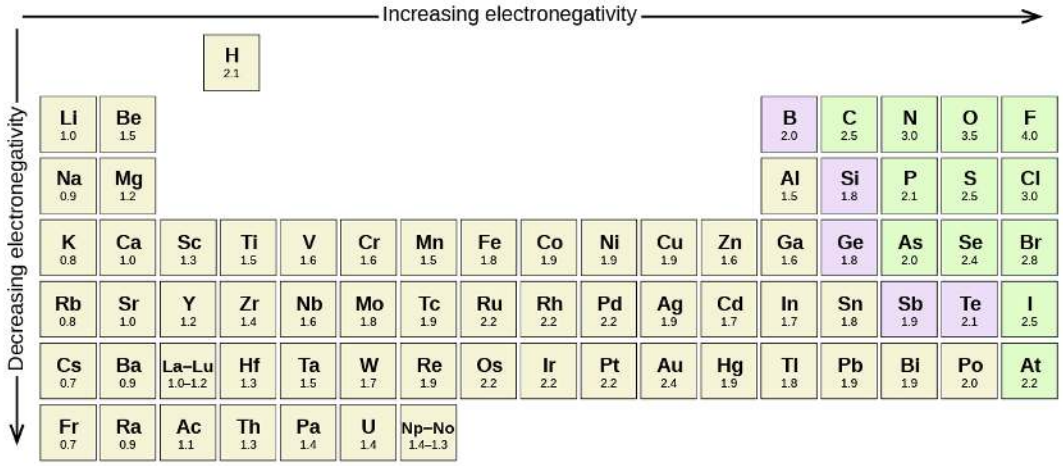


Figure **2.0.1**: Pauling scale electronegativities of elements

Electronegativity of an atom is not a simple, fixed property that can be directly measured in a single experiment. In fact, an atom's electronegativity should depend to some extent on its chemical environment because the properties of an atom are influenced by the neighboring atoms in a chemical compound. Nevertheless, when different methods for measuring the electronegativity of an atom are compared, they all tend to assign similar relative values to a given element. ***Figure* 2.0.1** shows the electronegativity values of the elements as proposed by one of the most famous chemists of the twentieth century: Linus Pauling. In this scale a value of 4.0 is arbitrarily given to the most electronegative element, fluorine, and the other electronegativities are scaled relative to this value. In general, electronegativity increases from left to right across a period in the periodic table and decreases down a group. Thus, the nonmetals, which lie in the upper right, tend to have the highest electronegativities, with fluorine the most electronegative element of all (EN = 4.0 as previously noted). It is important to notice that the elements most important to organic chemistry, carbon, nitrogen, and oxygen have some of the highest electronegativites in the periodic table (EN = 2.5, 3.0, 3.5 respectively). Metals, on the left, tend to be less electronegative elements, with cesium having the lowest (EN = 0.7). Note that noble gases are excluded from this figure because these atoms usually do not share electrons with others atoms since they have a full valence shell.

> Electronegativity is defined as the ability of an atom in a particular molecule to attract electrons to itself. The **larger** the electronegativity value, the **greater** the attraction.

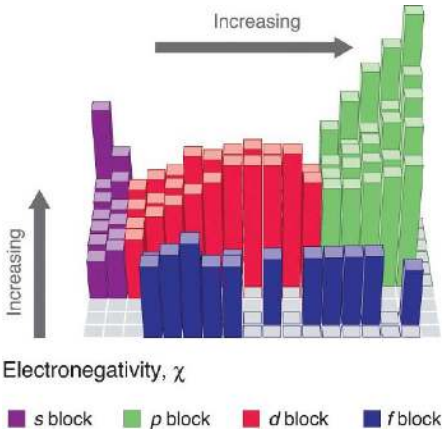


Figure **2.0.2**: Visual representation of electronegativities. (CC BY-SA-NC; Anonyumous via LibreTexts)

ELECTRONEGATIVITY AND BOND TYPE

The two idealized extremes of chemical bonding: (1) **ionic bonding**—in which one or more electrons are transferred completely from one atom to another, and the resulting ions are held together by purely electrostatic forces—and (2) **covalent bonding**, in which electrons are shared equally between two atoms. Most compounds, however, have **polar covalent bonds**, which means that electrons are shared unequally between the bonded atoms. Electronegativity determines how the shared electrons are distributed between the two atoms in a polar covalent bond. The more strongly an atom attracts the electrons in its bonds, the larger its electronegativity. Electrons in a polar covalent bond are shifted toward the more electronegative atom; thus, the more electronegative atom is the one with the partial negative

charge. The greater the difference in electronegativity, the more polarized the electron distribution and the larger the partial charges of the atoms. Recall that a lowercase Greek delta (δ) is used to indicate that a bonded atom possesses a partial positive charge, indicated by δ^+ , or a partial negative charge, indicated by δ^- , and a bond between two atoms that possess partial charges is a polar bond.

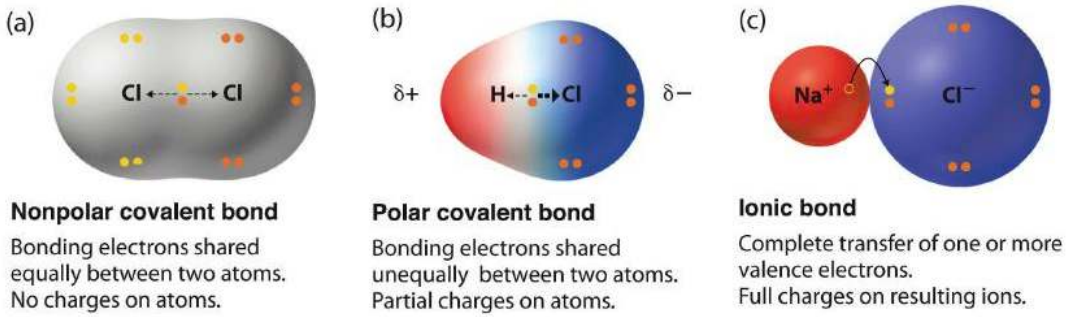
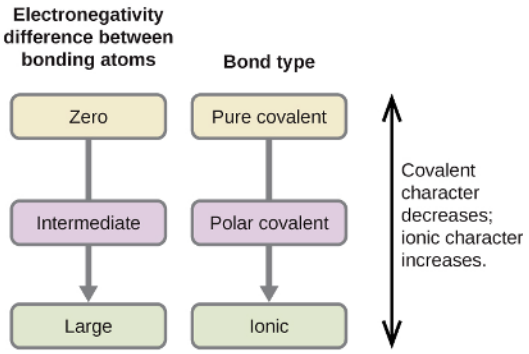


Figure **2.0.3**: The Electron Distribution in a Nonpolar Covalent Bond, a Polar Covalent Bond, and an Ionic Bond Using Lewis Electron Structures. Electron-rich (negatively charged) regions are shown in blue; electron-poor (positively charged) regions are shown in red. (CC BY-SA-NC; Anonymous via LibreTexts)

Whether a bond is **ionic**, **nonpolar covalent**, or **polar covalent** can be estimated by by calculating the absolute value of the difference in electronegativity (ΔEN) of two bonded atoms. When the difference is very small or zero, the bond is covalent and nonpolar. When it is large, the bond is polar covalent or ionic. The absolute values of the electronegativity differences between the atoms in the bonds H–H, H–Cl, and Na–Cl are 0 (nonpolar), 0.9 (polar covalent), and 2.1 (ionic), respectively. The degree to which electrons are shared between atoms varies from completely equal (pure covalent bonding) to not at all (ionic bonding). Figure 7.2.4 shows the relationship between electronegativity difference and bond type. This table is just a general guide, however, with many exceptions. The best guide to the covalent or ionic character of a bond is to consider the types of atoms involved and their relative positions in the periodic table. Bonds between two nonmetals are generally covalent; bonding between a metal and a nonmetal is often ionic.



Bond Type	Electronegativity Difference
pure covalent	< 0.4
polar covalent	between 0.4 and 1.8
ionic	> 1.8

Figure **2.0.4**: As the electronegativity difference increases between two atoms, the bond becomes more ionic. (CC BY 4.0; OpenStax)

Some compounds contain both covalent and ionic bonds. The atoms in polyatomic ions, such as OH^-, NO_3^-, and NH_4^+, are held together by polar covalent bonds. However, these polyatomic ions form ionic compounds by combining with ions of opposite charge. For example, potassium nitrate, KNO_3, contains the K^+ cation and the polyatomic NO_3^- anion. Thus, bonding in potassium nitrate is ionic, resulting from the electrostatic attraction between the ions K^+ and NO_3^-, as well as covalent between the nitrogen and oxygen atoms in NO_3^-.

✔ EXAMPLE 2.0.1

Bond polarities play an important role in determining the structure of proteins. Using the electronegativity values in Table A2, arrange the following covalent bonds—all commonly found in amino acids—in order of increasing polarity. Then designate the positive and negative atoms using the symbols δ+ and δ–:

C–H, C–N, C–O, N–H, O–H, S–H

Solution

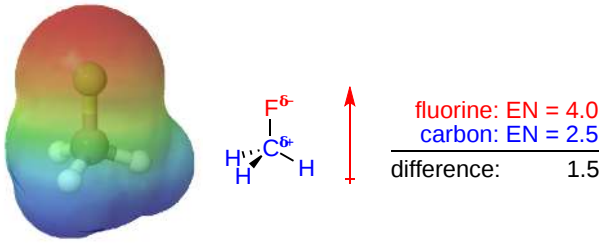
The polarity of these bonds increases as the absolute value of the electronegativity difference increases. The atom with the δ– designation is the more electronegative of the two. Table **2.0.1** shows these bonds in order of increasing polarity.

Table **2.0.1**: Bond Polarity and Electronegativity Difference

Bond	ΔEN	Polarity
C–H	0.4	$\overset{\delta-}{C}-\overset{\delta+}{H}$
S–H	0.4	$\overset{\delta-}{S}-\overset{\delta+}{H}$
C–N	0.5	$\overset{\delta+}{C}-\overset{\delta-}{N}$
N–H	0.9	$\overset{\delta-}{N}-\overset{\delta+}{H}$
C–O	1.0	$\overset{\delta+}{C}-\overset{\delta-}{O}$
O–H	1.4	$\overset{\delta-}{O}-\overset{\delta+}{H}$

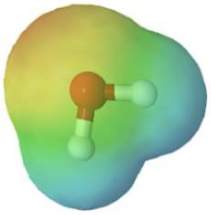
VISUALIZING BONDING

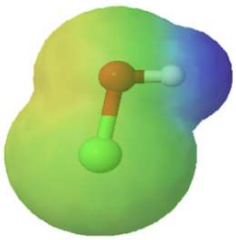
Calculated charge distributions in molecules can easily be visualized by using electrostatic potential maps. The color red is used to indicate electron-rich regions of a molecule while the color blue is used to indicated electron-poor regions. An easier method for visually representing electron displacement in a molecule uses a crossed arrow. By convention the arrow point in the direction of the electron-rich region of a molecule and away from the electron-poor. An example is shown in the molecule fluoromethane. The C-F bond is polarized drawing the bonding electrons toward the more electronegative fluorine giving it a partial negative charge. Consequently, the bonding electrons are drawn away from the less electronegative carbon giving it a partial positive charge. The the electron-rich fluorine is shown as red in the electrostatic potential map and while the electron-poor carbon is shown as blue. The crossed arrow points in the direction of the electron-rich fluorine.



Electrostatic Potential Map and Dipole Moment of Fluoromethane

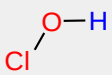
Chemists often use the term, **inductive effect**, to describe the shifting of electrons in a sigma by the electronegativity of atoms. Relatively electronegative atoms, such as fluorine, tend to inductively draw electrons towards themselves and away from nearby atoms. The inductive effect will be used to explain chemical reactivity in many situations in organic chemistry. An excellent example of the inductive effect is seen when comparing the O-H bond polarities of water (H_2O) and hypochlorous acid (ClOH). Replacing the less electronegative hydrogen (EN = 2.1) in water with the more electronegative chlorine (EN = 3.0) in hypochlorous acid creates a greater bond polarity. The chlorine draws electrons away giving the hydrogen a greater partial positive charge. This is shown in the electrostatic potential map as an increase in the blue color around hydrogen.







water

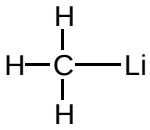


hypochlorous acid

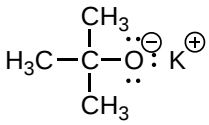
A "SPECTRUM" OF BONDS

There is no clear-cut division between covalent and ionic bonds. In a pure non-polar covalent bond, the electrons are held on average exactly half way between the atoms. In a polar bond, the electrons have been dragged slightly towards one end. How far does this dragging

have to go before the bond counts as ionic? There is no real answer to that. Sodium chloride is typically considered an ionic solid, but even here the sodium has not completely lost control of its electron. Because of the properties of sodium chloride, however, we tend to count it as if it were purely ionic. Lithium iodide, on the other hand, would be described as being "ionic with some covalent character". In this case, the pair of electrons has not moved entirely over to the iodine end of the bond. Lithium iodide, for example, dissolves in organic solvents like ethanol - not something which ionic substances normally do. Many bonds between metals and non-metal atoms, are considered ionic, however some of these bonds cannot be simply identified as one type of bond. Examples of this are the lithium - carbon bond in methyllithium which is usually considered as polar covalent (somewhat between covalent and ionic) and the potassium - oxygen bond in potassium *tert*-butoxide which is considered more ionic than covalent.



methyllithium



potassium *tert*-butoxide

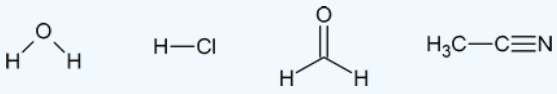
SUMMARY

Covalent bonds form when electrons are shared between atoms and are attracted by the nuclei of both atoms. In pure covalent bonds, the electrons are shared equally. In polar covalent bonds, the electrons are shared unequally, as one atom exerts a stronger force of attraction on the electrons than the other. The ability of an atom to attract a pair of electrons in a chemical bond is called its electronegativity. The difference in electronegativity between two atoms determines how polar a bond will be. In a diatomic molecule with two identical atoms, there is no difference in electronegativity, so the bond is nonpolar or pure covalent. When the electronegativity difference is very large, as is the case between metals and nonmetals, the bonding is characterized as ionic.

- No electronegativity difference between two atoms leads to a non-polar covalent bond.
- A small electronegativity difference leads to a polar covalent bond.
- A large electronegativity difference leads to an ionic bond.

? EXERCISE 2.0.1

Identify the positive and negative ends of each of the bonds shown below.



? EXERCISE 2.0.2

Which of the following elements is the more electronegative?

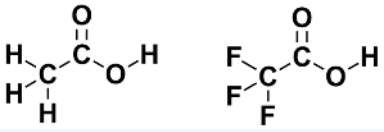
a. Br or C
b. C or H
c. Cl or I
d. C or Li

Answer

a. Br
b. C
c. Cl
d. C

? EXERCISE 2.0.3

Which of the following molecules would you expect to have the more polarized O-H bond?

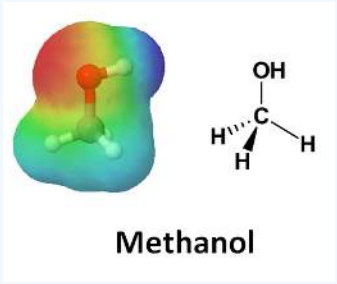


Answer

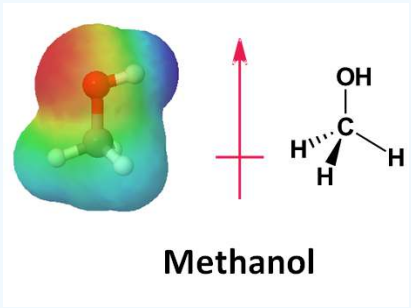
The molecule on the right would have the more polarized O-H bond. The presence of the highly electronegative fluorines would draw electrons away by the inductive effect.

EXERCISE 2.0.4

Predict the direction of polarizing C-O bond in methanol by looking at its electrostatic potential map.



Answer



EXERCISE 2.0.5

Rank the following from least polar to most polar using knowledge of electronegativity

CH_3CH_2-Li CH_3CH_2-K CH_3CH_2-F CH_3CH_2-OH

Answer

(least polar) OH < F < Li < K (most polar)

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2.1: POLAR COVALENT BONDS - DIPOLE MOMENTS

LEARNING OBJECTIVES

After completing this section, you should be able to

- explain how dipole moments depend on both molecular shape and bond polarity.
- predict whether a molecule will possess a dipole moment from the molecular formula or structure.
- use the presence or absence of a dipole moment as an aid to deducing the structure of a given compound.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- dipole moment

STUDY NOTES

You must be able to combine your knowledge of molecular shapes and bond polarities to determine whether or not a given compound will have a dipole moment. Conversely, the presence or absence of a dipole moment may also give an important clue to a compound's structure. BCl_3, for example, has no dipole moment, while NH_3 does. This suggests that in BCl_3 the chlorines around boron are in a trigonal planar arrangement, while the hydrogens around nitrogen in NH_3 have a less symmetrical arrangement - trigonal pyramidal.

Remember that the C-H bond is assumed to be non-polar.

MOLECULAR DIPOLE MOMENTS

In molecules containing more than one polar bond, the molecular dipole moment is just the vector combination of what can be regarded as individual "**bond dipole moments**". Mathematically, dipole moments are *vectors*; they possess both a *magnitude* and a *direction*. The dipole moment of a molecule is therefore the *vector sum* of the dipole moments of the individual bonds in the molecule. If the individual bond dipole moments cancel one another, there is no net dipole moment. Such is the case for CO_2, a linear molecule (Figure **2.1.1*a***). Each C–O bond in CO_2 is polar, yet experiments show that the CO_2 molecule has no dipole moment. Because the two C–O bond dipoles in CO_2 are equal in magnitude and oriented at 180° to each other, they cancel. As a result, the CO_2 molecule has no *net* dipole moment even though it has a substantial separation of charge. In contrast, the H_2O molecule is not linear (Figure **2.1.1*b***); it is bent in three-dimensional space, so the dipole moments do not cancel each other. Thus a molecule such as H_2O has a net dipole moment. We expect the concentration of negative charge to be on the oxygen, the more electronegative atom, and positive charge on the two hydrogens. This charge polarization allows H_2O to hydrogen-bond to other polarized or charged species, including other water molecules.

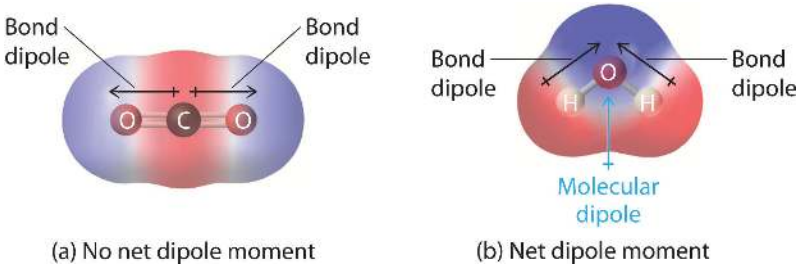


Figure **2.1.1**: How Individual Bond Dipole Moments Are Added Together to Give an Overall Molecular Dipole Moment for Two Triatomic Molecules with Different Structures. (a) In CO_2, the C–O bond dipoles are equal in magnitude but oriented in opposite directions (at 180°). Their vector sum is zero, so CO_2 therefore has no net dipole. (b) In H_2O, the O–H bond dipoles are also equal in magnitude, but they are oriented at 104.5° to each other. Hence the vector sum is not zero, and H_2O has a net dipole moment. (CC BY-SA-NC 3.0; anonymous)

The following is a simplified equation for a simple separated two-charge system that is present in diatomic molecules or when considering a bond dipole within a molecule.

$$\mu_{diatomic} = Q \times r \tag{2.1.1}$$

This bond dipole, μ (Greek mu) is interpreted as the dipole from a charge separation over a distance r between the partial charges Q^+ and Q^- (or the more commonly used terms δ^+ - δ^-); the orientation of the dipole is along the axis of the bond. The units on dipole moments are typically debyes (D) where one debye is equal to 3.336 x 10^{30} coulomb meters (C · m) in SI units. Consider a simple system of a single

electron and proton separated by a fix distance. The unit charge on an electron is 1.60 X 1019 C and the proton & electron are 100 pm apart (about the length of a typical covalent bond), the dipole moment is calculated as:

$$\begin{aligned} \mu &= Qr \\ &= (1.60 \times 10^{-19}\, C)(1.00 \times 10^{-10}\, m) \\ &= 1.60 \times 10^{-29}\, C \cdot m \end{aligned} \tag{2.1.2}$$

$$\begin{aligned} \mu &= (1.60 \times 10^{-29}\, C \cdot m)\left(\frac{1\ D}{3.336 \times 10^{-30}\, C \cdot m}\right) \\ &= 4.80\ D \end{aligned} \tag{2.1.3}$$

4.80 D is a key reference value and represents a pure charge of +1 and -1 separated by 100 pm. However, if the charge separation were increased then the dipole moment increases (linearly):

- If the proton and electron were separated by 120 pm:

$$\mu = \frac{120}{100}(4.80\ D) = 5.76\, D$$

- If the proton and electron were separated by 150 pm:

$$\mu = \frac{150}{100}(4.80\ D) = 7.20\, D$$

- If the proton and electron were separated by 200 pm:

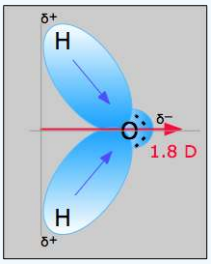
$$\mu = \frac{200}{100}(4.80\ D) = 9.60\, D$$

EXAMPLE 2.1.1: WATER

The water molecule in Figure 2.1.1 can be used to determine the direction and magnitude of the dipole moment. From the electronegativities of oxygen and hydrogen, the difference is 1.2e for each of the hydrogen-oxygen bonds. Next, because the oxygen is the more electronegative atom, it exerts a greater pull on the shared electrons; it also has two lone pairs of electrons. From this, it can be concluded that the dipole moment points from between the two hydrogen atoms toward the oxygen atom. Using the equation above, the dipole moment is calculated to be 1.85 D by multiplying the distance between the oxygen and hydrogen atoms by the charge difference between them and then finding the components of each that point in the direction of the net dipole moment (the angle of the molecule is 104.5˚).

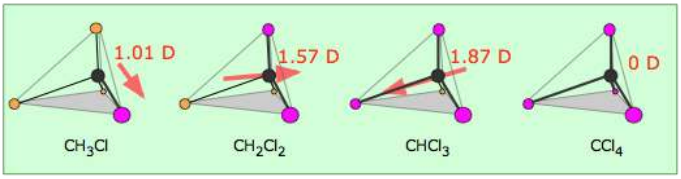
The bond moment of O-H bond =1.5 D, so the net dipole moment is

$$\mu = 2(1.5)\cos\left(\frac{104.5^\circ}{2}\right) = 1.84\ D$$



DIPOLES WITH DIFFERING ATOMS

In more complex molecules with more than one polar covalent bonds, the three-dimensional geometry and the compound's symmetry determine whether the molecule has a net dipole moment. The manner in which the individual bonds contribute to the dipole moment of the molecule is nicely illustrated by the series of chloromethanes shown below. The electronegative chlorine draws electrons towards itself.



Consider CCl_4, (left panel in figure below), which as a molecule is not polar - in the sense that it doesn't have an end (or a side) which is slightly negative and one which is slightly positive. The whole of the outside of the molecule is somewhat negative, but there is no overall separation of charge from top to bottom, or from left to right. In contrast, $CHCl_3$ is a polar molecule (right panel in figure above). However, although a molecule like $CHCl_3$ has a tetrahedral geometry, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments do not cancel one another, and the result is a molecule which has a dipole moment. The hydrogen at the top of the molecule is less electronegative than carbon and so is slightly positive. This means that the molecule now has a slightly positive "top" and a slightly negative "bottom", and so is overall a polar molecule.

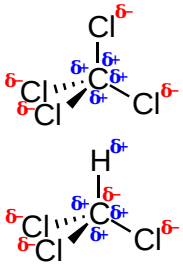


Figure **2.1.3**: Bond polarities for CCl_4 (left) and $CHCl_3$(right)

Electron densities in a molecule (and the dipole moments that unbalanced electron distributions can produce) are easily visualized with electrostatic potential maps. In this example, $CHCl_3$, the blue area centered on carbon represents a electron-deficient positive area, of the molecule, the red area centered on the chlorine, represents a electron-abundant negative area. This charge separation creates a net dipole moment of 1.87 D which points in the direction of the chlorine. In, CCl_4 the evenly spaced red areas represent that there is no separation of charge in the molecule. CCl_4 has a net dipole moment of zero which makes it a nonpolar molecule.

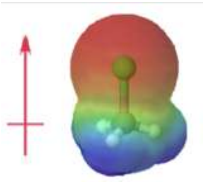
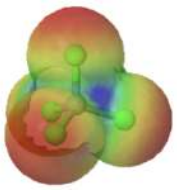
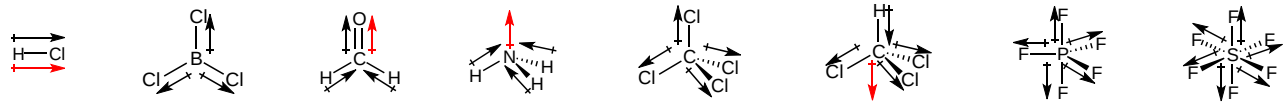
	
chloromethane	tetrachloromethane
(μ = 1.87 D)	(μ = 0 D)

***Figure* 2.1.4:** Electrostatic potential maps and dipole moments for chloromethane and tetrachloromethane (carbon tetrachloride).

Molecules with asymmetrical charge distributions have a net dipole moment

Other examples of molecules with polar bonds are shown in Figure **2.1.2**. In molecules like BCl_3 and CCl_4, that have only one type of bond and a molecular geometries that are highly symmetrical (trigonal planar and tetrahedral), the individual bond dipole moments completely cancel, and there is no net dipole moment. However, although a molecule like $CHCl_3$ has a tetrahedral geometry, the atoms bonded to carbon are not identical. Consequently, the bond dipole moments do not cancel one another, and the result is a molecule which has a dipole moment.



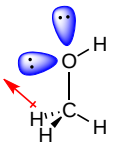
net dipole	no net dipole	net dipole	net dipole	no net dipole	net dipole	no net dipole	no net dipole
HCl	BCl_3	CH_2O	NH_3	CCl_4	$CHCl_3$	PF_5	SF_6

***Figure* 2.1.5**: *Molecules with Polar Bonds. Individual bond dipole moments are indicated in black. Due to their different three-dimensional structures, some molecules with polar bonds have a net dipole moment (HCl, CH_2O, NH_3, and $CHCl_3$), indicated in red, whereas others do not because the bond dipole moments cancel (BCl_3, CCl_4, PF_5, and SF_6).*

Table **2.1.1**: Dipole Moments of Some Compounds

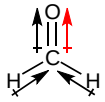
Compound	Dipole Moment (Debyes)
NaCl	9.0 (measured in the gas phase)
CH_2O	2.33
CH_3Cl	1.87
H_2O	1.85
CH_3OH	1.70
NH_3	1.47
CH_3NH_2	1.31
CO_2	0
CCl_4	0
CH_4	0
CH_3CH_3	0

The table above give the dipole moment of some common substances. Sodium chloride has the largest dipole listed (9.00 D) because it is an ionic compounds. Even small organic compounds such as formaldehyde (CH_2O, 2.33 D) and methanol (CH_3OH, 1.70 D) have significant dipole moments. Both of these molecules contain the strongly electronegative oxygen atom lone pair electrons which gives rise to considerable dipole moments.



methanol

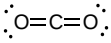
(μ = 1.70 D)



formaldehyde

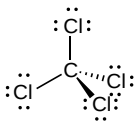
(μ = 2.33 D)

In contrast many organic molecule have a zero dipole moment despite the fact that they are made up of polar covalent bonds. In, structures with highly symmetrical molecular geometries, the polar bonds and the lone pair electrons can can exactly cancel leaving no overall charge separation.



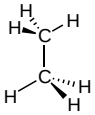
carbon dioxide

(μ = 0 D)



carbon tetrachloride

(μ = 0 D)

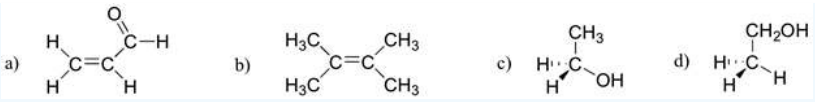


ethane

(μ = 0 D)

? EXERCISE 2.1.1

Which of the molecules below have molecular dipole moments?



Answer

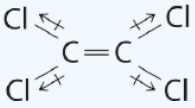
Only molecule (b) does *not* have a molecular dipole, due to its symmetry (bond dipoles are equal and in opposite directions). Add texts here.

EXERCISE 2.1.2

Draw out the line structure of the molecule with a molecular formula of C_2Cl_4. Indicate all of the individual bond polarities and predict if the molecule is polar or nonpolar.

Answer

Although the C–Cl bonds are rather polar, the individual bond dipoles cancel one another in this symmetrical structure, and \(\ce{Cl2C=CCl2}\) moment.



EXERCISE 2.1.3

The following molecule has no net dipole moment, explain.

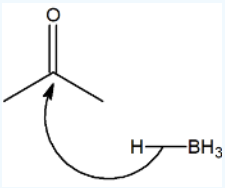


Answer

The hydroxyl groups are oriented opposite of one another and therefore the dipole moments would “cancel” one another out. Therefore having a zero net-dipole.

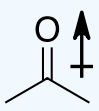
EXERCISE 2.1.4

Within reactions with carbonyls, such as a hydride reduction reaction, the carbonyl is attacked from the carbon side and not the oxygen side. Using knowledge of electronegativity explain why this happens.



Answer

The oxygen is more electronegative than the carbon and therefore creates a dipole along the bond. This leads to having a partial positive charge on the carbon and the reduction can take place.



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EXERCISE 2.1.1

Which molecule(s) has a net dipole moment?

a. H_2S
b. NHF_2
c. BF_3

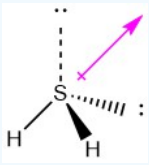
Answer

Strategy:

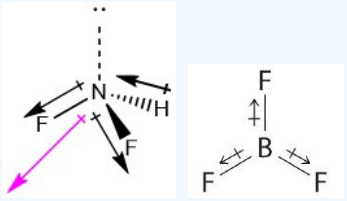
For each three-dimensional molecular geometry, predict whether the bond dipoles cancel. If they do not, then the molecule has a net dipole moment.

Solution:

The total number of electrons around the central atom, S, is eight, which gives four electron pairs. Two of these electron pairs are bonding pairs and two are lone pairs, so the molecular geometry of H_2S is bent. The bond dipoles cannot cancel one another, so the molecule has a net dipole moment.



Difluoroamine has a trigonal pyramidal molecular geometry. Because there is one hydrogen and two fluorines, and because of the lone pair of electrons on nitrogen, the molecule is not symmetrical, and the bond dipoles of NHF_2 cannot cancel one another. This means that NHF_2 has a net dipole moment. We expect polarization from the two fluorine atoms, the most electronegative atoms in the periodic table, to have a greater affect on the net dipole moment than polarization from the lone pair of electrons on nitrogen.

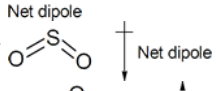


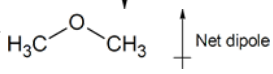
The molecular geometry of BF_3 is trigonal planar. Because all the B–F bonds are equal and the molecule is highly symmetrical, the dipoles cancel one another in three-dimensional space. Thus BF_3 has a net dipole moment of zero:

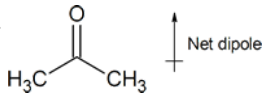
ADDITIONAL EXERCISES

1. Determine whether each of the compounds listed below possesses a dipole moment. For the polar compounds, indicate the direction of the dipole moment.
   a. O=C=O
   b. *ICl*
   c. SO_2
   d. $CH_3–O–CH_3$
   e. $CH_3C(=O)CH_3$

Answers:

1. a. CO_2 nonpolar
   b. I—Cl
   
   Net dipole
   c. 

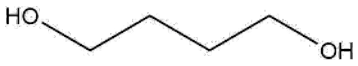
   d. 

e. 

QUESTIONS

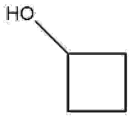
Q2.2.1

The following molecule has no dipole moment in the molecule itself, explain.

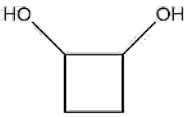


Q2.2.2

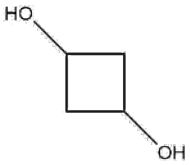
Which of the following molecules has a net dipole?



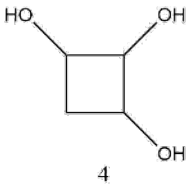
1



3



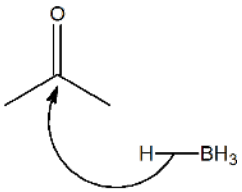
2



4

Q2.2.3

Within reactions with carbonyls, such as a reduction reaction, the carbonyl is attacked from the carbon side and not the oxygen side. Using knowledge of electronegativity explain why this happens.



SOLUTIONS

S2.2.1

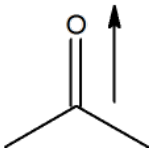
The hydroxyl groups are oriented opposite of one another and therefore the dipole moments would “cancel” one another out. Therefore having a zero net-dipole.

S2.2.2

1, 3, and 4 have a net dipoles.

S2.2.3

The oxygen is more electronegative than the carbon and therefore creates a dipole along the bond. This leads to having a partial positive charge on the carbon and the reduction can take place.



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2.2: FORMAL CHARGES

OBJECTIVES

After completing this section, you should be able to

- calculate the formal charge of an atom in an organic molecule or ion.
- identify and recognize the bonding patterns for atoms of carbon, hydrogen, oxygen, nitrogen and the halogens that have a formal charge of zero.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- valence electrons
- bonding and non-bonding electrons
- formal charge
- carbocations

STUDY NOTES

It is more important that students learn to easily identify atoms that have formal charges of zero, than it is to actually calculate the formal charge of every atom in an organic compound. Students will benefit by memorizing the "normal" number of bonds and non-bonding electrons around atoms whose formal charge is equal to zero.

DETERMINING THE FORMAL CHARGE ON AN ATOM

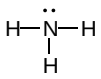
A **formal charge** (FC) compares the number of electrons around a "neutral atom" (an atom not in a molecule) versus the number of electrons around an atom in a molecule. Formal charge is assigned to an atom in a molecule by assuming that electrons in all chemical bonds are shared equally between atoms, regardless of relative electronegativity. To calculate formal charges, we assign electrons in the molecule to individual atoms according to these rules:

- Non-bonding electrons are assigned to the atom on which they are located.
- Bonding electrons are divided equally between the two bonded atoms, so one electron from each bond goes to each atom.

The formal charge of each atom in a molecule can be calculated using the following equation:

Misplaced '#'

To illustrate this method, let's calculate the formal charge on the atoms in ammonia ($\mathbf{NH_3}$) whose Lewis structure is as follows:



A neutral nitrogen atom has five valence electrons (it is in group 15). From the Lewis structure, the nitrogen atom in ammonia has one lone pair and three bonds with hydrogen atoms. Substituting into Equation ???, we obtain

$$\begin{aligned} FC(N) &= (\text{5 valence electrons}) - (\text{2 lone pair electrons}) - \frac{1}{2}(\text{6 bonding electrons}) \\ &= 0 \end{aligned}$$

A neutral hydrogen atom has one valence electron. Each hydrogen atom in the molecule has no non-bonding electrons and one bond. Using Equation ??? to calculate the formal charge on hydrogen, we obtain

$$\begin{aligned} FC(H) &= (\text{1 valence electrons}) - (\text{0 lone pair electrons}) - \frac{1}{2}(\text{2 bonding electrons}) \\ &= 0 \end{aligned}$$

The sum of the formal charges of each atom must be equal to the overall charge of the molecule or ion. In this example, the nitrogen and each hydrogen has a formal charge of zero. When summed the overall charge is zero, which is consistent with the overall neutral charge of the $\mathbf{NH_3}$ molecule.

Typically, the structure with the most formal charges of zero on atoms is the more stable Lewis structure. In cases where there MUST be positive or negative formal charges on various atoms, the most stable structures generally have negative formal charges on the more electronegative atoms and positive formal charges on the less electronegative atoms. The next example further demonstrates how to calculate formal charges for polyatomic ions.

✔ EXAMPLE 2.2.1

Calculate the formal charges on each atom in the $\mathbf{NH_4^+}$ ion.

Given: chemical species

Asked for: formal charges

Strategy:

Identify the number of valence electrons in each atom in the $\mathbf{NH_4^+}$ ion. Use the Lewis electron structure of $\mathbf{NH_4^+}$ to identify the number of bonding and non-bonding electrons associated with each atom and then use Equation ??? to calculate the formal charge on each atom.

Solution:

The Lewis electron structure for the $\mathbf{NH_4^+}$ ion is as follows:



The nitrogen atom in ammonium has zero non-bonding electrons and 4 bonds. Using Equation ???, the formal charge on the nitrogen atom is therefore

$$FC(N) = (5 \text{ valence electrons}) - (0 \text{ lone pair electrons}) - \frac{1}{2}(8 \text{ bonding electrons})$$
$$= +1$$

Each hydrogen atom in has one bond and zero non-bonding electrons. The formal charge on each hydrogen atom is therefore

$$FC(H) = (1 \text{ valence electrons}) - (0 \text{ lone pair electrons}) - \frac{1}{2}(2 \text{ bonding electrons})$$
$$= 0$$

The formal charges on the atoms in the $\mathbf{NH_4^+}$ ion are thus

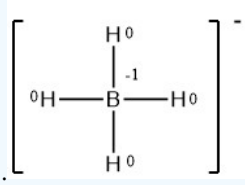


Adding together the formal charges on the atoms should give us the total charge on the molecule or ion. In this case, the sum of the formal charges is 0 + 1 + 0 + 0 + 0 = 1+, which is the same as the total charge of the ammonium polyatomic ion.

? EXERCISE 2.2.1

Write the formal charges on all atoms in $\mathbf{BH_4^-}$.

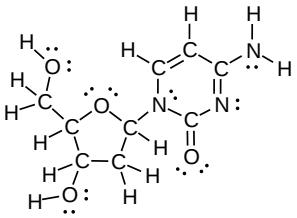
Answer



DETERMINING THE CHARGE OF ATOMS IN ORGANIC STRUCTURES

The calculation method reviewed above for determining formal charges on atoms is an essential starting point for a novice organic chemist, and works well when dealing with small structures. But this method becomes unreasonably time-consuming when dealing with larger structures. It would be exceptionally tedious to determine the formal charges on each atom in 2'-deoxycytidine (one of the four nucleoside

building blocks that make up DNA) using Equation ???. As you get more experience with organic structures, you will be able to quickly look at this type of complicated structure and determine charges on each atom.



2'-deoxycytidine

You need to develop the ability to quickly and efficiently draw large structures and determine formal charges. Fortunately, this only requires some practice with recognizing common bonding patterns.

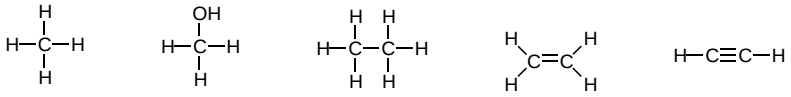
Organic chemistry only deals with a small part of the periodic table, so much so that it becomes convenient to be able to recognize the bonding forms of these atoms. The figure below contains the most important bonding forms. These will be discussed in detail below. An important idea to note is most atoms in a molecule are neutral. Pay close attention to the neutral forms of the elements below because that is how they will appear most of the time.

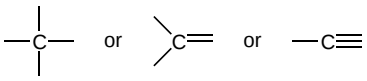
Figure **2.2.1**: Structures of common organic atoms and ions.

Atom	Positive	Neutral	Negative
C			
N			
O			
Cl (halogens)			

CARBON

Carbon, the most important element for organic chemists. In the structures of methane, methanol, ethane, ethene, and ethyne, there are four bonds to the carbon atom. And each carbon atom has a formal charge of zero. In other words, carbon is ***tetravalent***, meaning that it commonly forms four bonds.





Carbon usually makes four bonds

Carbon is tetravalent in most organic molecules, but there are exceptions. Later in this chapter and throughout this book are examples of organic ions called ‘carbocations’ and carbanions’, in which a carbon atom has a positive or negative formal charge, respectively. ***Carbocations*** occur when a carbon has only three bonds and no lone pairs of electrons. Carbocations have only 3 valence electrons and a formal charge of 1+. ***Carbanions*** occur when the carbon atom has three bonds plus one lone pair of electrons. Carbanions have 5 valence electrons and a formal charge of 1−.

		
carbocation: 3 bonds & no lone pair	carbanion: 3 bonds & one lone pair	carbon radical: 3 bonds & one unpaired electron

Two other possibilities are carbon radicals and carbenes, both of which have a formal charge of zero. A ***carbon radical*** has three bonds and a single, unpaired electron. Carbon radicals have 4 valence electrons and a formal charge of zero. ***Carbenes*** are a highly reactive species, in

which a carbon atom has two bonds and one lone pair of electrons, giving it a formal charge of zero. Though carbenes are rare, you will encounter them in section 8.10 Addition of Carbenes to Alkenes.

You should certainly use the methods you have learned to check that these formal charges are correct for the examples given above. More importantly, you will need, before you progress much further in your study of organic chemistry, to simply recognize these patterns (and the patterns described below for other atoms) and be able to identify carbons that bear positive and negative formal charges by a quick inspection.

HYDROGEN

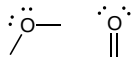
The common bonding pattern for hydrogen is easy: hydrogen atoms in organic molecules typically have only one bond, no unpaired electrons and a formal charge of zero. The exceptions to this rule are the proton, H^+, the hydride ion, H^-, and the hydrogen radical, $H\cdot$. The ***proton*** is a hydrogen with no bonds and no lone pairs and a formal charge of 1+. The ***hydride ion*** is a is a hydrogen with no bonds, a pair of electrons, and a formal charge of 1−. The ***hydrogen radical*** is a hydrogen atom with no bonds, a single unpaired electron and a formal charge of 0. Because this book concentrates on organic chemistry as applied to living things, however, we will not be seeing 'naked' protons and hydrides as such, because they are too reactive to be present in that form in aqueous solution. Nonetheless, the *idea* of a proton will be very important when we discuss acid-base chemistry, and the *idea* of a hydride ion will become very important much later in the book when we discuss organic oxidation and reduction reactions. As a rule, though, all hydrogen atoms in organic molecules have one bond, and no formal charge.



Neutral Hydrogen: one bond, no lone pair

OXYGEN

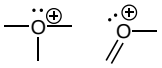
The common arrangement of oxygen that has a formal charge of zero is when the oxygen atom has 2 bonds and 2 lone pairs. Other arrangements are oxygen with 1 bond and 3 lone pairs, that has a 1− formal charge, and oxygen with 3 bonds and 1 lone pair that has a formal charge of 1+. All three patterns of oxygen fulfill the octet rule.



neutral oxygen: 2 bonds & 2 lone pairs



negative oxygen: 1 bond & 3 lone pairs



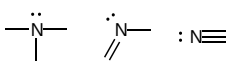
positive oxygen: 3 bonds & one lone pair

If it has two bonds and two lone pairs, as in water, it will have a formal charge of zero. If it has one bond and three lone pairs, as in hydroxide ion, it will have a formal charge of 1−. If it has three bonds and one lone pair, as in hydronium ion, it will have a formal charge of 1+.

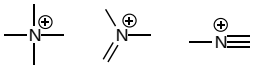
Oxygen can also exist as a radical, such as where an oxygen atom has one bond, two lone pairs, and one unpaired (free radical) electron, giving it a formal charge of zero. For now, however, concentrate on the three main non-radical examples, as these will account for most oxygen containing molecules you will encounter in organic chemistry.

NITROGEN

Nitrogen has two major bonding patterns, both of which fulfill the octet rule:



neutral nitrogen: 3 bonds & 1 lone pair



positive nitrogen: 4 bonds

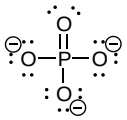


negative nitrogen: 2 bonds & 2 lone pairs

If a nitrogen has three bonds and a lone pair, it has a formal charge of zero. If it has four bonds (and no lone pair), it has a formal charge of 1+. In a fairly uncommon bonding pattern, negatively charged nitrogen has two bonds and two lone pairs.

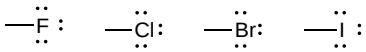
PHOSPHORUS AND SULFUR

Two third row elements are commonly found in biological organic molecules: phosphorus and sulfur. Although both of these elements have other bonding patterns that are relevant in laboratory chemistry, in a biological context sulfur almost always follows the same bonding/formal charge pattern as oxygen, while phosphorus is present in the form of phosphate ion (PO_4^{3-}), where it has five bonds (almost always to oxygen), no lone pairs, and a formal charge of zero. Remember that elements in the third row of the periodic table have *d* orbitals in their valence shell as well as *s* and *p* orbitals, and thus are not bound by the octet rule.



HALOGENS

The halogens (fluorine, chlorine, bromine, and iodine) are very important in laboratory and medicinal organic chemistry, but less common in naturally occurring organic molecules. Halogens in organic compounds usually are seen with one bond, three lone pairs, and a formal charge of zero. Sometimes, especially in the case of bromine, we will encounter reactive species in which the halogen has two bonds (usually in a three-membered ring), two lone pairs, and a formal charge of 1+.



Common Neutral Bonding Patterns for Halogens



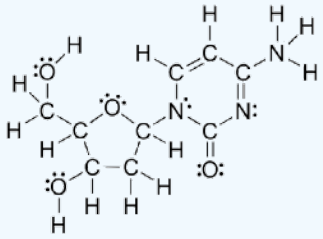
Common Positive Bonding Pattern for Halogens

These rules, if learned and internalized so that you don't even need to think about them, will allow you to draw large organic structures, complete with formal charges, quite quickly.

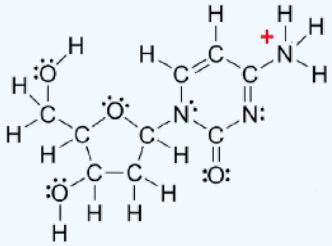
Once you have gotten the hang of drawing Lewis structures, it is not always necessary to draw lone pairs on heteroatoms, as you can assume that the proper number of electrons are present around each atom to match the indicated formal charge (or lack thereof). Occasionally, though, lone pairs are drawn if doing so helps to make an explanation more clear.

? EXERCISE

Please identify an atom with a non-neutral charge in the following atom:

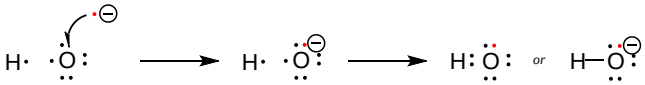


Answer

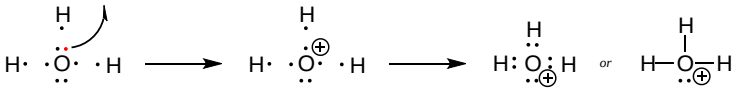


DRAWING THE LEWIS STRUCTURE OF IONIC MOLECULAR COMPOUNDS

The hydroxide ion, OH^-, is drawn simply by showing the oxygen atom with its six valence electrons, then adding one more electron to account for the negative charge. By changing the number of valence electrons the bonding characteristic of oxygen are now changed. Now the oxygen has three non-bonding lone pairs, and can only form one bond to a hydrogen.



To draw a Lewis structure of the hydronium ion, H_3O^+, you again start with the oxygen atom with its six valence electrons, then take one away to account for the positive charge to give oxygen five valence electrons. The oxygen has one non-bonding lone pair and three unpaired electrons which can be used to form bonds to three hydrogen atoms.



USING FORMAL CHARGES TO DISTINGUISH BETWEEN LEWIS STRUCTURES

As an example of how formal charges can be used to determine the most stable Lewis structure for a substance, we can compare two possible structures for CO_2. Both structures conform to the rules for Lewis electron structures.

EXAMPLE 2.2.1: CARBON DIOXIDE

What are the Lewis structures of CO_2 and which is the most stable?

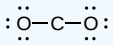
Solution

1. C is less electronegative than O, so it is the central atom.

2. C has 4 valence electrons and each O has 6 valence electrons, for a total of 16 valence electrons.

3. Placing one electron pair between the C and each O gives O–C–O, with 12 electrons left over.

4. Dividing the remaining electrons between the O atoms gives three lone pairs on each atom:



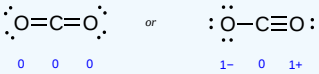
This structure has an octet of electrons around each O atom but only 4 electrons around the C atom.

5. No electrons are left for the central atom.

6. To give the carbon atom an octet of electrons, we can convert two of the lone pairs on the oxygen atoms to bonding electron pairs. There are, however, two ways to do this. We can either take one electron pair from each oxygen to form a symmetrical structure or take both electron pairs from a single oxygen atom to give an asymmetrical structure:



Both Lewis electron structures give all three atoms an octet. How do we decide between these two possibilities? The formal charges for the two Lewis electron structures of CO2 are as follows:



Both Lewis structures have a net formal charge of zero, but the structure on the right has a 1+ charge on the more electronegative atom (O). Thus the symmetrical Lewis structure on the left is predicted to be more stable, and it is, in fact, the structure observed experimentally. Remember, though, that formal charges do *not* represent the actual charges on atoms in a molecule or ion. They are used simply as a bookkeeping method for predicting the most stable Lewis structure for a compound.

NOTE

The Lewis structure with the set of formal charges closest to zero is usually the most stable.

EXAMPLE 2.2.2: THIOCYANATE ION

The thiocyanate ion (SCN^-), which is used in printing and as a corrosion inhibitor against acidic gases, has at least two possible Lewis electron structures. Draw two possible structures, assign formal charges on all atoms in both, and decide which is the preferred arrangement of electrons.

Given: chemical species

Asked for: Lewis electron structures, formal charges, and preferred arrangement

Strategy:

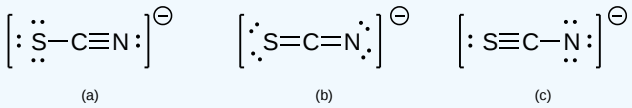
A Use the step-by-step procedure to write two plausible Lewis electron structures for SCN^-.

B Calculate the formal charge on each atom using Equation ???.

C Predict which structure is preferred based on the formal charge on each atom and its electronegativity relative to the other atoms present.

Solution:

A Possible Lewis structures for the SCN^- ion are as follows:



(a) (b) (c)

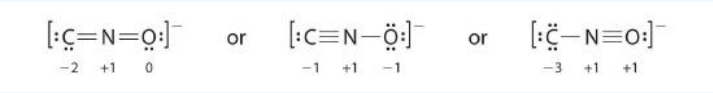
B We must calculate the formal charges on each atom to identify the more stable structure. If we begin with carbon, we notice that the carbon atom in each of these structures shares four bonding pairs, the number of bonds typical for carbon, so it has a formal charge of zero. Continuing with sulfur, we observe that in (a) the sulfur atom shares one bonding pair and has three lone pairs and has a total of six valence electrons. The formal charge on the sulfur atom is therefore 6 - (6 + 2/2) = 1−. In (b), the sulfur atom has a formal charge of 0. In (c), the sulfur atom has a formal charge of 1+. Continuing with the nitrogen, we observe that in (a) the nitrogen atom shares three bonding pairs and has one lone pair and has a total of 5 valence electrons. The formal charge on the nitrogen atom is therefore 5 - (2 + 6/2) = 0. In (b), the nitrogen atom has a formal charge of 1−. In (c), the nitrogen atom has a formal charge of 2−.

C Which structure is preferred? Structure (b) is preferred because the negative charge is on the more electronegative atom (N), and it has lower formal charges on each atom as compared to structure (c): 0, 1− versus 1+, 2−.

? EXERCISE 2.2.2: FULMINATE ION

Salts containing the fulminate ion (CNO^-) are used in explosive detonators. Draw three Lewis electron structures for CNO^- and use formal charges to predict which is more stable. (Note: **N** is the central atom.)

Answer



The second structure is predicted to be the most stable.

? EXERCISE 2.2.3

Draw the Lewis structure of each of these molecules: CH_3^+, NH_2^-, CH_3^-, NH_4^+, BF_4^-. In each case, use the method of calculating formal charge described to satisfy yourself that the structures you have drawn do in fact carry the charges shown

? EXERCISE 2.2.4

Give the formal charges for all non-hydrogen atoms in the following molecules: BH_4^-, H_2O, CH_3O^-

Answer

BH_4^- (B = −1)

H_2O (O = 0)

CH_3O^- (C = 0, O = −1)

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2.3: RESONANCE

OBJECTIVE

After completing this section, you should be able to

- draw resonance forms for molecules and ions.

KEY TERMS

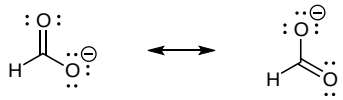
Make certain that you can define, and use in context, the key term below.

- resonance form
- delocalization

RESONANCE DELOCALIZATION

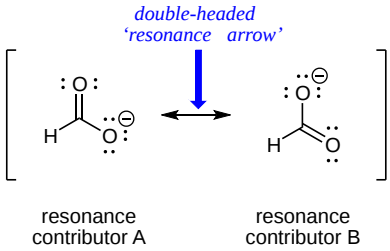
Sometimes, even when formal charges are considered, the bonding in some molecules or ions cannot be described by a single Lewis structure. **Resonance** is a way of describing **delocalized** electrons within certain molecules or polyatomic ions where the bonding cannot be expressed by a single Lewis formula. A molecule or ion with such delocalized electrons is represented by several contributing structures (also called resonance contributors or canonical forms). Resonance contributors involve the 'imaginary movement' of pi-bonded electrons or of lone-pair electrons that are adjacent to pi bonds. Note, sigma bonds cannot be broken during resonance – if you show a sigma bond forming or breaking, you are showing a chemical reaction taking place. Likewise, the positions of atoms in the molecule **cannot change** between resonance contributors.

When looking at the structure of the molecule, formate, we see that there are two equivalent structures possible. Which one is correct? There are two simple answers to this question: 'both' and 'neither one'. Both ways of drawing the molecule are equally acceptable approximations of the bonding picture for the molecule, but neither one, by itself, is an accurate picture of the delocalized pi bonds. The two alternative drawings, however, when considered together, give a much more accurate picture than either one on its own. This is because they imply, together, that the carbon-carbon bonds are not double bonds, not single bonds, but about halfway in between.

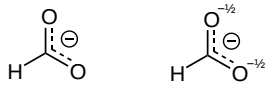


Formate Ion Structures are Equivalent in Energy

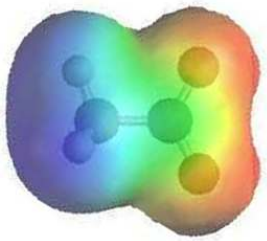
When it is possible to draw more than one valid structure for a compound or ion, we have identified **resonance contributors**: two or more different Lewis structures depicting the same molecule or ion that, when considered together, do a better job of approximating delocalized pi-bonding than any single structure. By convention, resonance contributors are linked by a double-headed arrow, and are sometimes enclosed by brackets:



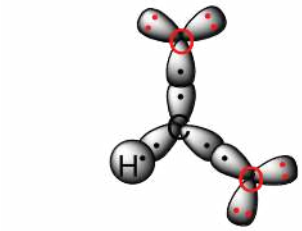
The depiction of formate using the two resonance contributors A and B in the figure above does *not* imply that the molecule at one moment looks like structure A, then at the next moment shifts to look like structure B. Rather, at all moments, the molecule is a combination, or **resonance hybrid** of both A and B. Each individual resonance contributor of the formate ion is drawn with one carbon-oxygen double bond (120 pm) and one carbon-oxygen single bond (135 pm), with a negative formal charge located on the single-bonded oxygen. However, the two carbon-oxygen bonds in formate are actually the same length (127 pm) which implies that neither resonance contributor is correct. Although there is an overall negative formal charge on the formate ion, it is shared equally between the two oxygens. Therefore, the formate ion can be more accurately depicted by a *pair* of resonance contributors. Alternatively, a single structure can be used, with a dashed line depicting the resonance-delocalized pi bond and the negative charge located in between the two oxygens.



The electrostatic potential map of formate shows that there is an equal amount of electron density (shown in red) around each oxygen.

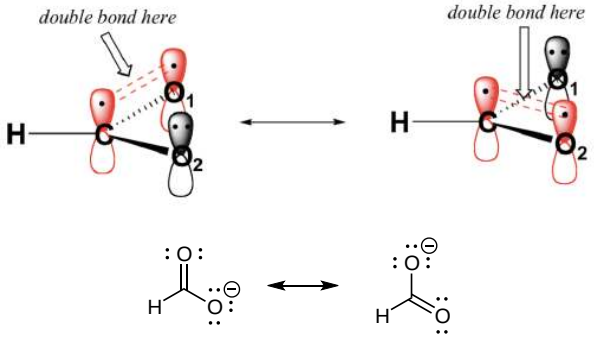


Valence bond theory can be used to develop a picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as well. Both carbon-oxygen sigma bonds, then, are formed from the overlap of carbon sp^2 orbitals and oxygen sp^2 orbitals.



the σ-bonding framework of formate

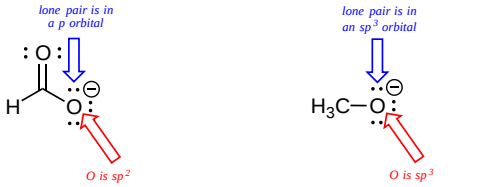
In addition, the carbon and both oxygens each have an un-hybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.



Overall, the situation is one of *three parallel, overlapping $2p_z$ orbitals sharing four delocalized pi electrons*. Because there is one more electron than there are $2p_z$ orbitals, the system has an overall charge of 1–. Resonance contributors are used to approximate overlapping $2p_z$ orbitals and delocalized pi electrons. Molecules with resonance are usually drawn showing only one resonance contributor for the sake of simplicity. However, identifying molecules with resonance is an important skill in organic chemistry.

This example shows an important exception to the general rules for determining the hybridization of an atom. The oxygen with the negative charge appears to be sp^3 hybridized because it is surrounded by four electron groups. However, this representation of the oxygen atom is not correct because it is actually part of a resonance hybrid. A pair of lone pair of electrons on the negatively charged oxygen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system. The stability gained though resonance is enough to cause the

expected sp^3 to become sp^2. The sp^2 hybridization gives the oxygen a p orbital allowing it to participate in conjugation. As a general rule sp^3 hybridized atoms with lone pair electrons tend to become sp^2 hybridized when adjacent to a conjugated system.



oxygen is *conjugated* oxygen is *not conjugated*

EXAMPLE: CARBONATE (CO_3^{2-})

Like formate, the electronic structure of the carbonate ion cannot be described by a single Lewis electron structure. Unlike O_3, though, the Lewis structures describing CO_3^{2-} has *three* equivalent representations.

1. Because carbon is the least electronegative element, we place it in the central position:

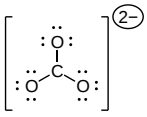


2. Carbon has 4 valence electrons, each oxygen has 6 valence electrons, and there are 2 more for the 2− charge. This gives 4 + (3 × 6) + 2 = 24 valence electrons.

3. Six electrons are used to form three bonding pairs between the oxygen atoms and the carbon:

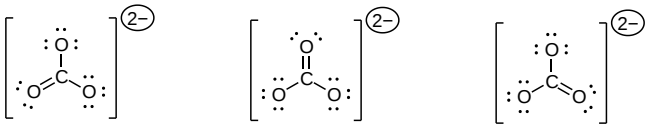


4. We divide the remaining 18 electrons equally among the three oxygen atoms by placing three lone pairs on each and indicating the 2− charge:

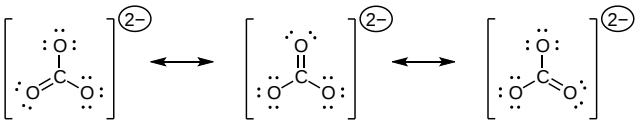


5. There are no electrons left for the central atom.

6. At this point, the carbon atom has only 6 valence electrons, so we must take one lone pair from an oxygen and use it to form a carbon–oxygen double bond. In this case, however, there are *three* possible choices:



As with formate, none of these structures describes the bonding exactly. Each predicts one carbon–oxygen double bond and two carbon–oxygen single bonds, but experimentally all C–O bond lengths are identical. We can write resonance structures (in this case, three of them) for the carbonate ion:



As the case for formate, the actual structure involves the formation of a molecular orbital from p_z orbitals centered on each atom and sitting above and below the plane of the CO_3^{2-} ion.

✔ EXAMPLE 2.4.1

Benzene is a common organic solvent that was previously used in gasoline; it is no longer used for this purpose, however, because it is now known to be a carcinogen. The benzene molecule (C_6H_6) consists of a regular hexagon of carbon atoms, each of which is also bonded to a hydrogen atom. Use resonance structures to describe the bonding in benzene.

Given: molecular formula and molecular geometry

Asked for: resonance structures

Strategy:

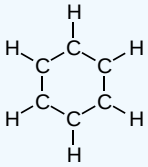
A Draw a structure for benzene illustrating the bonded atoms. Then calculate the number of valence electrons used in this drawing.

B Subtract this number from the total number of valence electrons in benzene and then locate the remaining electrons such that each atom in the structure reaches an octet.

C Draw the resonance structures for benzene.

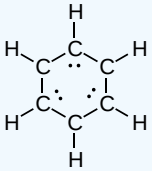
Solution:

A Each hydrogen atom contributes 1 valence electron, and each carbon atom contributes 4 valence electrons, for a total of (6 × 1) + (6 × 4) = 30 valence electrons. If we place a single bonding electron pair between each pair of carbon atoms and between each carbon and a hydrogen atom, we obtain the following:



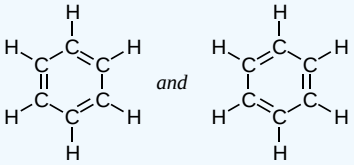
Each carbon atom in this structure has only 6 electrons and has a formal charge of 1+, but we have used only 24 of the 30 valence electrons.

B If the 6 remaining electrons are uniformly distributed pair-wise on alternate carbon atoms, we obtain the following:

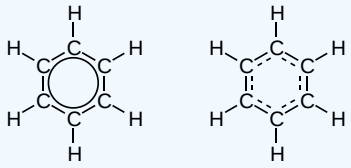


Three carbon atoms now have an octet configuration and a formal charge of 1−, while three carbon atoms have only 6 electrons and a formal charge of 1+. We can convert each lone pair to a bonding electron pair, which gives each atom an octet of electrons and a formal charge of 0, by making three C=C double bonds.

C There are, however, two ways to do this:

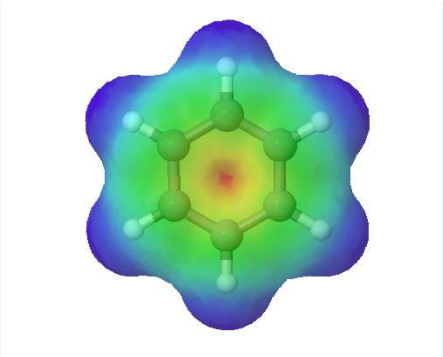


Each structure has alternating double and single bonds, but experimentation shows that each carbon–carbon bond in benzene is identical, with bond lengths (139.9 pm) intermediate between those typically found for a C–C single bond (154 pm) and a C=C double bond (134 pm). We can describe the bonding in benzene using the two resonance structures, but the actual electronic structure is an average of the two. The existence of multiple resonance structures for aromatic hydrocarbons like benzene is often indicated by drawing either a circle or dashed lines inside the hexagon:



benzene

This combination of *p* orbitals for benzene can be visualized as a ring with a node in the plane of the carbon atoms. As can be seen in an electrostatic potential map of benzene, the electrons are distributed symmetrically around the ring.



? EXERCISE 2.3.1

The sodium salt of nitrite is used to relieve muscle spasms. Draw two resonance structures for the nitrite ion (NO_2^-).

Answer

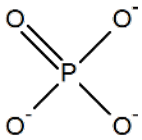


EXERCISES

QUESTIONS

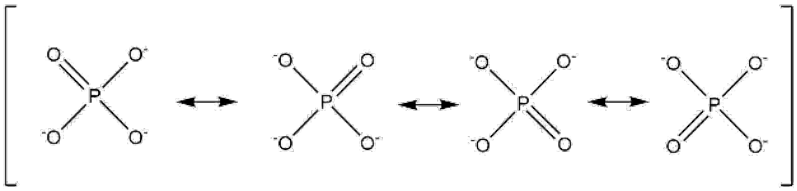
Q2.4.1

Draw the resonance structures for the following molecule:



SOLUTIONS

S2.4.1



EXTRA EXAMPLE - O_3

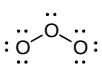
A molecule or ion with such delocalized electrons is represented by several contributing structures (also called resonance structures or canonical forms). Such is the case for ozone (O_3), an allotrope of oxygen with a V-shaped structure and an O–O–O angle of 117.5°.

1. We know that ozone has a V-shaped structure, so one O atom is central:



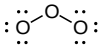
2. Each O atom has 6 valence electrons, for a total of 18 valence electrons.

3. Assigning one bonding pair of electrons to each oxygen–oxygen bond gives



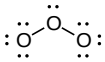
with 14 electrons left over.

4. If we place three lone pairs of electrons on each terminal oxygen, we obtain

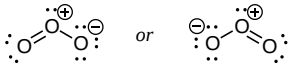


and have 2 electrons left over.

5. At this point, both terminal oxygen atoms have octets of electrons. We therefore place the last 2 electrons on the central atom:



6. The central oxygen has only 6 electrons. We must convert one lone pair on a terminal oxygen atom to a bonding pair of electrons—but which one? Depending on which one we choose, we obtain either



Which is correct? In fact, neither is correct. Both predict one O–O single bond and one O=O double bond. If the bonds were of different types (one single and one double, for example), they would have different lengths. It turns out, however, that both O–O bond distances are identical, 127.2 pm, which is shorter than a typical O–O single bond (148 pm) and longer than the O=O double bond in O_2 (120.7 pm).

Equivalent Lewis dot structures, such as those of ozone, are called resonance structures . The position of the *atoms* is the same in the various resonance structures of a compound, but the position of the *electrons* is different. Double-headed arrows link the different resonance structures of a compound:

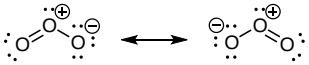
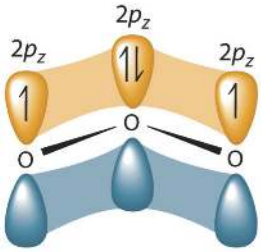


Figure 2.4.1).



The resonance structure of ozone involves a molecular orbital extending all three oxygen atoms.In ozone, a molecular orbital extending over all three oxygen atoms is formed from three atom centered p_z orbitals. Similar molecular orbitals are found in every resonance structure.

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2.4: RULES FOR RESONANCE FORMS

OBJECTIVES

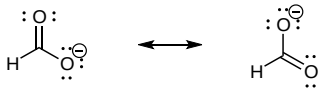
After completing this section, you should be able to

- use the concept of resonance to explain structural features of molecules and ions.
- understand the relationship between resonance and relative stability of molecules and ions.

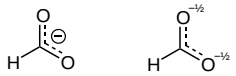
RULES FOR DRAWING AND WORKING WITH RESONANCE CONTRIBUTORS

Recognizing, drawing, and evaluating the relative stability of resonance contributors is essential to understanding organic reaction mechanisms. When learning to draw and interpret resonance structures, there are a few basic guidelines to help. .

1. There is ONLY ONE REAL STRUCTURE for each molecule or ion. This real structure (the **resonance hybrid**) takes its character from the average of all the individual **resonance contributors**. When looking at a resonance contributors, we are seeing the exact same molecule or ion depicted in different ways. Resonance hybrids are really a single, unchanging structure.

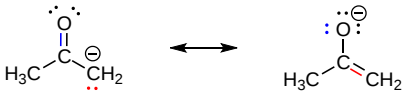


Major resonance contributors of the formate ion

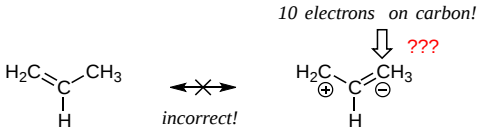


Representations of the formate resonance hybrid

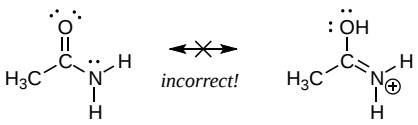
2. The resonance hybrid is more stable than any individual resonance structures. Often, resonance structures represent the movement of a charge between two or more atoms. The charge is spread out amongst these atoms and therefore more stabilized. When looking at the picture above the resonance contributors represent the negative charge as being on one oxygen or the other. The resonance hybrid shows the negative charge being shared equally between two oxygens. In the resonance hybrid, the negative charge is spread out over a larger part of the molecule and is therefore more stable.
3. Resonance contributors do not have to be equivalent. Because of this, resonance structures do necessarily contribute equally to the resonance hybrid. The two resonance structures shown below are not equivalent because one show the negative charge on an oxygen while the other shows it on a carbon. Later, we will show that the contributor with the negative charge on the oxygen is the more stable of the two. Also, this means that the resonance hybrid will not be an exact mixture of the two structures.



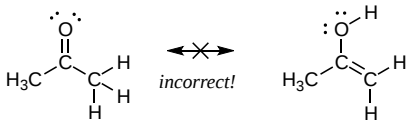
4. All resonance contributors must be correct Lewis structures. Each atom should have a complete valence shell and be shown with correct formal charges. A carbocation (carbon with only 6 valence electrons) is the only allowed exception to the valence shell rules. The structure below is an invalid resonance structure even though it only shows the movement of a pi bond. The resulting structure contains a carbon with ten electrons, which violates the octet rule, making it invalid.



5. All resonance contributors must have the same molecular formula, the same number of electrons, and same net charge. The molecules in the figure below are not resonance structures of the same molecule because then have different molecular formulas (C_2H_5NO Vs. C_2H_6NO). Also, the two structures have different net charges (neutral Vs. positive).

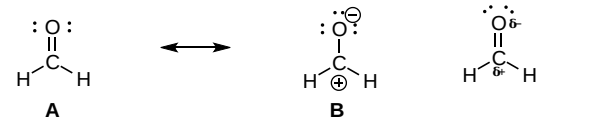


6. Resonance contributors only differ by the positions of pi bond and lone pair electrons. Sigma bonds are never broken or made, because of this atoms must maintain their same position. The molecules in the figure below are not resonance structures of the same molecule even though they have the same molecular formula (C_3H_6O). These molecules are considered structural isomers because their difference involves the breaking of a sigma bond and moving a hydrogen atom.



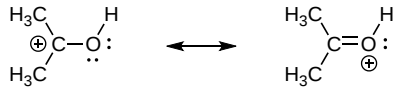
MAJOR AND MINOR RESONANCE CONTRIBUTORS

As previously state the true structure of a resonance hybrid is the combination of all the possible resonance structures. If the resonance structures are equal in stability they the contribute equally to the structure of the hybrid. However, if the resonance structures have different stabilities they contribute to the hybrid's structure in proportions related to their relative stabilities. It can be said the the resonance hybrid's structure resembles the most stable resonance structure. Because of this it is important to be able to compare the stabilities of resonance structures. In the example below, structure **B** is much less important in terms of its contribution to the hybrid because it contains the violated octet of a carbocation. The relative stabilities of the two structures are so vastly different that molecules which contain a C=O bond are almost exclusively written in a form like structure **A**. However, as will learn in chapter 19, the positively charged carbon created by structure **B** will explain how the C=O bond will react with electron rich species.

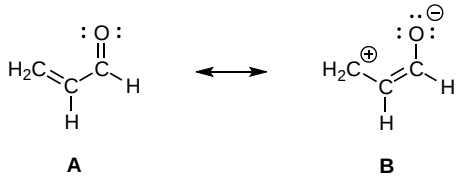


RULES FOR ESTIMATING STABILITY OF RESONANCE STRUCTURES

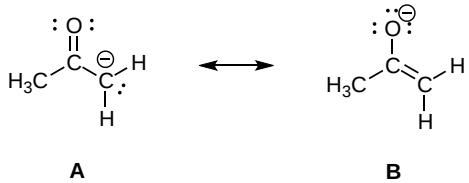
1. The resonance structures in which all atoms have complete valence shells is more stable. This means most atoms have a full octet. In the example below structure **A** has a carbon atom with a positive charge and therefore an incomplete octet. Based on this criterion, structure **A** is less stable and is a more minor contributor to the resonance hybrid than structure **B**.



2. The structures with the **least number of formal charges** is more stable. Based on this, structure **B** is less stable because is has two atoms with formal charges while structure **A** has none. Structure **A** would be the major resonance contributor.

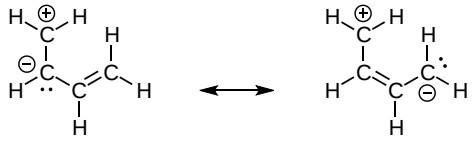


3. The structures with a **negative charge on the more electronegative atom** will be more stable. The difference between the two resonance structures is the placement of a negative charge. Structure **B** is the more stable and the major resonance contributor, because it places the negative charge on the more electronegative oxygen.



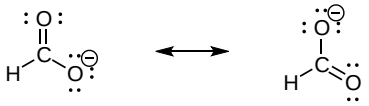
4. The structures with a **positive charges on the least electronegative atom** (most electropositive) is more stable.

5. The structures with the **least separation of formal charges** is more stable. The only difference between the two structures below are the relative positions of the positive and negative charges. In structure **A** the charges are closer together making it more stable.



A **B**

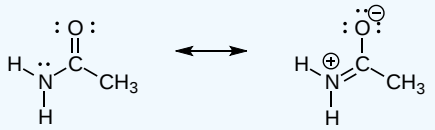
6. **Resonance forms that are equivalent have no difference in stability**. When looking at the two structures below no difference can be made using the rules listed above. This means the two structures are equivalent in stability and would make equal structural contributions to the resonance hybrid.



A **B**

EXAMPLE 2.4.1

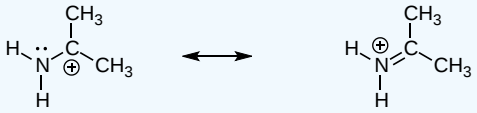
Example 1



major contributor
(neutral structure)

minor contributor
(charge separation)

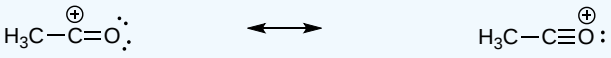
Example 2



minor contributor
(Incomplete octet on carbon.)

major contributor
(All atoms have octets, even though there is a positive charge on nitrogen.)

Example 3

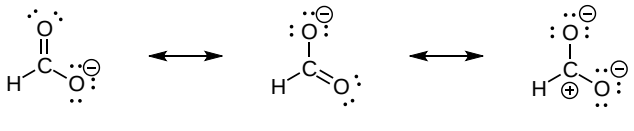


minor contributor
(Incomplete octet on carbon, but more important in terms of reactivity.)

major contributor
(All atoms have octets, even though there is a positive charge on oxygen.)

CARBOXYLATE EXAMPLE

In the case of carboxylates, contributors **A** and **B** below are equivalent in terms of their relative contribution to the hybrid structure. However, there is also a third resonance contributor **C**, in which the carbon bears a positive formal charge (a carbocation) and both oxygens are single-bonded and bear negative charges.



A **B** **C**

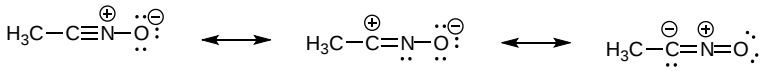
minor contributor
(separation of charge)

Structure **C** makes a less important contribution to the overall bonding picture of the group relative to **A** and **B**. How do we know that structure **C** is the 'minor' contributor? Apply the rules below:

- The carbon in contributor **C** does not have an octet. In general, resonance contributors in which a carbon does not fulfill the octet rule are relatively less important. (rule #1)
- In structure **C**, there are only three bonds, compared to four in **A** and **B**. In general, a resonance structure with a lower number of total bonds is relatively less important. (rule #2)
- Structure **C** also has more formal charges than are present in **A** or **B**. In general, resonance contributors in which there is more/greater separation of charge are relatively less important. (rule #3)
- Structures **A** and **B** are equivalent and will be equal contributors to the resonance hybrid. (rule #5).
- The resonance contributor in which a negative formal charge is located on a more electronegative atom, usually oxygen or nitrogen, is more stable than one in which the negative charge is located on a less electronegative atom such as carbon. An example is in the upper left expression in the next figure. (rule #4)

MOLECULES WITH THREE RESONANCE STRUCTURES

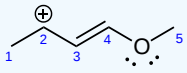
Molecules with more than 2 resonance structures can also be considered using the rules listed above. Of the resonance structures listed below, structure **A** would be the most stable because all the non-hydrogen atoms have a full octet and the negative charge is on the more electronegative atom (oxygen). Structure **C** would be next in stability because all of the non-hydrogen atoms have full octets, though now the negative charge is on carbon rather than oxygen. Structure **B** would be the least stable of the three because it has the carbocation does not have an octet. Of the three, structure **A** would be the major resonance structure and would most resemble the structure of the true resonance hybrid. Structure **B** is considered a minor resonance contributor and would have very little effect on the structure of the resonance hybrid.



A **B** **C**

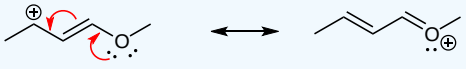
EXAMPLE 2.4.1

Draw the major resonance contributor of the structure below. Include in your figure the appropriate curved arrows showing how you got from the given structure to your structure. Explain why your contributor is the major one. In what kind of orbitals are the two lone pairs on the oxygen?



Solution

In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see the rules for drawing resonance contributors to convince yourself that these are 'legal' moves).

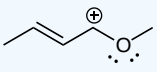


minor
(Carbon does not have a complete octet.)

major
(All atoms have a complete octet.)

The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #1 and #2 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, and C_4, plus one on oxygen) sharing four pi electrons. One lone pair on the oxygen is in an unhybridized *2p* orbital and is part of the conjugated pi system, and the other is located in an sp^2 orbital.

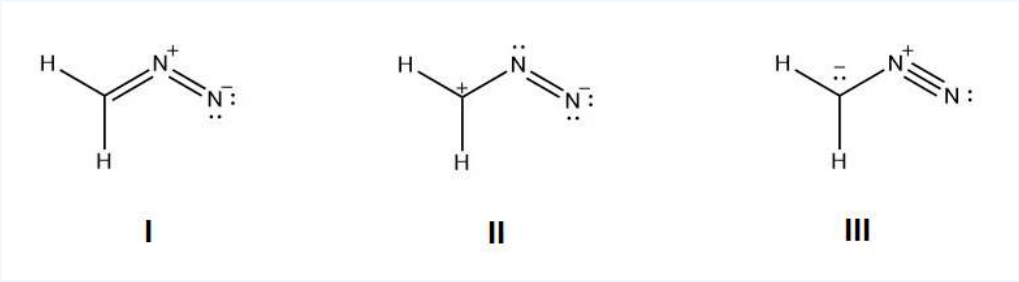
Also note that one additional contributor can be drawn, but it is also minor because it has a carbon with an incomplete octet:



minor

EXERCISE 2.4.2

For the following resonance structures please rank them in order of stability. Indicate which would be the major contributor to the resonance hybrid.

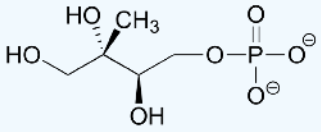


Answer

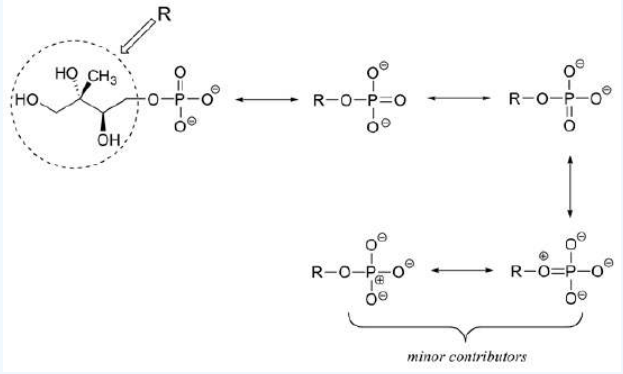
Structure I would be the most stable because all the non-hydrogen atoms have a full octet and the negative charge is on the more electronegative nitrogen. Structure III would be the next in stability because all of the non-hydrogen atoms have full octets. Structrure II would be the least stable because it has the violated octet of a carbocation.

EXERCISE 2.4.3

Draw four additional resonance contributors for the molecule below. Label each one as major or minor (the structure below is of a major contributor).



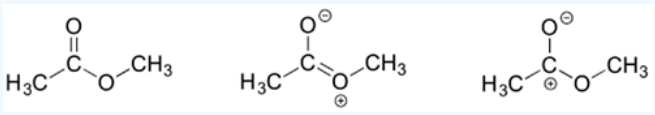
Answer



EXERCISE 2.4.4

Draw three resonance contributors of methyl acetate (an ester with the structure CH_3COOCH_3), and order them according to their relative importance to the bonding picture of the molecule. Explain your reasoning.

Answer

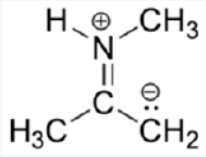


- The contributor on the left is the most stable: there are no formal charges.
- The contributor on the right is least stable: there are formal charges, and a carbon has an incomplete octet.

- The contributor in the middle is intermediate stability: there are formal charges, but all atoms have a complete octet.

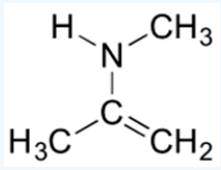
EXERCISE 2.4.5

Below is a minor resonance contributor of a species known as an ‘enamine’, which we will study more in Section 19.8 (formation of enamines) Section 23.12 (reactions of enamines). Draw the major resonance contributor for the enamine, and explain why your contributor is the major one.



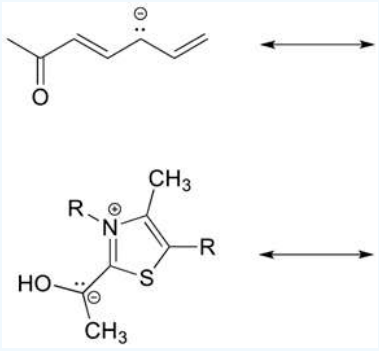
Answer

This contributor is major because there are no formal charges.

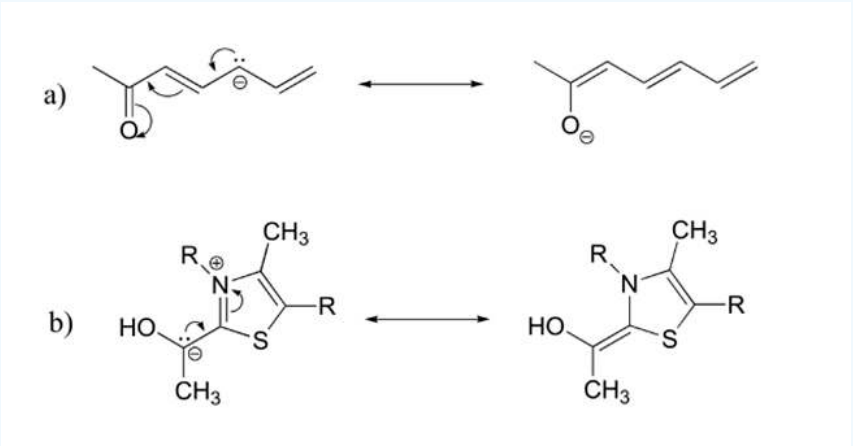


EXERCISE 2.4.6

Draw the major resonance contributor for each of the anions below:

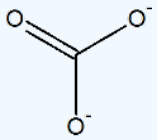


Answer



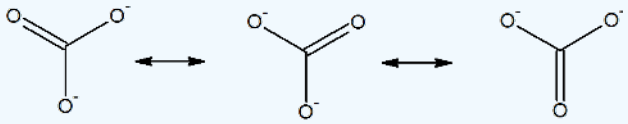
EXERCISE 2.4.7

Are all the bond lengths the same in the carbonate ion, CO_3^{2-}?



Answer

Yes, the bond lengths in carbonate ion are all the same. Carbonate ion exists as the resonance hybrid of the three resonance forms below.

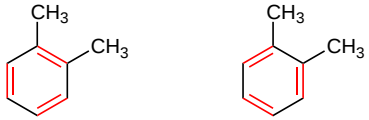


ADDITIONAL RESONANCE TOPICS

RECOGNIZING RESONANCE

Resonance contributors involve the 'imaginary movement' of pi-bonded electrons or of lone-pair electrons that are adjacent to (i.e. conjugated to) pi bonds. You can never shift the location of electrons in sigma bonds – if you show a sigma bond forming or breaking, you are showing a chemical reaction taking place. Likewise, the positions of atoms in the molecule cannot change between two resonance contributors.

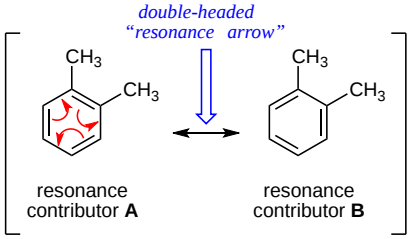
Because benzene will appear throughout this course, it is important to recognize the stability gained through the resonance delocalization of the six pi electrons throughout the six carbon atoms. Benzene also illustrates one way to recognize resonance - when it is possible to draw two or more equivalent Lewis structures. If we were to draw the structure of an aromatic molecule such as 1,2-dimethylbenzene, there are two ways that we could draw the double bonds:



Is this correct… *…or is this?*

Which way is correct? There are two simple answers to this question: 'both' and 'neither one'. Both ways of drawing the molecule are equally acceptable approximations of the bonding picture for the molecule, but neither one, by itself, is an accurate picture of the delocalized pi bonds. The two alternative drawings, however, when considered together, give a much more accurate picture than either one on its own. This is because they imply, together, that the carbon-carbon bonds are not double bonds, not single bonds, but about halfway in between.

When it is possible to draw more than one valid structure for a compound or ion, we have identified **resonance contributors**: two or more different Lewis structures depicting the same molecule or ion that, when considered together, do a better job of approximating delocalized pi-bonding than any single structure. By convention, resonance contributors are linked by a double-headed arrow, and are sometimes enclosed by brackets:



In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the 'movement' of two pi electrons. In the drawing of resonance contributors, however, this electron 'movement' occurs only

in our minds, as we try to visualize delocalized pi bonds. Nevertheless, use of the curved arrow notation is an essential skill that you will need to develop in drawing resonance contributors.

The depiction of benzene using the two resonance contributors A and B in the figure above does *not* imply that the molecule at one moment looks like structure A, then at the next moment shifts to look like structure B. Rather, at all moments, the molecule is a combination, or **resonance hybrid** of both A and B.

CAUTION

It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken place.

Benzene is often drawn as only one of the two possible resonance contributors (it is assumed that the reader understands that resonance hybridization is implied). However, sometimes benzene will be drawn with a circle inside the hexagon, either solid or dashed, as a way of drawing a resonance hybrid.



resonance contributor drawings resonance hybrid drawings

EXAMPLE 2.4.2: EXAMPLES OF RESONANCE

Molecules with a Single Resonance Configuration

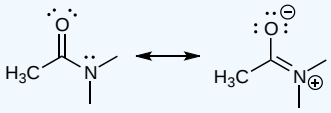
Example 1



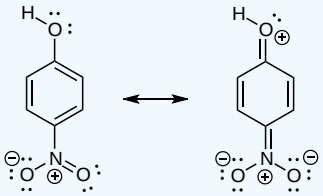
Example 2



Example 3



Example 4

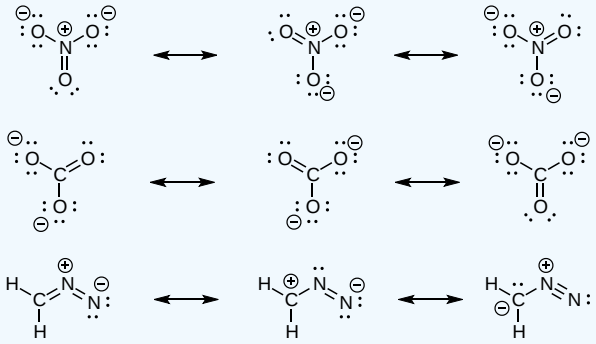


The above resonance structures show that the electrons are delocalized within the molecule and through this process the molecule gains extra stability. Ozone with both of its opposite formal charges creates a neutral molecule and through resonance it is a stable molecule. The extra electron that created the negative charge one terminal oxygen can be delocalized by resonance through the other terminal oxygen.

Benzene is an extremely stable molecule due to its geometry and molecular orbital interactions, but most importantly, due to its resonance structures. The delocalized electrons in the benzene ring make the molecule very stable and with its characteristics of a nucleophile, it will react with a strong electrophile only and after the first reactivity, the substituted benzene will depend on its resonance to direct the next position for the reaction to add a second substituent.

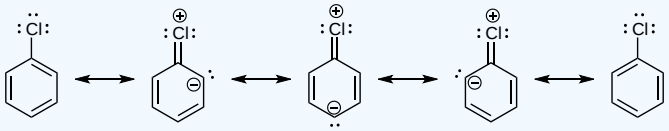
EXAMPLE 2.4.8: MULTIPLE RESONANCE OF OTHER MOLECULES

Molecules and ions with more than one resonance form:



Some structural resonance conformations are the major contributor or the dominant forms that the molecule exists. For example, if we look at the above rules for estimating the stability of a molecule, we see that for the third molecule the first and second forms are the major contributors for the overall stability of the molecule. The nitrogen is more electronegative than carbon so, it can handle the negative charge more than carbon. A carbon with a negative charge is the least favorable conformation for the molecule to exist, so the last resonance form contributes very little for the stability of the Ion.

Hybrid Resonance



The different resonance forms of the molecule help predict the reactivity of the molecule at specific sites.

The Hybrid Resonance forms show the different Lewis structures with the electron been delocalized. This is very important for the reactivity of chloro-benzene because in the presence of an electrophile it will react and the formation of another bond will be directed and determine by resonance. The lone pair of electrons delocalized in the aromatic substituted ring is where it can potentially form a new bond with an electrophile, as it is shown there are three possible places that reactivity can take place, the first to react will take place at the *para* position with respect to the chloro- substituent and then to either *ortho*- position.

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2.5: DRAWING RESONANCE FORMS

OBJECTIVES

After completing this section, you should be able to

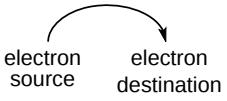
- draw the resonance structures of molecules or ions that exhibit delocalization.
- determine the relative stability of resonance structures using a set of rules.
- use the concept of resonance to explain structural features of molecules and ions.

KEY WORDS

- resonance structure
- resonance hybrid

CURVED ARROWS COMMUNICATE ELECTRON FLOW (MOVEMENT)

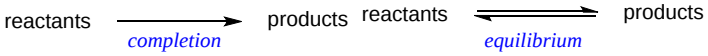
Organic chemistry has developed a system to show how electrons move between resonance structures. This system will also be used to help describe how electrons from in reactions. Curved double barbed arrows indicates the flow of two electrons. The base of the curved arrow is placed at the source of the electrons that are moving. The head of the arrow is placed at the destination of the electrons.



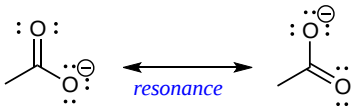


It is also important to consciously use the correct type of arrow. There are four primary types of arrows used by chemists to communicate one of the following: completion reaction, equilibrium reaction, electron movement, and resonance forms. The three other types of arrows are shown below to build discernment between them. Note, the electron movement arrows are the only ones that are curved.

Reaction Arrows



Resonance Arrows



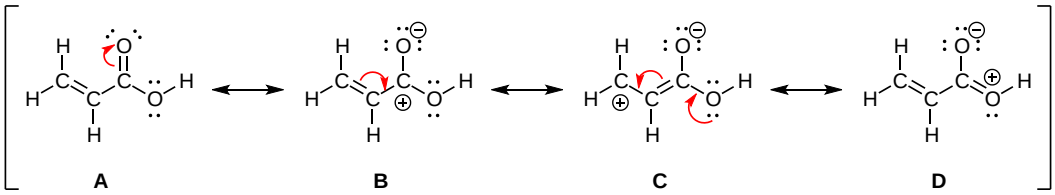
USING CURVED ARROWS TO SHOW ELECTRON MOVEMENT

Because the double barbed arrow represents the movement of two electrons, they usually involve lone pair electrons or pi bonds. There are only three types of electron "motion" in resonance. They are:

1. **A lone pair forms a pi bond to an adjacent atom**
2. **A pi bond forms a new pi bond to an adjacent atom**
3. **A pi bond forms a lone pair on adjacent atom**

Let's look at the resonance within acrylic acid to demonstrate these three types of resonance.

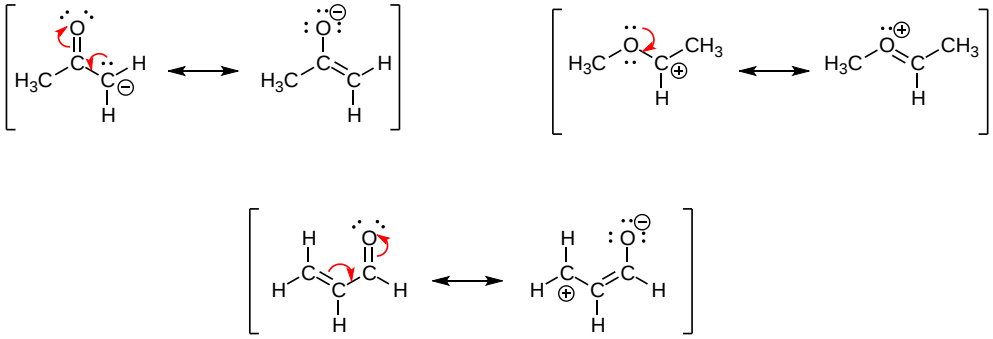
acrylic acid



The curved arrow in structure A represents the type 3 resonance "motion" - the pi bond between the carbon and oxygen breaks to form another lone pair on the oxygen. The curved arrow in structure B represents type 2 resonance "motion" - the pi bond breaks to form a new pi bond to the carbocation carbon. In structure C, there are two curved arrows. The curved arrow from the oxygen lone pair is type 1 resonance motion - the lone pairs forms a new pi bond between the oxygen and carbon. The other arrow in structure C moves the pi bond to the end of the chain and represents resonance type 2. By combining these three basic types of electron movement we can describe virtually any type of resonance.

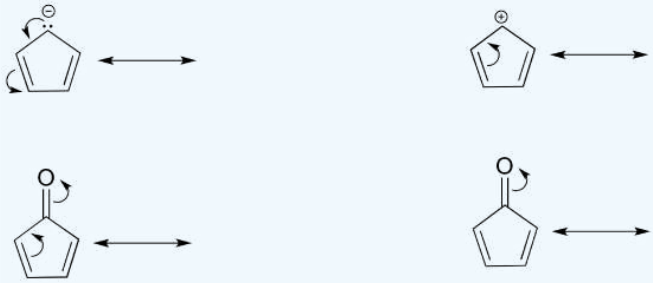
EXAMPLE:

Below are a few more examples of 'legal' resonance expressions. Confirm for yourself that the octet rule is not exceeded for any atoms, that formal charges are correct, and identify which type of electron movement is being represented by each arrow.

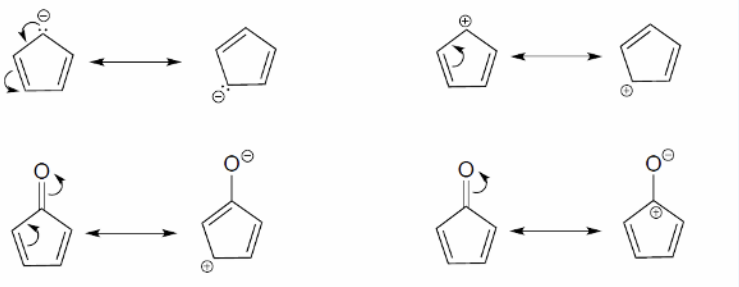


EXERCISE 2.5.1

Draw the resonance contributors that correspond to the curved, two-electron movement arrows in the resonance expressions below. Then identify the type of resonance motion in each structure below.

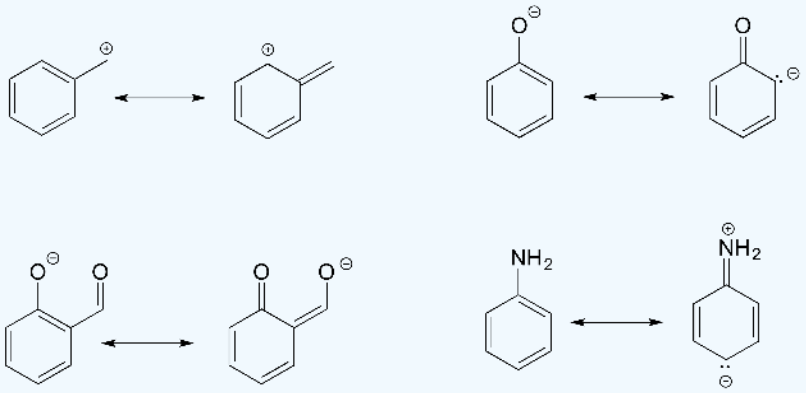


Answer

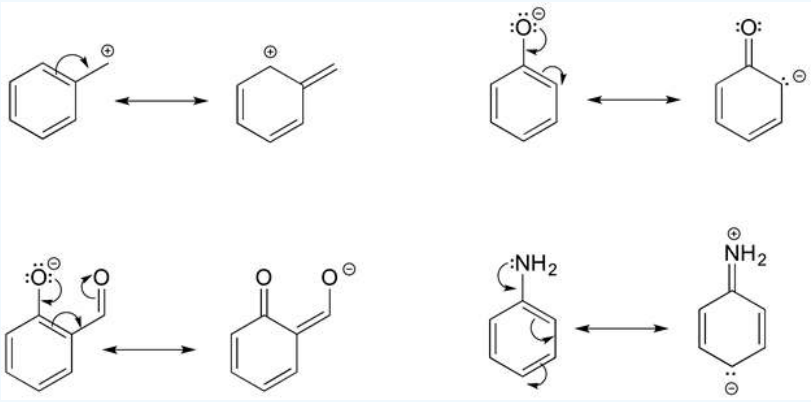


? EXERCISE 2.5.2

In each resonance expression, identify the type of resonance motion. Then draw curved arrows on the left-side contributor that shows how we get to the right-side contributor.



Answer



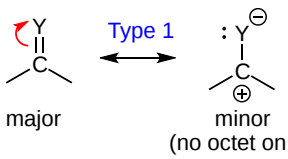
RECOGNIZING COMMON PATTERNS OF RESONANCE

If you examine a large number of resonance examples, you will begin to notice that they nearly always match common patterns, of which there are only three. It is important to be able to identify atoms that participate in resonance. In complex resonance cases, multiple types of resonance may occur simultaneously.

TYPE I - NEUTRAL SPECIES

The electrons of a pi bond move to become a set of lone pair electrons on a electronegative atom. The resonance structure made has a carbon with a violated octet which make it a minor contributor. This type of resonance is commonly used to the polarity in certain double bonds.

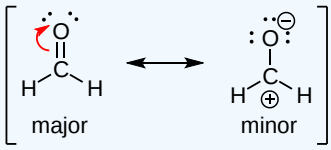
Neutral Species



Note: Y is an electronegative atom, usually N, O, or S.

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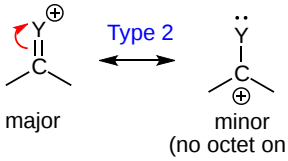
TYPE I EXAMPLE



TYPE II - CHARGED SPECIES

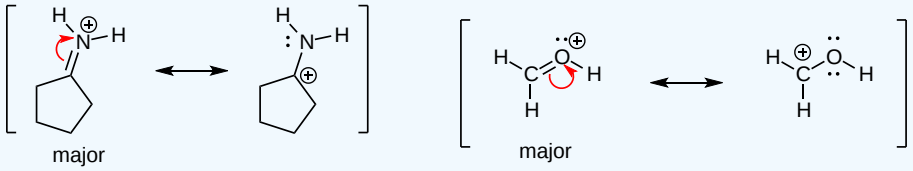
Type II resonance is only seen with a + charge, and usually involves a positive charge on oxygen or nitrogen being shared onto a carbon; the carbocation form has only six valence electrons on the carbon, so it is a less stable form than the major form (which has complete octets).

Charged Species



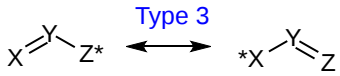
Note: Y is an electronegative atom, usually N, O, S, sometimes halogen

TYPE II EXAMPLE



TYPE III - ALLYLIC RESONANCE

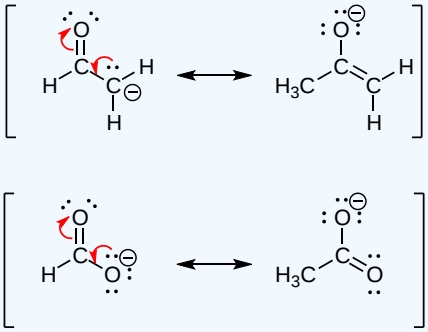
Type III resonance is very common and important because is serves to stabilize positive charges, negative charges, or lone pairs. It is sometimes referred to as “allylic” resonance, especially in cases with all carbon. This type of resonance can be identified by a three-atom group of atoms each with sp^2 hybridization and a *p* orbital.

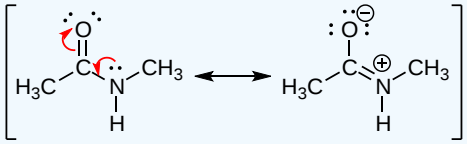


* represents a charge or an unpaired electron

TYPE III EXAMPLE

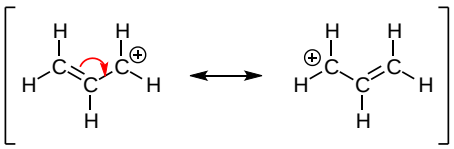
Atoms with lone pair electrons next to a pi bond can be sp^2 hybridized and have the lone pair of electrons in a p orbital despite the fact that they are surrounded by four electron groups. The lone pair electrons contained in the p orbital cause the ion to be stabilized due to resonance.

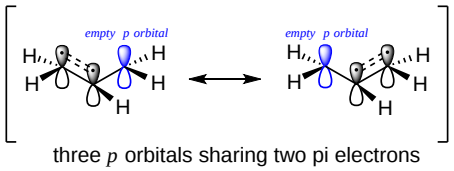




Similarly, carbocations are sp^2-hybridized, with an empty *2p* orbital oriented perpendicular to the plane formed by three sigma bonds. If a carbocation is adjacent to a double bond, then three *2p* orbitals can overlap and share the two pi electrons - another kind of conjugated pi system in which the positive charge is shared over two carbons.

charge is delocalized over two carbons

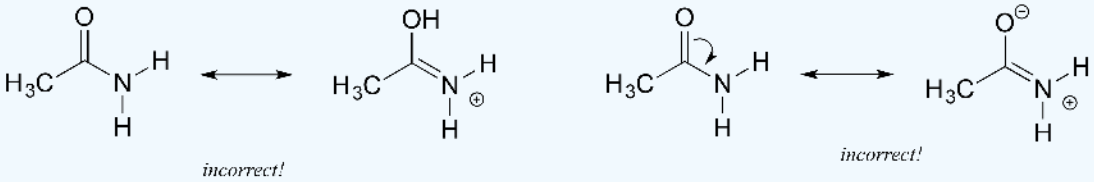


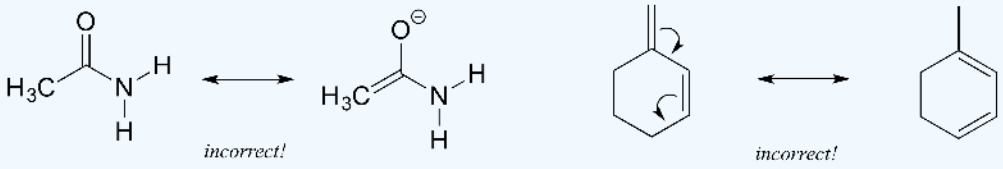


three *p* orbitals sharing two pi electrons

EXERCISE 2.5.3

Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in each.







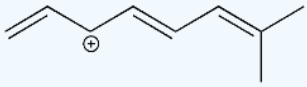
Answer

The first pair are not resonance structures since there is an additional hydrogen on the second structure oxygen. The second pair pushed electrons toward nitrogen which already has a lone pair and would exceed its octet. The third pair includes a structure with 5 bonds to carbon. The fourth pair requires moving carbon-hydrogen bonds, therefore is not resonance. The fifth pair show electrons

moving toward the negatively charged oxygen which would exceed an octet. The fifth pair shows a sigma bond breaking on the ring, rather than pi bond.

EXERCISE 2.5.4

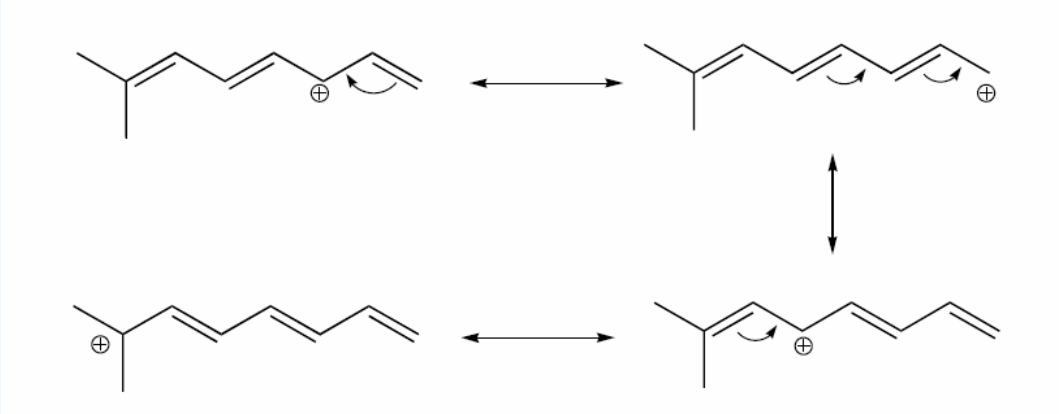
a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.



b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Answer

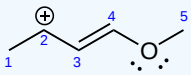
a)



b) The conjugated pi system in this carbocation is composed of seven p orbitals containing six delocalized pi electrons.

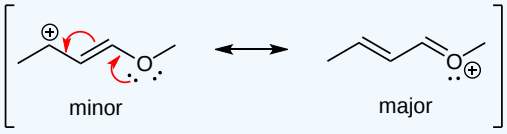
EXAMPLE 2.5.1

Draw the major resonance contributor of the structure below. Include in your figure the appropriate curved arrows showing how you got from the given structure to your structure. Explain why your contributor is the major one. In what kind of orbitals are the two lone pairs on the oxygen?



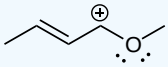
Solution

In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see the rules for drawing resonance contributors to convince yourself that these are 'legal' moves).



The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #1 and #2 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, and C_4, plus one on oxygen) sharing four pi electrons. One lone pair on the oxygen is in an unhybridized *2p* orbital and is part of the conjugated pi system, and the other is located in an sp^2 orbital.

Also note that one additional contributor can be drawn, but it is also minor because it has a carbon with an incomplete octet:



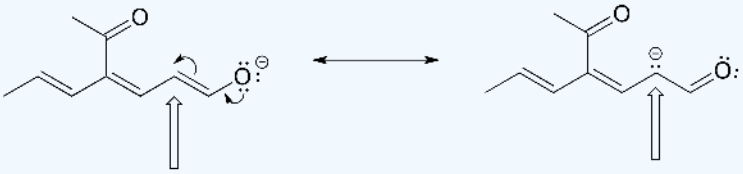
minor

EXERCISE 2.5.5

The figure below shows how the negative formal charge on an oxygen (of an enol) can be delocalized to the carbon indicated by an arrow. More resonance contributors can be drawn in which negative charge is delocalized to three other atoms on the molecule.

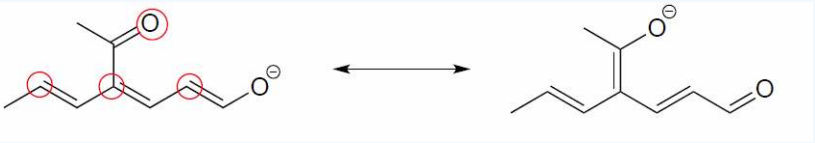
a) Circle these atoms that can also have a resonance structure with a negative charge.

b) Draw the two most important resonance contributors for the enolate ion.



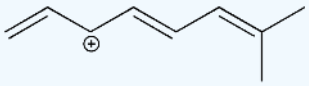
Answer

The two major contributors are those in which the negative formal charge is located on an oxygen rather than on a carbon.



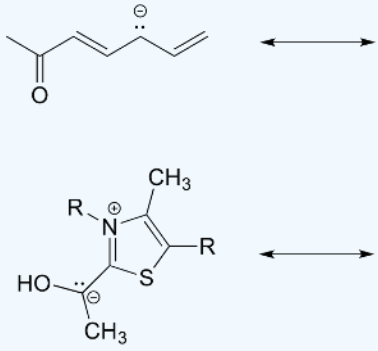
Exercise 2.6.5:

a) Draw three additional resonance contributors for the carbocation below. Include in your figure the appropriate curved arrows showing how one contributor is converted to the next.



b) Fill in the blanks: the conjugated pi system in this carbocation is composed of _____ *2p* orbitals sharing _____ delocalized pi electrons.

Exercise 2.6.6: Draw the major resonance contributor for each of the anions below.

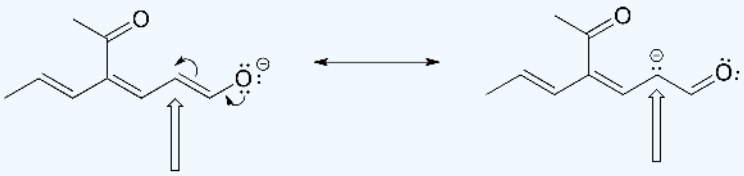


c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

Exercise 2.6.7: The figure below shows how the negative formal charge on the oxygen can be delocalized to the carbon indicated by an arrow. More resonance contributors can be drawn in which negative charge is delocalized to three other atoms on the molecule.

a) Circle these atoms.

b) Draw the two most important resonance contributors for the molecule.



A word of advice

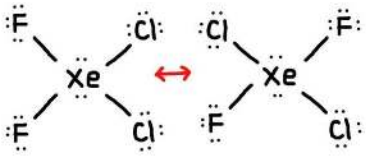
Becoming adept at drawing resonance contributors, using the curved arrow notation to show how one contributor can be converted to another, and understanding the concepts of conjugation and resonance delocalization are some of the most challenging but also most important jobs that you will have as a beginning student of organic chemistry. If you work hard now to gain a firm grasp of these ideas, you will have come a long way toward understanding much of what follows in your organic chemistry course. Conversely, if you fail to come to grips with these concepts now, a lot of what you see later in the course will seem like a bunch of mysterious and incomprehensible lines, dots, and arrows, and it will be difficult to be successful in organic chemistry.

REFERENCES

1. Petrucci, Ralph H., et al. *General Chemistry: Principles and Modern Applications*. New Jersey: Pearson Prentice Hall, 2007. Print.
2. Ahmad, Wan-Yaacob and Zakaria, Mat B. "Drawing Lewis Structures from Lewis Symbols: A Direct Electron Pairing Approach." Journal of Chemical Education: Journal 77.3: n. pag. Web. March 2000. Link to this journal: pkukmweb.ukm.my/~mbz/c_penerb...83%29/p329.pdf

PROBLEMS

1. True or False, The picture below is a resonance structure?

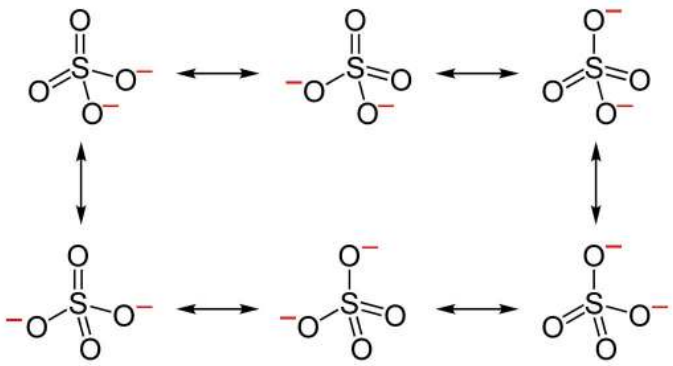


2. Draw the Lewis Dot Structure for $\mathbf{SO_4^{2-}}$ and all possible resonance structures. Which of the following resonance structure is not favored among the Lewis Structures? Explain why. Assign Formal Charges.
3. Draw the Lewis Dot Structure for $\mathbf{CH_3COO^-}$ and all possible resonance structures. Assign Formal Charges. Choose the most favorable Lewis Structure.
4. Draw the Lewis Dot Structure for $\mathbf{HPO_3^{2-}}$ and all possible resonance structures. Assign Formal Charges.
5. Draw the Lewis Dot Structure for $\mathbf{CHO_2^{1-}}$ and all possible resonance structures. Assign Formal Charges.
6. Draw the Resonance Hybrid Structure for $\mathbf{PO_4^{3-}}$.
7. Draw the Resonance Hybrid Structure for $\mathbf{NO_3^-}$.

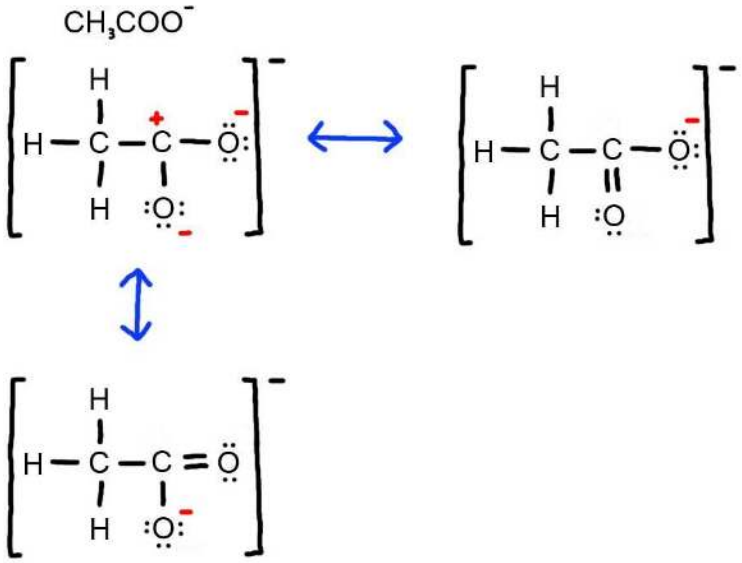
ANSWERS

1. False, because the electrons were not moved around, only the atoms (this violates the Resonance Structure Rules).

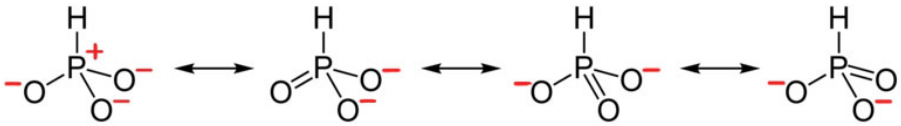
2. Below are the all Lewis dot structure with formal charges (in red) for Sulfate ($\mathbf{SO_4^{2-}}$). There isn't a most favorable resonance of the Sulfate ion because they are all identical in charge and there is no change in Electronegativity between the Oxygen atoms.



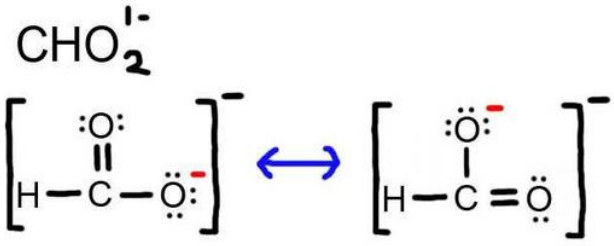
3. Below is the resonance for **CH_3COO^-**, formal charges are displayed in red. The Lewis Structure with the most formal charges is not desirable, because we want the Lewis Structure with the least formal charge.



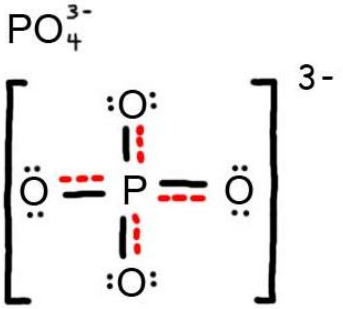
4. The resonance for **HPO_3^{2-}**, and the formal charges (in red).



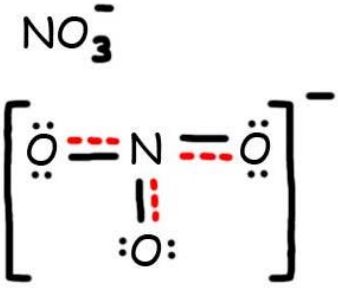
5. The resonance for **CHO_2^{1-}**, and the formal charges (in red).



6. The resonance hybrid for **PO_4^{3-}**, hybrid bonds are in red.



7. The resonance hybrid for $\mathbf{NO_3^-}$, hybrid bonds are in red.



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2.6: ACIDS AND BASES - THE BRØNSTED-LOWRY DEFINITION

OBJECTIVES

After completing this section, you should be able to

1. state the Brønsted-Lowry definition of an acid and a base.
2. identify the Brønsted-Lowry acid and base in a given acid-base reaction.
3. identify the conjugate base of an acid and identify the conjugate acid of a base.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Brønsted-Lowry acid
- Brønsted-Lowry base
- conjugate acid
- conjugate base

STUDY NOTES

You should already be familiar with the Brønsted-Lowry concept of acidity and the differences between strong and weak acids. You may wish to review this topic before proceeding.

In 1923, chemists Johannes Brønsted and Martin Lowry independently developed definitions of acids and bases based on compounds abilities to either donate or accept protons (H^+ ions). Here, acids are defined as being able to donate protons in the form of hydrogen ions; whereas bases are defined as being able to accept protons. This took the Arrhenius definition one step further as water is no longer required to be present in the solution for acid and base reactions to occur.

BRØNSTED-LOWRY DEFINITION

J.N. Brønsted and T.M. Lowry independently developed the theory of proton donors and proton acceptors in acid-base reactions, coincidentally in the same region and during the same year. The Arrhenius theory where acids and bases are defined by whether the molecule produces hydrogen ion or hydroxide ion when dissolved in water was too limiting, because not all chemical reactions, especially organic reactions, occur in water. The Brønsted-Lowry Theory defines an acid a proton donor, while a base is a proton acceptor. This is illustrated in the following reactions:

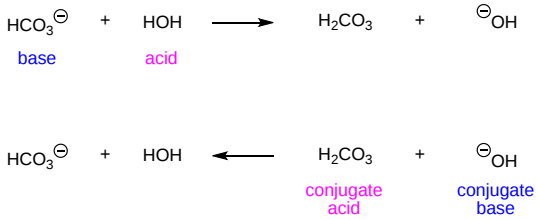
$$HCl + HOH \rightarrow H_3O^+ + Cl^-$$

$$HOH + NH_3 \rightarrow NH_4^+ + OH^-$$

Acid	Base	
Donates hydrogen ions	**Accepts hydrogen ions.**	
HCl	HOH →	$H_3O^+ + Cl^-$
HOH	NH_3→	$NH_4^+ + {}^-OH$

The determination of a substance as a Brønsted-Lowry acid or base can only be done by examining the reaction, since many chemicals can be either an acid or a base. For example, HOH is a base in the first reaction and an acid in the second reaction.

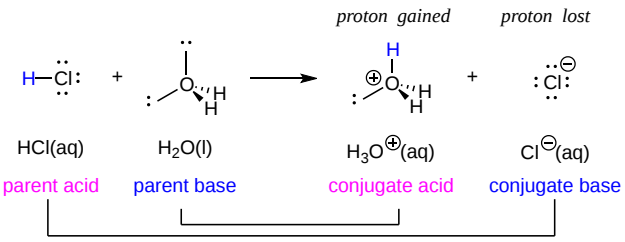
Bronsted-Lowry Acids and Bases



To determine whether a substance is an acid or a base, count the hydrogens on each substance before and after the reaction. If the number of hydrogens has decreased, then that substance is the acid (donates hydrogen ions). If the number of hydrogens has increased, then that substance is the base (accepts hydrogen ions). These definitions are normally applied to the reactants on the left. If the reaction is viewed in reverse a new acid and base can be identified. The substances on the right side of the equation are called the conjugate acid and conjugate base compared to those on the left. Also note that an acid turns into a conjugate base, and the base turns into the conjugate acid after the reaction is over.

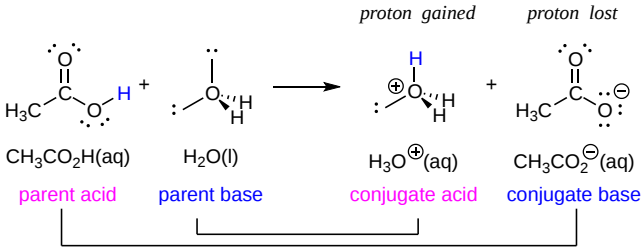
CONJUGATE ACID–BASE PAIRS

In aqueous solutions, acids and bases can be defined in terms of the transfer of a proton from an acid to a base. Thus for every acidic species in an aqueous solution, there exists a species derived from the acid by the loss of a proton. These two species that differ by only a proton constitute a conjugate acid–base pair. For example, in the reaction of HCl with water shown below, HCl , the parent acid, donates a proton to a water molecule, the parent base, thereby forming Cl-. Thus HCl and Cl- constitute a conjugate acid–base pair. By convention, we always write a conjugate acid–base pair as the acid followed by its conjugate base. In the reverse reaction, the Cl- ion in solution acts as a base to accept a proton from H_3O^+, forming H_2O and HCl. Thus H_3O^+ and H_2O constitute a second conjugate acid–base pair. In general, any acid–base reaction must contain two conjugate acid–base pairs, which in this case are HCl/Cl- and H_3O^+/H_2O.

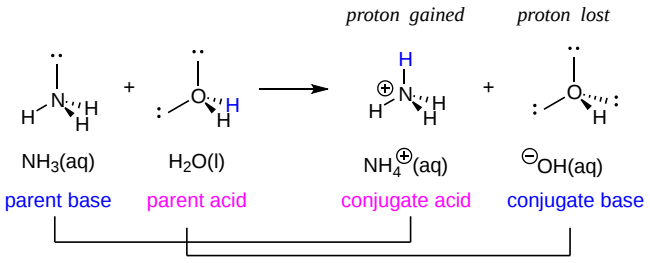


> *All acid–base reactions contain two conjugate acid–base pairs.*

Similarly, in the reaction of acetic acid with water, acetic acid donates a proton to water, which acts as the base. In the reverse reaction, H_3O^+ is the acid that donates a proton to the acetate ion, which acts as the base. Once again, we have two conjugate acid–base pairs: the parent acid and its conjugate base ($CH_3CO_2H/CH_3CO_2^-$) and the parent base and its conjugate acid (H_3O^+/H_2O).



In the reaction of ammonia with water to give ammonium ions and hydroxide ions, ammonia acts as a base by accepting a proton from a water molecule, which in this case means that water is acting as an acid. In the reverse reaction, an ammonium ion acts as an acid by donating a proton to a hydroxide ion, and the hydroxide ion acts as a base. The conjugate acid–base pairs for this reaction are NH_4^+/NH_3 and H_2O/OH^-.



EXAMPLE 2.6.1

Aniline ($C_6H_5NH_2$) is slightly soluble in water. It has a nitrogen atom that can accept a hydrogen ion from a water molecule just like the nitrogen atom in ammonia does. Write the chemical equation for this reaction and identify the Brønsted-Lowry acid and base.

Solution

$C_6H_5NH_2$ and H_2O are the reactants. When $C_6H_5NH_2$ accepts a proton from H_2O, it gains an extra H and a positive charge and leaves an OH^- ion behind. The reaction is as follows:

$$\mathbf{C_6H_5NH_2\,(aq) + H_2O(\ell) \rightleftharpoons C_6H_5NH_3{}^+\,(aq) + OH^-\,(aq)}$$

Because $C_6H_5NH_2$ accepts a proton, it is the Brønsted-Lowry base. The H_2O molecule, because it donates a proton, is the Brønsted-Lowry acid.

EXAMPLE 2.6.1

Identify the conjugate acid-base pairs in this equilibrium.

$$\boldsymbol{(CH_3)_3N + H_2O \rightleftharpoons (CH_3)_3NH^+ + OH^-}$$

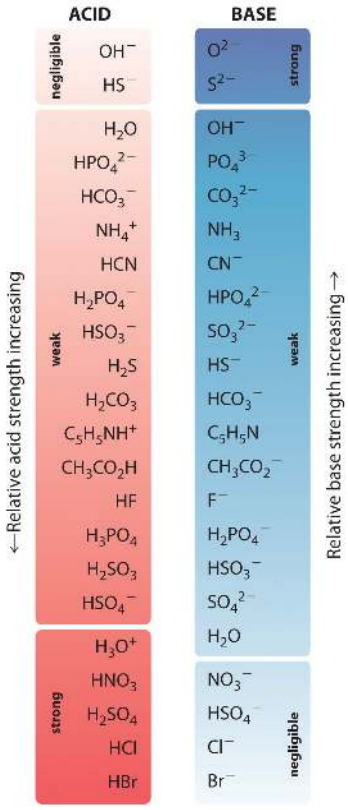
Solution

One pair is H2O and OH^-, where H2O has one more H^+ and is the conjugate acid, while OH^- has one less H^+ and is the conjugate base.

The other pair consists of (CH3)3N and (CH3)3NH^+, where (CH3)3NH^+ is the conjugate acid (it has an additional proton) and (CH3)3N is the conjugate base.

Some common conjugate acid–base pairs are shown in Figure 2.7.1. The strongest acids are at the bottom left, and the strongest bases are at the top right. The conjugate base of a strong acid is a very weak base, and, conversely, the conjugate acid of a strong base is a very weak acid.

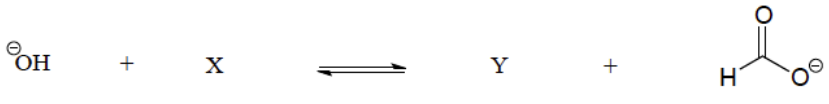
Figure 2.7.1 *The Relative Strengths of Some Common Conjugate Acid–Base Pairs*



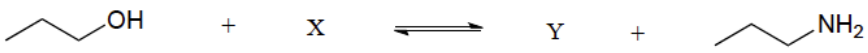
EXERCISES

1. Identify the Brønsted-Lowry acids and bases in the reactions given below.
   a. $CH3CH2O^- + H2O <=> CH3CH2OH + OH^-$
   b. $CH3CH2OH + H2SO4 <=> CH3CH2OH2 + + HSO4-$
2. Show the structures of species X and Y in the following acid-base reactions:

a)



b)

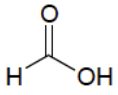


Answer:

1. a. $CH_3CH_2O^- + H_2O \rightleftharpoons CH_3CH_2OH + OH^-$

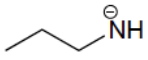
   b. $\underset{\text{base}}{CH_3CH_2OH} + \underset{\text{acid}}{H_2SO_4} \rightleftharpoons \underset{\text{acid}}{CH_3CH_2OH_2^+} + \underset{\text{base}}{HSO_4^-}$

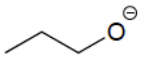
2. a)

   X: 

   Y: H_2O

   b)

   X: 

   Y: 

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QUESTIONS

Q2.7.1

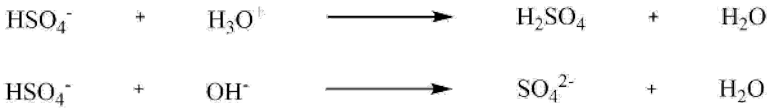
Is the following molecule a Brønsted acid or base?

HSO_4^-

SOLUTIONS

S2.7.1

It can be both, consider the following schemes:



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2.7: ACID AND BASE STRENGTH

OBJECTIVES

After completing this section, you should be able to

- write the expression for the K_a of a weak acid.
- convert a given K_a value into a pK_a value, and *vice versa*.
- arrange a series of acids in order of increasing or decreasing strength, given their K_a or pK_a values.
- arrange a series of bases in order of increasing or decreasing strength, given the K_a or pK_a values of their conjugate acids.

KEY TERMS

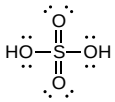
Make certain that you can define, and use in context, the key terms below.

- acidity constant, K_a
- equilibrium constant, K_{eq}

STUDY NOTES

Calculations and expressions involving K_a and pK_a were covered in detail in your first-year general chemistry course. Note that acidity constant is also known as the acid dissociation constant.

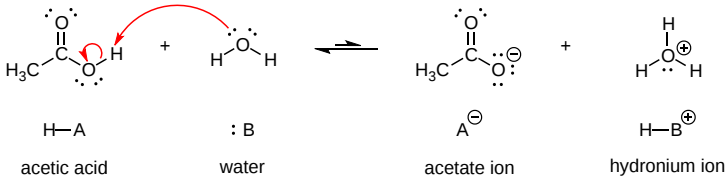
You are no doubt aware that some acids are stronger than others. Sulfuric acid is strong enough to be used as a drain cleaner, as it will rapidly dissolve clogs of hair and other organic material.



Not surprisingly, concentrated sulfuric acid will also cause painful burns if it touches your skin, and permanent damage if it gets in your eyes (there's a good reason for those safety goggles you wear in chemistry lab!). Acetic acid (vinegar), will also burn your skin and eyes, but is not nearly strong enough to make an effective drain cleaner. Water, which we know can act as a proton donor, is obviously not a very strong acid. Even hydroxide ion could *theoretically* act as an acid – it has, after all, a proton to donate – but this is not a reaction that we would normally consider to be relevant in anything but the most extreme conditions.

The relative acidity of different compounds or functional groups – in other words, their relative capacity to donate a proton to a common base under identical conditions – is quantified by a number called the **acid dissociation constant**, abbreviated $\mathbf{K_a}$. The common base chosen for comparison is water.

We will consider acetic acid as our first example. When a small amount of acetic acid is added to water, a proton-transfer event (acid-base reaction) occurs to some extent.



Notice the phrase 'to some extent' – this reaction does *not* run to completion, with all of the acetic acid converted to acetate, its conjugate base. Rather, a *dynamic equilibrium* is reached, with proton transfer going in both directions (thus the two-way arrows) and finite concentrations of all four species in play. The nature of this equilibrium situation, as you recall from General Chemistry, is expressed by an equilibrium constant, K.

The equilibrium constant is actually a ratio of activities (represented by the symbol $\boldsymbol{a}$), but activities are rarely used in courses other than analytical or physical chemistry. To simplify the discussion for general chemistry and organic chemistry courses, the activities of all of the solutes are replaced with molarities, and the activity of the solvent (usually water) is defined as having the value of 1.

In our example, we added a small amount of acetic acid to a large amount of water: water is the *solvent* for this reaction. Therefore, in the course of the reaction, the concentration of water changes very little, and the water can be treated as a pure solvent, which is always assigned an activity of 1. The acetic acid, acetate ion and hydronium ion are all *solutes*, and so their activities are approximated with molarities. The acid dissociation constant, or K_a, for acetic acid is therefore defined as:

$$K_{eq} = \frac{a_{CH_3COO^-} \cdot a_{H_3O^+}}{a_{CH_3COOH} \cdot a_{H_2O}} \approx \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH][1]}$$

Because dividing by 1 does not change the value of the constant, the "1" is usually not written, and K_a is written as:

$$K_{eq} = K_a = \frac{[CH_3COO^-][H_3O^+]}{[CH_3COOH]} = 1.75 \times 10^{-5}$$

In more general terms, the dissociation constant for a given acid is expressed as:

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{2.7.1}$$

or

$$K_a = \frac{[A][H_3O^+]}{[HA^+]} \tag{2.7.2}$$

Equation 2.7.1 applies to a neutral acid such as like HCl or acetic acid, while Equation 2.7.2 applies to a cationic acid like ammonium (NH_4^+).

The value of K_a = 1.75 x 10^{-5} for acetic acid is very small - this means that very little dissociation actually takes place, and there is much more acetic acid in solution at equilibrium than there is acetate ion. Acetic acid is a relatively weak acid, at least when compared to sulfuric acid ($K_a = 10^9$) or hydrochloric acid ($K_a = 10^7$), both of which undergo essentially complete dissociation in water.

A number like 1.75 x 10^{-5} is not very easy either to say or to remember. Chemists often use **pK_a** values as a more convenient term to express relative acidity. **pK_a** is related to **K_a** by the following equation

$$pK_a = -\log K_a$$

Doing the math, we find that the pK_a of acetic acid is 4.8. The use of pK_a values allows us to express the acidity of common compounds and functional groups on a numerical scale of about –10 (very strong acid) to 50 (not acidic at all). Table **2.7.1** at the end of the text lists exact or approximate pK_a values for different types of protons that you are likely to encounter in your study of organic and biological chemistry. Looking at Table **2.7.1**, you see that the pK_a of carboxylic acids are in the 4-5 range, the pK_a of sulfuric acid is –10, and the pK_a of water is 14. Alkenes and alkanes, which are not acidic at all, have pK_a values above 30. *The lower the pK_a value, the stronger the acid.*

Table* 2.7.1*: *Representative acid constants*

 sulfuric acid pK_a −10	 hydrochloric acid pK_a −7	 hydronium pK_a 0.00	 protonated ketone pK_a ~ −7	 protonated alcohol pK_a ~ −3
 phosphate monoester pK_a ~ 1	 phosphate diester pK_a ~ 1.5	 phosphoric acid pK_a 2.2	 protonated aniline pK_a ~ 4.6	 carboxylic acid pK_a ~ 4-5
 pyridinium pK_a 5.3	 carbonic acid pK_a 6.4	hydrogen cyanide pK_a ~ 9.2	 ammonium pK_a 9.2	 phenol pK_a 9.9
 thiol pK_a ~ 10-11	 water pK_a 14.00	 amide pK_a ~ 17	 alcohol pK_a ~ 16-18	 alpha-proton pK_a ~ 18-20
	terminal alkyne pK_a ~ 25	 terminal alkene pK_a ~ 35	 ammonia pK_a ~ 35	

It is important to realize that pK_a is *not* the same thing as pH: pK_a is an inherent property of a compound or functional group, while pH is the measure of the hydronium ion concentration in a particular aqueous solution:

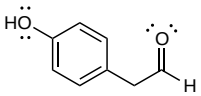
$$pH = -\log[H_3O^+]$$

Any particular acid will always have the same pK_a (assuming that we are talking about an aqueous solution at room temperature) but different aqueous solutions of the acid could have different pH values, depending on how much acid is added to how much water.

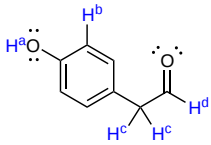
Our table of pK_a values will also allow us to compare the strengths of different bases by comparing the pK_a values of their conjugate acids. The key idea to remember is this: *the stronger the conjugate acid, the weaker the conjugate base*. Sulfuric acid is the strongest acid on our list with a pK_a value of –10, so HSO_4^- is the weakest conjugate base. You can see that hydroxide ion is a stronger base than ammonia (NH_3), because ammonium (NH_4^+, pK_a = 9.2) is a stronger acid than water (pK_a = 14.00).

> *The stronger the conjugate acid, the weaker the conjugate base.*

While Table **2.7.1** provides the pK_a values of only a limited number of compounds, it can be very useful as a starting point for estimating the acidity or basicity of just about any organic molecule. Here is where your familiarity with organic functional groups will come in very handy. What, for example, is the pK_a of cyclohexanol? It is not on the table, but as it is an alcohol it is probably somewhere near that of ethanol (pK_a = 16). Likewise, we can use Table **2.7.1** to predict that para-hydroxyphenyl acetaldehyde, an intermediate compound in the biosynthesis of morphine, has a pK_a in the neighborhood of 10, close to that of our reference compound, phenol.



Notice in this example that we need to evaluate the potential acidity at *four* different locations on the molecule.



pK_a H^a ~ 10
pK_a H^b = not on table (not acidic)

pK_a H^c ~ 19

pK_a H^d = not on table (not acidic)

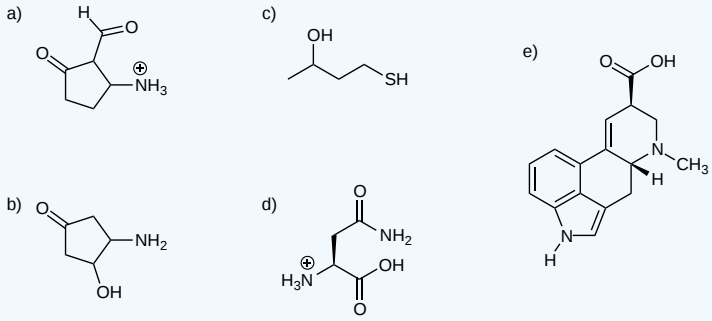
Aldehyde and aromatic protons are not at all acidic (pK_a values are above 40 – not on our table). The two protons on the carbon next to the carbonyl are slightly acidic, with pK_a values around 19-20 according to the table. The most acidic proton is on the phenol group, so if the compound were to be reacted with a single molar equivalent of strong base, this is the proton that would be donated first.

As you continue your study of organic chemistry, it will be a very good idea to commit to memory the approximate pK_a ranges of some important functional groups, including water, alcohols, phenols, ammonium, thiols, phosphates, carboxylic acids and carbons next to carbonyl groups (so-called a-carbons). These are the groups that you are most likely to see acting as acids or bases in biological organic reactions.

A word of caution: when using the pK_a table, be absolutely sure that you are considering the correct conjugate acid/base pair. If you are asked to say something about the basicity of ammonia (NH_3) compared to that of ethoxide ion ($CH_3CH_2O^-$), for example, the relevant pK_a values to consider are 9.2 (the pK_a of ammonium ion) and 16 (the pK_a of ethanol). From these numbers, you know that ethoxide is the stronger base. Do not make the mistake of using the pK_a value of 38: this is the pK_a of ammonia *acting as an acid*, and tells you how basic the NH_2^- ion is (very basic!)

EXAMPLE 2.7.1: ACIDIC GROUPS

Using the pK_a table, estimate pK_a values for the most acidic group on the compounds below, and draw the structure of the conjugate base that results when this group donates a proton. Use the pKa table above and/or from the Reference Tables.



Answer

a. The most acidic group is the protonated amine, pKa ~ 5-9

b. Alpha proton by the C=O group, pKa ~ 18-20

c. Thiol, pKa ~ 10

d. Carboxylic acid, pKa ~ 5

e. Carboxylic acid, pKa ~ 5

EXAMPLE 2.7.2

Acetic acid (CH_3COOH) is known to have a pK_a of 4.76. Please determine the Ka for acetic acid.

Solution

Solving for K_a algebraically you get the following:

$pK_a = -\text{Log}(K_a)$

$-pK_a = \text{Log}(K_a)$

$10^{-pK_a} = K_a$

Using a calculator first enter in the value for the pK_a (4.76). The make the number negative (-4.76). Next, use the inverse log function. All calculators are slightly different so this function may appear as: ANTILOG, INV LOG, or 10^X. Often it is the second function of the LOG button.

K_a for acetic acid = $10^{-pK_a} = 1.74 \times 10^{-5}$

EXERCISES

1. Write down an expression for the acidity constant of acetic acid, CH_3COOH.
2. The pK_a of acetic acid is 4.72; calculate its K_a.
3. The K_a of benzoic acid is 6.5×10^{-5}; determine its pK_a.
4. From your answers to the questions above, determine whether acetic acid or benzoic acid is stronger

ANSWERS

1. $K_a = \frac{[CH_3CO_2^-][H^+]}{[CH_3CO_2H]}$ or $K_a = \frac{[CH_3CO_2^-][H_3O^+]}{[CH_3CO_2H]}$
2. $pK_a = -\log_{10} K_a = 4.74$ Thus, $\log_{10} K_a = -4.72$ and K_a = anti-log$(-4.72) = 1.9 \times 10^{-5}$
3. $pK_a = -\log_{10} K_a = -\log_{10} 6.5 \times 10^{-5} = -(-4.19) = 4.19$
4. Benzoic acid is stronger than acetic acid. [Benzoic acid has a higher K_a and a lower pK_a.]

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2.8: PREDICTING ACID-BASE REACTIONS FROM PKA VALUES

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OBJECTIVE

After completing this section, you should be able to

- use pK_a values to calculate K_{eq}
- use pK_a values to predict the equilibrium direction of an acid-base reaction.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- pK_a

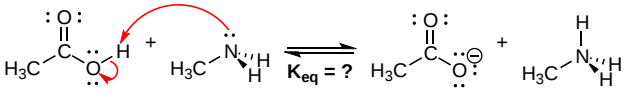
USING PK$_A$ VALUES TO PREDICT REACTION EQUILIBRIA

By definition, the pK_a value tells us the extent to which an acid will react with water as the base, but by extension, we can also calculate the equilibrium constant for a reaction between any acid-base pair. Mathematically, it can be shown that:

$$K_{eq} \text{ (for the acid base reaction in question)} = 10^{\Delta pKa}$$

where ΔpK_a is the pK_a of product acid minus pK_a of reactant acid

Consider a reaction between methylamine and acetic acid:



pK$_a$ = 4.8 (stronger acid)

pK$_a$ = 10.6

First, we need to identify the acid species on either side of the equation. On the left side, the acid is of course acetic acid, while on the right side the acid is methyl ammonium. The specific pK_a values for these acids are not on our very generalized pK_a table, but are given in the figure above. Without performing any calculations, you should be able to see that this equilibrium lies far to the right-hand side: acetic acid has a lower pK_a, is a stronger acid, and thus it wants to give up its proton more than methyl ammonium does. Doing the math, we see that

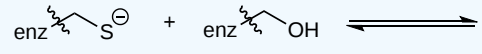
$$K_{eq} = 10^{\Delta pK_a} = 10^{10.6-4.8} = 10^{5.8} = 6.3 \times 10^5$$

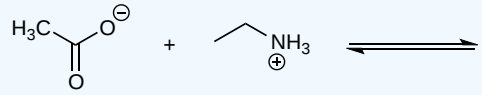
So K_{eq} is a very large number (much greater than 1) and the equilibrium lies far to the right-hand side of the equation, just as we had predicted.

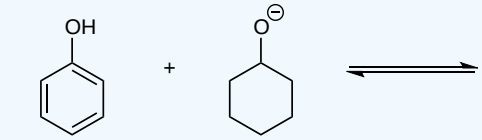
If you had just wanted to approximate an answer without bothering to look for a calculator, you could have noted that the difference in pK_a values is approximately 6, so the equilibrium constant should be somewhere in the order of 10^6, or one million. Using the pK_a table in this way, and making functional group-based pK_a approximations for molecules for which we don't have exact values, we can easily estimate the extent to which a given acid-base reaction will proceed.

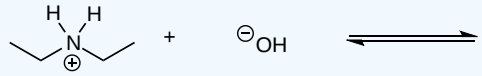
EXAMPLE 2.8.1

Show the products of the following acid-base reactions, and estimate the value of K_{eq}. Use the pK_a table from Section 2.8 and/or from the Reference Tables.

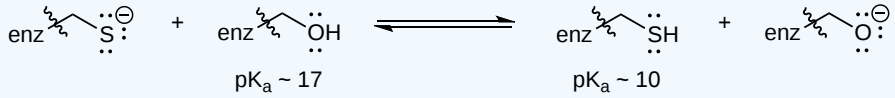
a) 

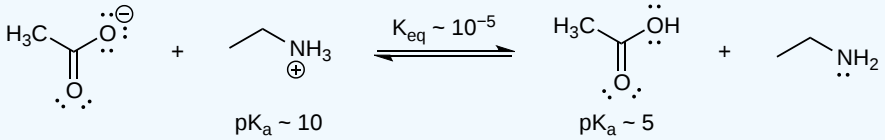
b) 

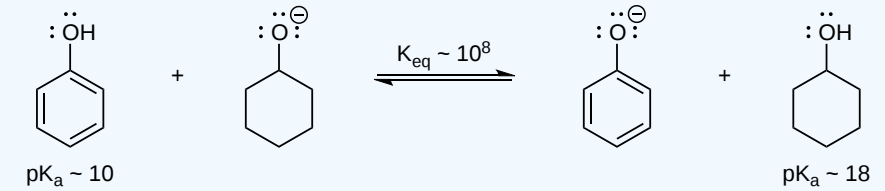
c) 

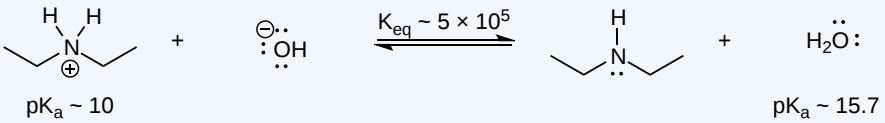
d) 

Answer

a) 

b) 

c) 

d) 

The pK_a of water is 14.0. Thus the K_{eq} for reaction d) is ~ 10^4.

EXERCISES

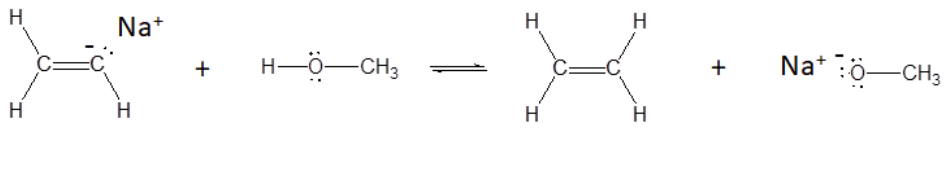
? EXERCISE 2.8.1

Use the pKa table from Section 2.8 and/or from the Reference Tables to determine if the following reactions would be expected to occur:

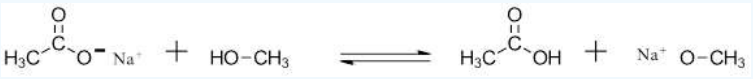
a) 

https://chem.libretexts.org/@go/page/31391

b)



c)



Answer

a) Yes - alkenes have pK_a values of ~35 while alkynes have pK_a values of ~25. This means that alkynes are more acidic and more likely to donate a proton.

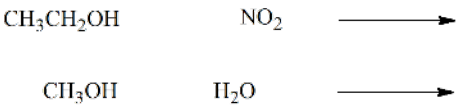
b) Yes - alkenes have pK_a values of ~35 while alcohols have pK_a values of ~16-18. This means that alcohols are more acidic and more likely to donate a proton.

c) No - carboxylic acids have pK_a values of ~4-5 while alcohols have pK_a values of ~16-18. This means that carboxylic acids are more acidic and more likely to donate a proton (so the reverse reaction would be expected to occur).

QUESTIONS

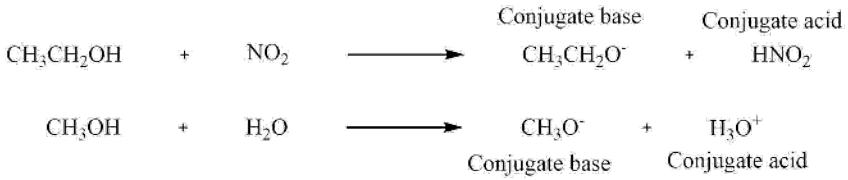
Q2.9.1

In the following reactions give the resulting products and label the conjugate acid and bases.



SOLUTIONS

S2.9.1



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2.9: ORGANIC ACIDS AND ORGANIC BASES

OBJECTIVE

After completing this section, you should be able to

- predict the relative acidity of two organic molecules from their structures.
- predict the relative basicity of two organic molecules from their structures.

This page explains the acidity of simple organic acids and looks at the factors which affect their relative strengths.

ORGANIC ACIDS AS WEAK ACIDS

For the purposes of this topic, we are going to take the definition of an acid as "a substance which donates hydrogen ions (protons) to other things". We are going to get a measure of this by looking at how easily the acids release hydrogen ions to water molecules when they are in solution in water.

An acid in solution sets up this equilibrium:

$$AH_{(aq)} + H_2O_{(l)} \rightleftharpoons A^-_{(aq)} + H_3O^+_{(aq)}$$

A hydronium ion is formed together with the anion (negative ion) from the acid. This equilibrium is sometimes simplified by leaving out the water to emphasize the ionization of the acid.

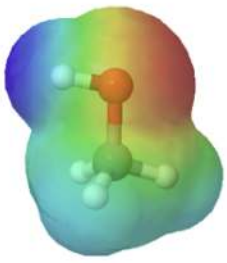
$$AH_{(aq)} \rightleftharpoons A^-_{(aq)} + H^+_{(aq)}$$

If you write it like this, you must include the state symbols - "(aq)". Writing $H^+_{(aq)}$ implies that the hydrogen ion is attached to a water molecule as H_3O^+. Hydrogen ions are always attached to something during chemical reactions.

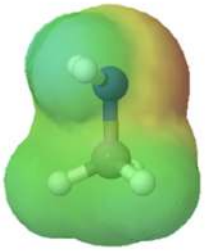
The organic acids are weak in the sense that this ionization is very incomplete. At any one time, most of the acid will be present in the solution as un-ionized molecules. For example, in the case of dilute ethanoic acid, the solution contains about 99% of ethanoic acid molecules - at any instant, only about 1% have actually ionized. The position of equilibrium therefore lies well to the left.

WEAK ACID POLARIZATION

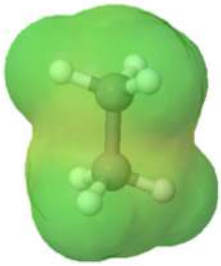
Organic acids can usually can be characterized in electrostatic potential maps by the presence of of a positively polarized hydrogen atom shown in blue. When looking at the maps below, methanol has a slightly polarized O-H bond and is considered very weakly acidic. The O-H bond in methyl amine is less polarized, as shown by the lighter blue color around the hydrogen, making it less acidic than methanol. However, the C-H bond in ethane lack virtually any polarity, as shown by the lack of a blue color, making it non-acidic. The following discussion will explain the difference in acidity of these and other organic molecules molecules.



methanol



methylamine



ethane

COMPARING THE STRENGTHS OF WEAK ACIDS

Acid strength is strongly correlated to stability of the conjugate base that will form by removing a proton. In order to analyze how acidic a molecule is likely to be, then you need to estimate the stability of its conjugate base.

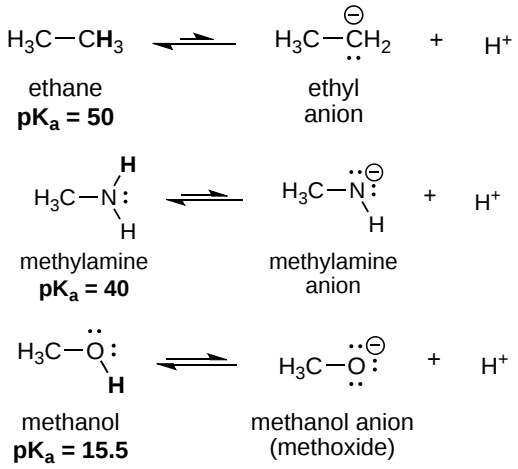
STABILIZATION OF THE CONJUGATE BASE - FOUR MAIN CONSIDERATIONS:

1. Size and electronegativity of the atom holding the charge
2. Can the charge be delocalized by resonance?
3. Are there any inductive effects?
4. Hybridization of orbital holding the charge

These considerations are listed in order of importance and are explained individually, but must be looked at collectively.

1. ***SIZE AND ELECTRONEGATIVITY EFFECTS IN ACIDITY***

When comparing elements, it depends on the positional relationship of the elements on the periodic table. When moving a period (aka across a row) of the main group elements, the valence electrons all occupy orbitals in the same shell. These electrons have comparable energy, so this factor does not help us discern differences relative stability. Differences in electronegativity are now the dominant factor. This trend is shown when comparing the pKa values of ethane, methyl amine, and methanol which reflects the relative electronegativities of the C < N < O. The key to understanding this trend is to consider the hypothetical conjugate base in each case*: the more stable the conjugate base, the stronger the acid*. In general, the more electronegative an atom, the better it is able to bear a negative charge. In the ethyl anion, the negative charge is borne by carbon, in the methylamine anion by nitrogen, and in the methoxide anion by an oxygen. Remember the periodic trend in electronegativity: it also increases as we move from left to right along a row, meaning that oxygen is the most electronegative of three elements being considered. This makes the negative charge on the methoxide anion the most stable of the three conjugate bases and methanol the strongest of the three acids. Likewise, carbon is the least electronegative making ethane the weakest of the three acids.



Within a Group (aka down a column) As we move down the periodic table, the electrons are occupying higher energy subshells creating a larger atomic size and volume. As the volume of an element increases, any negative charge present tends to become more spread out which decreases electron density and increases stability. The figure below shows spheres representing the atoms of the *s* and *p* blocks from the periodic table to scale, showing the two trends for the atomic radius.

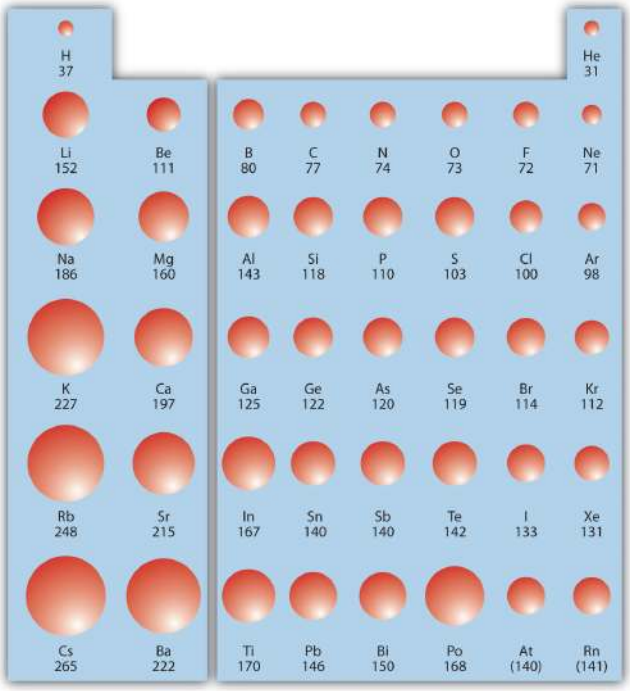
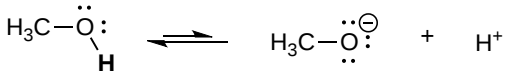
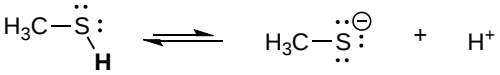


Figure **2.9.1**: Atomic Radii Trends on the Periodic Table. Although there are some reversals in the trend (e.g., see Po in the bottom row), atoms generally get smaller as you go across the periodic table and larger as you go down any one column. Numbers are the radii in pm.

This relationship of atomic size and electron density is illustrated when we compare the relative acidities of methanol, CH_3OH, with methanethiol, CH_3SH. The lower pKa value of 10.4 for methanethiol indicates that it is a stronger acid than methanol with a pKa value of 15.5. It is important to remember that neither compound is considered an acid. These relationships become useful when trying to deprotonate compounds to increase their chemical reactivity in non-aqueous reaction conditions.

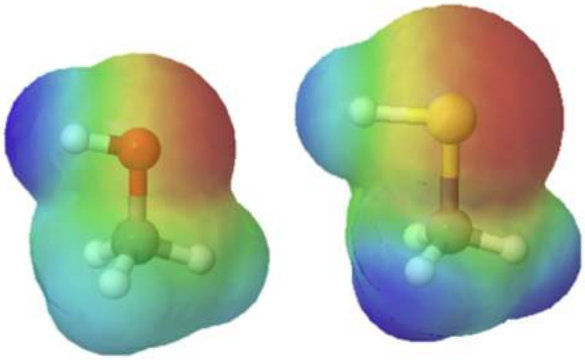


methanol
pK_a = 15.5

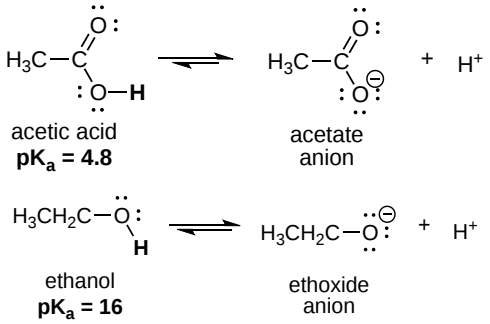


methanethiol
pK_a = 10.4

The difference in size can easily be seen when looking at the electrostatic potential maps for methanol (Left) and methanethiol (Right). The sulfur atom methanethiol is larger than the oxygen atom in methanol. The larger size of sulfur will be better able to delocalize and stabilize the negative charge in its conjugate base metanethiolate.



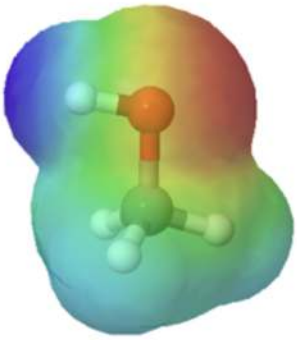
This section will focus on how the resonance structures of different organic groups contributes to their relative acidity even though the same element acts as the proton donor. When evaluating conjugate bases for the presence of resonance contributors, remember to look for movable electrons (lone pairs and pi bonding electrons). Delocalizing electrons over two or more atoms spreads out the electron density, increasing the stability of the conjugate base, and increasing the acidity of the corresponding acid. A classic example compares the relative acidity of ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups. Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different.

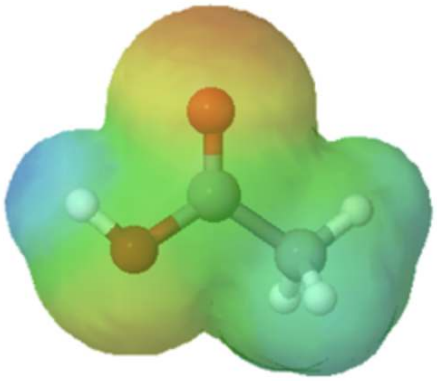


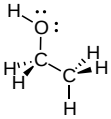
In both species, the negative charge on the conjugate base is held by an oxygen, so periodic trends cannot be invoked. For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is drawn on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy, according to our 'rules of resonance' (Section 2.5). What this means is that the negative charge on the acetate ion is not located on one oxygen or the other: rather it is shared between the two. Chemists use the term 'delocalization of charge' to describe this situation. In the ethoxide ion, by contrast, the negative charge is 'locked' on the single oxygen. This stabilization leads to a markedly increased acidity.

The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of nearly 12 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so we are talking about a difference of over 10^{12} between the acidity constants for the two molecules). The acetate ion is much more stable than the ethoxide ion, due to the effects of resonance delocalization.

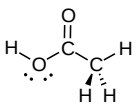
The effects of conjugation can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid as shown by its darker blue color.







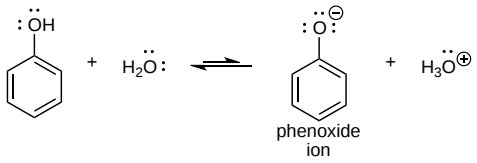
ethanol



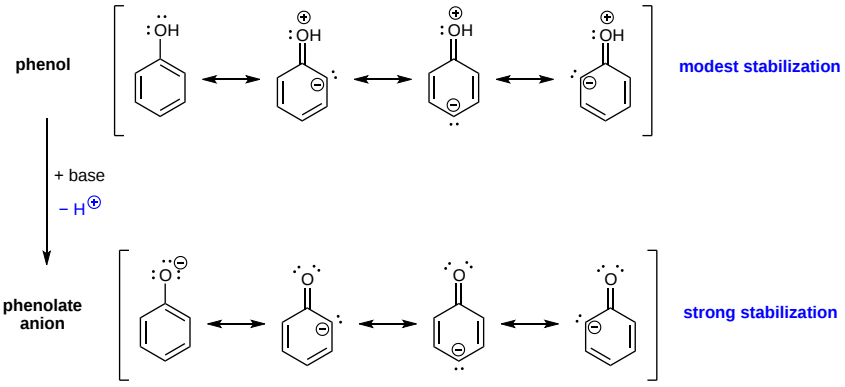
acetic acid

WHY IS PHENOL ACIDIC?

Compounds like alcohols and phenol which contain an -OH group attached to a hydrocarbon are very weak acids. Alcohols are so weakly acidic that, for normal lab purposes, their acidity can be virtually ignored. However, phenol is sufficiently acidic for it to have recognizably acidic properties - even if it is still a very weak acid. A hydrogen ion can break away from the -OH group and transfer to a base. For example, in aqueous solution:

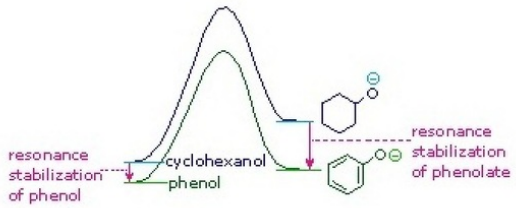


Since phenol is a very weak acid, the position of equilibrium lies well to the left. However, phenol can lose a hydrogen ion because the phenoxide ion (or phenolate ion - the two terms can be used interchangeably) formed is stabilized due to resonance. The negative charge on the oxygen atom is delocalized around the ring since one of the lone pairs on the oxygen atom can be in a p orbital and overlap with the pi electrons on the benzene ring.



This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion. Spreading the charge around makes the ion more stable than it would be if all the charge remained on the oxygen. However, oxygen is the most electronegative element in the ion and the delocalized electrons will be drawn towards it. That means that there will still be a lot of charge around the oxygen which will tend to attract the hydrogen ion back again. That is why phenol is only a very weak acid.

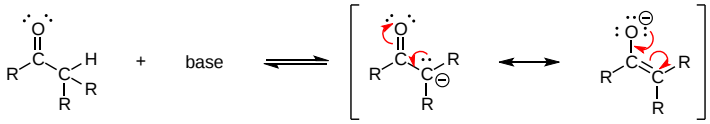
This explains why phenol is a much stronger acid than cyclohexanol. As can be seen in the following energy diagram, resonance stabilization is increased for the conjugate base of phenol vs. cyclohexanol after removal of a proton.



The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of contributors to the resonance hybrid. The contributing structures to the phenol hybrid all suffer charge separation, resulting in very modest stabilization of this compound. On the other hand, the phenolate anion is already charged, and the canonical contributors act to disperse the charge, resulting in a substantial stabilization of this species. The conjugate bases of simple alcohols are not stabilized by charge delocalization, so the acidity of these compounds is similar to that of water. An energy diagram showing the effect of resonance on cyclohexanol and phenol acidities is shown on the right. Since the resonance stabilization of the phenolate conjugate base is much greater than the stabilization of phenol itself, the acidity of phenol relative to cyclohexanol is increased. Supporting evidence that the phenolate negative charge is delocalized on the ortho and para carbons of the benzene ring comes from the influence of electron-withdrawing substituents at those sites.

ACIDITY OF HYDROGEN A (ALPHA) TO CARBONYL

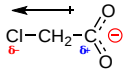
Alkyl hydrogen atoms bonded to a carbon atom in a α (alpha) position (directly adjacent) relative to a C=O group display unusual acidity. While the pKa values for alkyl C-H bonds in is typically on the order of 40-50, pKa values for these alpha hydrogens is more on the order of 19-20. This is almost exclusively due to the resonance stabilization of the product carbanion, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pKa for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25).



enolate ion

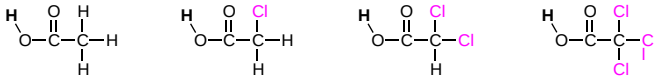
3. INDUCTIVE EFFECTS

The inductive effect is an experimentally observed effect of the transmission of charge through a chain of atoms in a molecule, resulting in a permanent dipole in a bond. For example, in a carboxylic acid group the presence of chlorine on adjacent carbons increases the acidity of the carboxylic acid group. A chlorine atom is more electronegative than hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. This further spreads out the electron density of the conjugate base, which has a stabilizing effect. In this context, the chlorine substituent is called an **electron-withdrawing group**. Notice that the pK_a-lowering effect of each chlorine atom, while significant, is not as dramatic as the delocalizing resonance effect illustrated by the difference in pK_a values between an alcohol and a carboxylic acid. In general, *resonance effects are more powerful than inductive effects*.



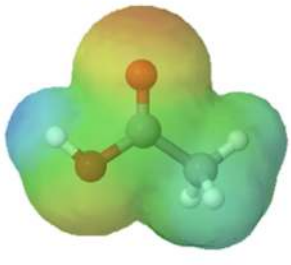
negative charge is delocalized by being pulled out onto chlorine atom

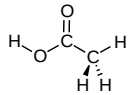
Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:



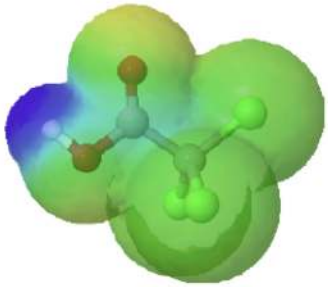
pK_a = 4.8 **pK_a = 2.8** **pK_a = 1.3** **pK_a = 0.64**

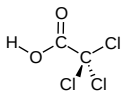
The inductive effects of chlorine can be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized as shown by the dark blue color. This illustrates that tricholoracetic acid is a much stronger acid than acetic acid.





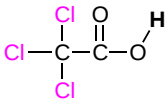
acetic acid



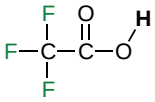


trichloroacetic acid

Because the inductive effect depends on electronegativity, fluorine substituents have a more pronounced pK_a-lowering effect than chlorine substituents.

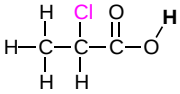


trichloroacetic acid
pK_a = 0.64

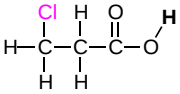


trifluoroacetic acid
pK_a = −0.25

In addition, the inductive takes place through covalent bonds, and its influence decreases markedly with distance – thus a chlorine two carbons away from a carboxylic acid group has a decreased effect compared to a chlorine just one carbon away. 2-chloropropanoic acid has a pK_a of 2.8 while for 3-chloropropanoic acid, the pK_a is 4.0.

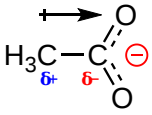


2-chloropropanoic acid
pK_a = 2.8
stronger acid



3-chloropropanoic acid
pK_a = 4.0

Alkyl groups (hydrocarbons) are weak inductive electron donators. In this case the inductive effect pushes electron density onto the conjugate base, causing the electron density to become more concentrated and producing a destabilizing effect.



more negative charge pushed towards already negative end

The inductive effects of alkyl groups causes a significant variation in the acidities of different carboxylic acids. Notice that the inductive effect drops off after the alkyl chain is about three carbons long.

	pK_a
HCOOH (Methanoic Acid or Formic Acid)	3.75
CH_3COOH (Ethanoic Acid or Acetic Acid)	4.76
CH_3CH_2COOH (Propanoic Acid)	4.87
$CH_3CH_2CH_2COOH$ (Butanoic Acid)	4.82

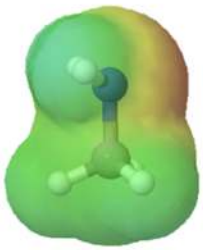
4. *ORBITAL HYBRIDIZATION*

The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals is $sp > sp^2 > sp^3$ since the percentage of s-character is decreasing as more p-orbitals are added to the hybrids. This trend indicates the sp hybridized orbitals are more stable with a negative charge than sp^3 hybridized orbitals. The table below shows how orbital hybridization influences relative acidity.

compound	conjugate base	hybridization	*s* character	pK_a	
		sp^3	25%	50	weakest acid
		sp^2	33%	44	↓
NH_3	$^{\ominus}NH_2$			36	↓
		sp	50%	25	↓
ROH	$RO^{\ominus}$			16	strongest acid

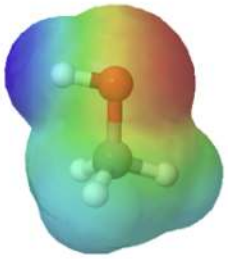
COMPARING THE STRENGTHS OF WEAK BASES

Technically, organic bases are characterized by the presence of an atom with lone pair electrons. These lone pairs contain a high electron density, which is shown red in the electrostatic potential maps, and can bond to H^+. Below are the maps of methanol, methyl amine, and acetone. All three compounds can be protonated with a sufficiently strong acid. Note, that all three of these compounds also have the ability to donate a proton when reacted with a strong enough base. Whether these compounds act as a acid or base depends on the conditions.



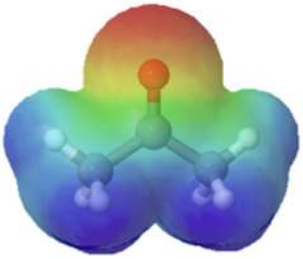


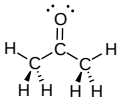
methylamine





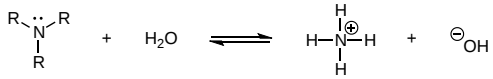
methanol



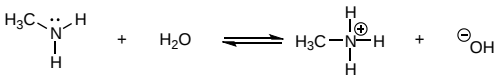


acetone

It is common to compare basicity's quantitatively by using the pK_a's of their conjugate acids rather than their pK_b's. Since $pK_a + pK_b = 14$, **the higher the pK_a the stronger the base**, in contrast to the usual inverse relationship of pK_a with acidity. Recall that ammonia (NH_3) acts as a base because the nitrogen atom has a lone pair of electrons that can accept a proton. The conjugate acid of most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their water solutions are basic (have a pH of 11 to 12, depending on concentration). This can be illustrated by the reaction below where an amine removes a proton from water to form substituted ammonium (e.g. NH_4^+) ions and hydroxide (OH^-) ions:



Amines are one of the only neutral functional groups which are considered basic. This is a direct consequence of the presence of the unshared electron pair on the nitrogen. The unshared electron pair is less tightly held by the nitrogen of an amine than the corresponding oxygen of an alcohol, which makes it more available to act as a base. As a specific example, methylamine reacts with water to form the methylammonium ion and the OH^- ion.



EXAMPLE: AMMONIA

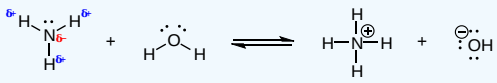
All of the have similarities to ammonia and so we'll start by looking at the reason for its basic properties. For the purposes of this topic, we are going to take the definition of a base as "a substance which combines with hydrogen ions (protons)". We are going to get a measure of this by looking at how easily the bases take hydrogen ions from water molecules when they are in solution in water.

Ammonia in solution sets up this equilibrium:

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^- \tag{2.10.1}$$

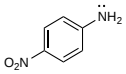
An ammonium ion is formed together with hydroxide ions. Because the ammonia is only a weak base, it doesn't hang on to the extra hydrogen ion very effectively and so the reaction is reversible. At any one time, about 99% of the ammonia is present as unreacted molecules. The position of equilibrium lies well to the left.

The ammonia reacts as a base because of the active lone pair on the nitrogen. Nitrogen is more electronegative than hydrogen and so attracts the bonding electrons in the ammonia molecule towards itself. That means that in addition to the lone pair, there is a build-up of negative charge around the nitrogen atom. That combination of extra negativity and active lone pair attracts the new hydrogen from the water.



When looking at the table below, it is clear that the basicity of nitrogen containing compounds is greatly influenced by their structures. The variance in the basicity of these compounds can mostly be explained by the effects of electron delocalization discussed above.

Table **2.9.1**: pKa of conjugate acids of a series of amines.

Compound										
pK_a	11.0	10.7	10.7	9.3	5.2	4.6	1.0	0.0	-1.0	-10.0

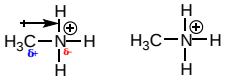
INDUCTIVE EFFECTS IN NITROGEN BASICITY

Alkylamines are more basic than ammonia since alkyl groups donate electrons to the more electronegative nitrogen. This inductive effect makes the electron density on the alkylamine nitrogen greater than the nitrogen of ammonium. That means that there will be a small amount of extra negative charge built up on the nitrogen atom. That extra negativity around the nitrogen makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



methyl group pushes electron density toward the nitrogen, making it more basic

Making the nitrogen more negative helps the lone pair to pick up a hydrogen ion. What about the effect on the positive methylammonium ion formed? Is this more stable than a simple ammonium ion? Compare the methylammonium ion with an ammonium ion:



CH_3 group pushes electron density toward nitrogen

In the methylammonium ion, the positive charge is spread around the ion by the "electron-pushing" effect of the methyl group. The more you can spread charge around, the more stable an ion becomes. In the ammonium ion there is not any way of spreading the charge.

To summarize:

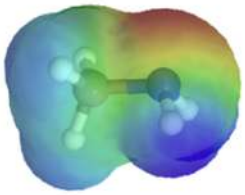
- The nitrogen is more negative in methylamine than in ammonia, and so it picks up a hydrogen ion more readily.
- The ion formed from methylamine is more stable than the one formed from ammonia, and so is less likely to shed the hydrogen ion again.

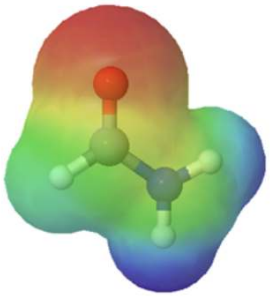
Taken together, these mean that methylamine is a stronger base than ammonia.

Compound	pK_a
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

RESONANCE EFFECTS IN NITROGEN BASICITY

The resonance effect also explains why a nitrogen atom is basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the lone pair of electrons in an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The lone pair is stabilized by resonance delocalization. Here's another way to think about it: the lone pair on an amide nitrogen is not available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map show the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost completely shifted towards the oxygen. This greatly decreases the basicity of the lone pair electrons on the nitrogen in an amide.





amine

pK_a of conjugate acid ~ 11

amide

pK_a of conjugate acid ~ −1

Aniline, the amine analog of phenol, is substantially less basic than an amine (as evidenced by the pK_a of the conjugate acids).



cyclohexylamine

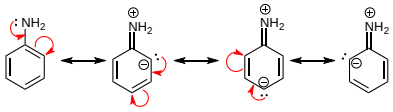
pK_a of conjugate acid ~ 10



aniline

pK_a of conjugate acid ~ 5

We can use the same reasoning that we used when comparing the acidity of a phenol to that of an alcohol. In aniline, the lone pair on the nitrogen atom is stabilized by resonance with the aromatic pi system, making it less available for bonding and thus less basic.



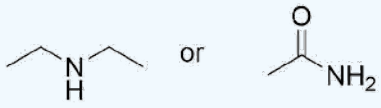
lone pair is stabilized through resonance

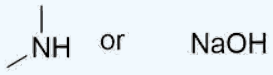
In these cases, you seem to be breaking the same oxygen-hydrogen bond each time, and so you might expect the strengths to be similar. The most important factor in determining the relative acid strengths of these molecules is the nature of the ions formed. You always get a hydronium ion - so that's constant - but the nature of the anion (the negative ion) varies markedly from case to case.

EXERCISES

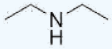
? EXERCISE 2.9.1

Select the more basic from each of the following pairs of compounds.

(a) 

(b) 

Answer

a)  The lone pair of electrons on the amide nitrogen are less available to react with a proton.

(b) NaOH -- The hydroxide has a negative charge with three lone pairs of electrons that can react with a proton.

? EXERCISE 2.9.2

The 4-methylbenzylammonium ion has a pK_a of 9.51, and the butylammonium ion has a pK_a of 10.59. Which is more basic? What's the pK_b for each compound?

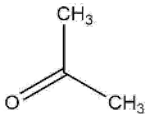
Answer

The butylammonium is more basic. Remember that $pK_a + pK_b = 14$. The pK_b for butylammonium is 3.41, the pK_b for 4-methylbenzylammonium is 4.49.

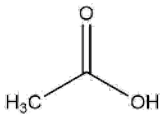
QUESTIONS

Q2.10.1

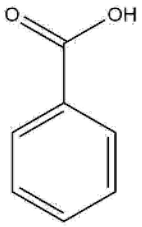
Determine which of the one of the molecules is an acid or a base.



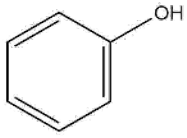
1



2



3



4

SOLUTIONS

S2.10.1

1 = Base

2 = Acid

3 = Acid

4 = Acid

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2.10: ACIDS AND BASES - THE LEWIS DEFINITION

OBJECTIVES

After completing this section, you should be able to

1. state the Lewis definition of an acid and a base.
2. identify a given compound as being a Lewis acid or Lewis base, given its Lewis structure or its Kekulé structure.
3. identify an organic molecule or ion in a reaction as either an electrophile or nucleophile.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Lewis acid
- Lewis base
- Electrophile
- Nucleophile

STUDY NOTES

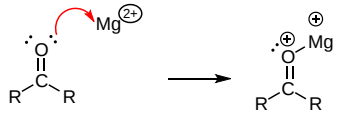
The Lewis concept of acidity and basicity will be of great use to you when you study reaction mechanisms. The realization that an ion such as



is electron deficient, and is therefore a Lewis acid, should help you understand why this ion reacts with substances which are Lewis bases (e.g., H_2O).

INTRODUCTION TO LEWIS ACID-BASE THEORY

The Brønsted acid-base theory has been used throughout the history of acid and base chemistry. However, this theory is very restrictive and focuses primarily on acids and bases acting as proton donors and acceptors. Sometimes conditions arise where the theory doesn't necessarily fit, such as in solids and gases. In 1923, G.N. Lewis from UC Berkeley proposed an alternate theory to describe acids and bases. His theory gave a generalized explanation of acids and bases based on structure and bonding. Through the use of the Lewis definition of acids and bases, chemists are now able to predict a wider variety of acid-base reactions. Lewis' theory used electrons instead of proton transfer and specifically stated that an acid is a species that accepts an electron pair while a base donates an electron pair.



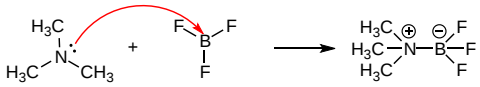
Example of Lewis base (oxygen atom from carbonyl) reacting with Lewis Acid (Mg^{2+} ion).

The reaction of a Lewis acid and a Lewis base will produce a coordinate covalent bond. A coordinate covalent bond is just a type of covalent bond in which one reactant donates both electrons to form the bond. In this case the Lewis base donates its electrons to form a bond to the Lewis acid. The resulting product is called an addition compound, or more commonly a complex. The electron-pair flow from Lewis base to Lewis acid is shown using curved arrows much like those used for resonance structures in Section 2.5. Curved arrows always mean that an electron pair moves from the atom at the tail of the arrow to the atom at the head of the arrow. In this case the lone pair on the Lewis base attacks the Lewis acid forming a bond. This new type of electron pair movement, along with those described in Section 2.5 will be used throughout this text to describe electron flow during reactions.

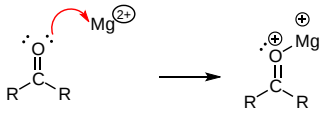
- Lewis Acid: a species that accepts an electron pair and will typically either have vacant orbitals or a polar bond involving hydrogen such that it can donate H^+ (which has an empty 1s orbital)
- Lewis Base: a species that donates an electron pair and will have lone-pair electrons of pi bonding electrons.

LEWIS ACIDS

Neutral compounds of boron, aluminum, and the other Group 13 elements, (BF_3, $AlCl_3$), which possess only six valence electrons, have a very strong tendency to gain an additional electron pair. Because these compounds are only surrounded by three electron groups, they are sp^2 hybridized, contained a vacant p orbital, and are potent Lewis acids. Trimethylamine's lone pair elections are contained in an sp^3 hybrid orbital making it a Lewis base. These two orbitals overlap, creating a covalent bond in a boron trifluoride-trimethylamine complex. The movement of electrons during this interaction is show by by an arrow.



Positive ions are often Lewis acids because they have an electrostatic attraction for electron donors. Examples include alkali and alkaline earth metals in the group IA and IIA columns. K^+, Mg^{2+} and Ca^{2+} are sometimes seen as Lewis acidic sites in biology, for example. These ions are very stable forms of these elements because of their low electron ionization potentials. However, their positive charges do attract electron donors.The interaction between a magnesium cation (Mg^{+2}) and a carbonyl oxygen is a common example of a Lewis acid-base reaction. The carbonyl oxygen (the Lewis base) donates a pair of electrons to the magnesium cation (the Lewis acid). As we will see in Chapter 19 when we begin the study of reactions involving carbonyl groups, this interaction has the very important effect of increasing the polarity of the carbon-oxygen double bond.



The eight-electron rule does not hold throughout the periodic table. In order to obtain noble gas configurations, some atoms may need eighteen electrons in their valence shell. Transition metals such as titanium, iron and nickel may have up to eighteen electrons and can frequently accept electron pairs from Lewis bases. Transition metals are often Lewis acids. For example, titanium has four valence electrons and can form four bonds in compounds such as titanium tetrakis (isopropoxide), below, or titanium tetrachloride, $TiCl_4$. However, the titanium atom in that compound has only eight valence electrons, not eighteen. It can easily accept electrons from donors.

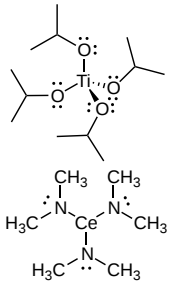


Figure **2.10.1**: *Although titanium has eight electrons in this molecule, titanium tetrakis(isopropoxide), it can accommodate up to eighteen. It is a Lewis acid. The cerium atom in cerium tris(dimethylamide) comes from a similar part of the periodic table and is also a Lewis acid.*

For example, when THF and $TiCl_4$ are combined, a Lewis acid-base complex is formed, $TiCl_4(THF)_2$. $TiCl_4(THF)_2$ is a yellow solid at room temperature.

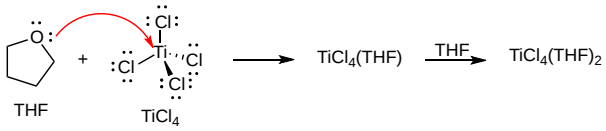
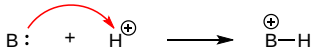


Figure **2.10.2**: *A Lewis acid-base complex between tetrahydrofuran (THF) and titanium tetrachloride.*

THE PROTON AS A COMMON LEWIS ACID

Perhaps the most common example of a Lewis acid is also the simplest. It is the hydrogen cation (H^+) or proton. It is called a proton because, in most hydrogen atoms, the only particle in the nucleus is a proton. If an electron is removed to make a cation, a proton is all that is left. A proton is a Lewis acid for a number of reasons. It has a positive charge, and so it will attract electrons, which are negative. Also, it lacks the electron configuration of its noble gas neighbor, helium. Helium has two electrons. If a Lewis base or nucleophile donates a pair of electrons to a proton, the proton will obtain a helium noble gas configuration.



B = base

Figure **2.10.3**: *Proton reacting as a Lewis acid.*

There is something about hydrogen cations that is not so simple, however. They are actually not so common. Instead, protons are generally always bound to a Lewis base. Hydrogen is almost always covalently (or coordinately) bonded to another atom. Many of the other elements commonly found in compounds with hydrogen are more electronegative than hydrogen. As a result, hydrogen often has a partial positive charge making is still act as a Lewis Acid.

A acid-base reaction involving protons might better be expressed as:

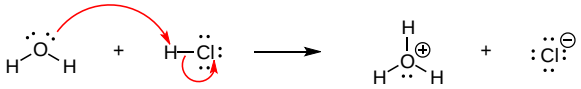


Figure **2.10.4**: *Proton transfer from one site to another.*

The Lewis acid-base interactions we have looked at so far are slightly different here. Instead of two compounds coming together and forming a bond, we have one Lewis base replacing another at a proton. Two specific movements of electrons are shown in the reaction both of which are show by arrows. Lone pair electrons on oxygen attack the hydrogen to form an O-H bond in the product. Also, the electrons of the H-Cl bond move to become a lone pair on chlorine as the H-Cl bond breaks. These two arrows together are said to represent the mechanism of this acid-base reaction.

LEWIS BASES

What makes a molecule (or an atom or ion) a Lewis base? It must have a pair of electrons available to share with another atom to form a bond. The most readily available electrons are those that are not already in bonds. Bonding electrons are low in energy. Non-bonding electrons are higher in energy and may be stabilized when they are delocalized in a new bond. Lewis bases usually have non-bonding electrons or lone pairs this makes oxygen and nitrogen compounds common Lewis bases. Lewis bases may be anionic or neutral. The basic requirement is that they have a pair of electrons to donate.

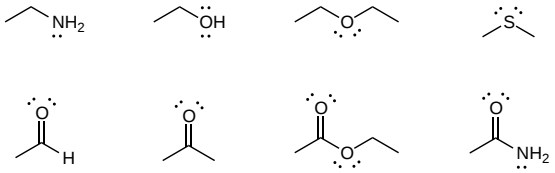
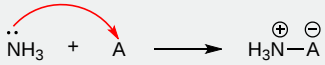


Figure **2.10.5**: Some common organic examples of Lewis bases. Most oxygen, nitrogen and sulfur containing compounds can act as Lewis Bases.

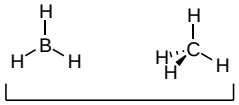
NOTE 1: AMMONIA

Ammonia, NH_3, has a lone pair and is a Lewis base. It can donate to compounds that will accept electrons.



Ammonia donating to an electron acceptor or Lewis acid.

Not all compounds can act as a Lewis base. For example, methane, CH_4, has all of its valence electrons in bonding pairs. These bonding pairs are too stable to donate under normal conditions therefore methane is not a Lewis base. Neutral boron compounds also have all electrons in bonding pairs. For example, borane, BH_3 has no lone pairs; all its valence electrons are in bonds. Boron compounds are not typically Lewis bases.



no lone pairs to donate

Figure **2.10.6**: *Carbon and boron compounds with all sigma bonds do not have lone pairs, and do not act as Lewis bases.*

EXERCISE 2.10.1

Which of the following compounds would you expect to be Lewis bases?

a) SiH_4 b) AlH_3 c) PH_3 d) SH_2 e) ^-SH

Answer

a) No, silicon has 4 valence electrons (like carbon) and all 4 are involved in sigma bonds

b) No, aluminum has 3 valence electrons and all 3 are involved in sigma bonds

c) Yes, phosphorus has 5 valence electrons, so there is one lone pair available

d) Yes, sulfur has 6 valence electrons, so there are two lone pairs available

e) Yes, this ion has 3 lone pairs available

LEWIS ACID-BASE COMPLEXES

What happens when a Lewis base donates a pair of electrons to a Lewis acid? The electron pushing formalism (arrows) we have been using to illustrate the behavior of Lewis acids and Lewis bases is meant to show the direction of electron movement from the donor to the acceptor. However, given that a bond can be thought of as a pair of electrons that are shared between two atoms (in this case, between the donor and the acceptor), these arrows also show where bonds are forming.

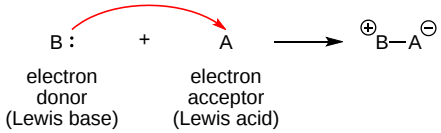


Figure **2.10.7**: Donation of electrons from a Lewis base to a Lewis acid.

The electrons donated from a Lewis base to a Lewis acid form a new bond. A new, larger compound is formed from the smaller Lewis acid and Lewis base. This compound is called a Lewis acid-base complex. A simple example of Lewis acid-base complexation involves ammonia and boron trifluoride. The nitrogen atom has a lone pair and is an electron donor. The boron has no octet and is an electron acceptor. The two compounds can form a Lewis acid-base complex or a coordination complex together.

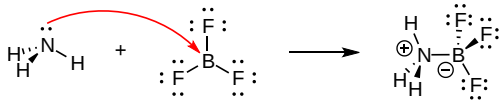


Figure **2.10.8**: *Formation of a Lewis acid-base complex from ammonia and boron trifluoride.*

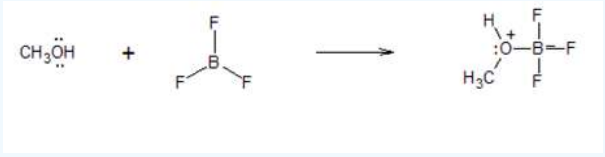
When the nitrogen donates a pair of electrons to share with the boron, the bond that forms is sometimes called a coordinate bond. A coordinate bond is any covalent bond that arose because one atom brought a pair of its electrons and donated them to another.

In organic chemistry terminology, the electron donor is called a **nucleophile** and the electron acceptor is called an **electrophile**. Ammonia is a nucleophile and boron trifluoride is an electrophile.

- Because Lewis bases are attracted to electron-deficient atoms, and because positive charge is generally associated with the nucleus of an atom, Lewis bases are sometimes refered to as "nucleophiles". Nucleophile means nucleus-loving.
- Because Lewis acids attract electron pairs, Lewis acids are sometimes called "electrophiles". Electrophile means electron-loving.

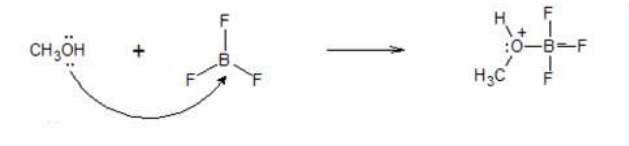
EXERCISE 2.10.2

For the following reaction, add curved arrows (electron pushing formalism) to indicate the electron flow.



Answer

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EXERCISE 2.10.3

A Lewis acid-base complex is formed between THF (tetrahyrofuran) and borane, BH_3.

a) Which compound is the Lewis acid? Which one is the Lewis base?

b) Which atom in the Lewis acid is the acidic site? Why?

c) Which atom in the Lewis base is the basic site? Why?

d) How many donors would be needed to satisfy the acidic site?

e) Show, using arrow notation, the reaction to form a Lewis acid-base complex.

f) Borane is highly pyrophoric; it reacts violently with air, bursting into flames. Show, using arrow notation, what might be happening when borane contacts the air.

g) Borane-THF complex is much less pyrophoric than borane. Why do you suppose that is so?

Add exercises text here.

Answer

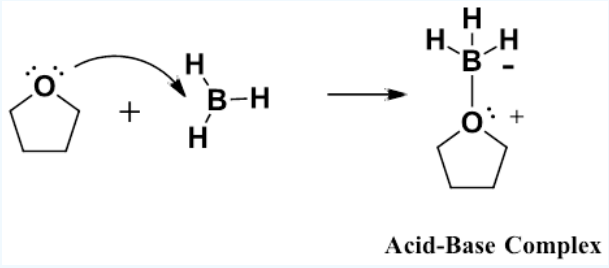
a) Borane is the Lewis acid. THF has lone pair electrons so it is the Lewis base.

b) The Boron atom has an unfilled octet so it has an empty p orbital that can accept electrons.

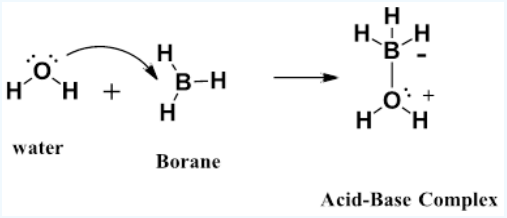
c) The oxygen atom in THF has lone pair electrons contained in a sp^3 hybridized orbital.

d) The boron in borane has six electrons around it so it would only need one lone pair donor to reach an octet.

e) Show, using arrow notation, the reaction to form a Lewis acid-base complex.



f) The Borane initially reacts with water in air.



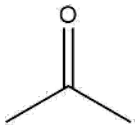
g) After the Borane-THF complex is formed, the boron atom has a complete octet making it less reactive.

EXERCISES

QUESTIONS

Q2.11.1

For the following molecules state wither they are Lewis acid or base and wither or not they are a Brønsted acid or base.



NH_4^+

SOLUTIONS

S2.11.1

Acetone is a Lewis base and a Brønsted base. Ammonium cation is both a Lewis acid and a weak Brønsted acid.

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2.11: NONCOVALENT INTERACTIONS BETWEEN MOLECULES

OBJECTIVES

After completing this section, you should be able to

1. identify the various intermolecular forces that may be at play in a given organic compound.
2. describe how intermolecular forces influence the physical properties, 3-dimensional shape and structure of compounds.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- dipole-dipole forces
- London dispersion forces
- hydrogen bond
- intermolecular forces
- noncovalent interaction
- van der Waals forces

STUDY NOTES

Much of the material in this section should be familiar to you from your pre-requisite general chemistry course. Nonetheless, this section is important, as it covers some of the fundamental factors that influence many physical and chemical properties.

INTRODUCTION

The properties of liquids are intermediate between those of gases and solids, but are more similar to solids. In contrast to *intra*molecular forces, such as the covalent bonds that hold atoms together in molecules and polyatomic ions, *inter*molecular forces hold molecules together in a liquid or solid. Intermolecular forces are generally much weaker than covalent bonds. For example, it requires 927 kJ to overcome the intramolecular forces and break both O–H bonds in 1 mol of water, but it takes only about 41 kJ to overcome the intermolecular attractions and convert 1 mol of liquid water to water vapor at 100°C. (Despite this seemingly low value, the intermolecular forces in liquid water are among the strongest such forces known!) Given the large difference in the strengths of intra- and intermolecular forces, changes between the solid, liquid, and gaseous states almost invariably occur for molecular substances *without breaking covalent bonds*.

NOTE

The properties of liquids are intermediate between those of gases and solids but are more similar to solids.

Intermolecular forces determine bulk properties such as the melting points of solids and the boiling points of liquids. Liquids boil when the molecules have enough thermal energy to overcome the intermolecular attractive forces that hold them together, thereby forming bubbles of vapor within the liquid. Similarly, solids melt when the molecules acquire enough thermal energy to overcome the intermolecular forces that lock them into place in the solid.

Intermolecular forces are electrostatic in nature; that is, they arise from the interaction between positively and negatively charged species. Like covalent and ionic bonds, intermolecular interactions are the sum of both attractive and repulsive components. Because electrostatic interactions fall off rapidly with increasing distance between molecules, intermolecular interactions are most important for solids and liquids, where the molecules are close together. These interactions become important for gases only at very high pressures, where they are responsible for the observed deviations from the ideal gas law.

In this section, we explicitly consider three kinds of intermolecular interactions: dipole-dipole forces, dispersion forces, and hydrogen bonds. These intermolecular interactions are also called van der Waals forces or noncovalent interactions. There are two additional types of electrostatic interaction that you are already familiar with: the ion–ion interactions that are responsible for ionic bonding and the ion–dipole interactions that occur when ionic substances dissolve in a polar substance such as water. These are less common with organic molecules, so will not be described further in this section.

DIPOLE–DIPOLE INTERACTIONS

Polar covalent bonds behave as if the bonded atoms have localized fractional charges that are equal but opposite (i.e., the two bonded atoms generate a *dipole*). If the structure of a molecule is such that the individual bond dipoles do not cancel one another, then the molecule has a net dipole moment. Molecules with net dipole moments tend to align themselves so that the positive end of one dipole is near the negative end of another and vice versa, as shown in Figure 2.12.1 parts (a and b). Arrangements in which two positive or two negative ends are adjacent (parts (c and d) in Figure 2.12.1) are higher energy as the similar charges would repel one another. Hence dipole–dipole interactions, such as those in parts (a and b) in Figure 2.12.1, are *attractive intermolecular interactions*, whereas those in part (c and d) are *repulsive intermolecular interactions*.

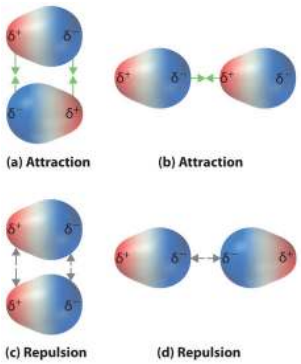


Figure 2.12.1 Attractive and Repulsive Dipole–Dipole Interactions. (a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions.

Because molecules in a liquid move freely and continuously, molecules always experience both attractive and repulsive dipole–dipole interactions simultaneously, as shown in Figure 2.12.2. On average, however, the attractive interactions dominate.

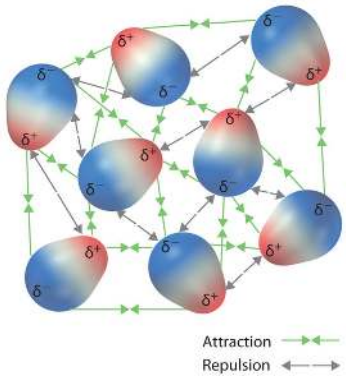
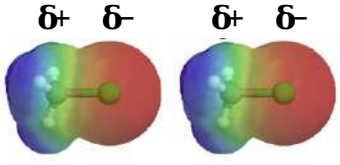


Figure 2.12.2 Both Attractive and Repulsive Dipole–Dipole Interactions Occur in a Liquid Sample with Many Molecules

Chloromethane is an example of a polar molecule. An electrostatic potential map shows a high electron density (seen in red) around the electronegative chlorine giving it a partial negative charge. The other end of the molecule has electron density pulled away from it giving it a partial positive charge seen in blue. The positive and negative ends of different chloromethane molecules are attracted to one another through this electrostatic interaction.





chloromethane

(μ = 1.87 D)

Because each end of a dipole possesses only a fraction of the charge of an electron, dipole–dipole interactions are substantially weaker than the interactions between two ions, each of which has a charge of at least ±1, or between a dipole and an ion, in which one of the species has

at least a full positive or negative charge. In addition, the attractive interaction between dipoles falls off much more rapidly with increasing distance than do ion–ion interactions. Recall that the attractive energy between two ions is proportional to $1/r$, where r is the distance between the ions. Doubling the distance ($r \rightarrow 2r$) decreases the attractive energy by one-half. In contrast, the energy of the interaction of two dipoles is proportional to $1/r^6$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^6, or 64-fold. Thus a substance such as HCl, which is partially held together by dipole–dipole interactions, is a gas at room temperature and 1 atm pressure, whereas NaCl, which is held together by ionic interactions, is a high-melting-point solid. Within a series of compounds of similar molar mass, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, as shown in Table 2.12.1. Using what we learned about predicting relative bond polarities from the electronegativities of the bonded atoms, we can make educated guesses about the relative boiling points of similar molecules.

Table 2.12.1: Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

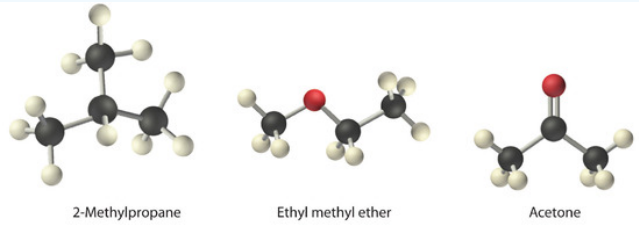
Compound	Molar Mass (g/mol)	Dipole Moment (D)	Boiling Point (K)
C_3H_6 (cyclopropane)	42	0	240
CH_3OCH_3 (dimethyl ether)	46	1.30	248
CH_3CN (acetonitrile)	41	3.9	355

NOTE

The attractive energy between two ions is proportional to $1/r$, whereas the attractive energy between two dipoles is proportional to $1/r^6$.

EXAMPLE 2.12.1

Arrange ethyl methyl ether ($CH_3OCH_2CH_3$), 2-methylpropane [isobutane, $(CH_3)_2CHCH_3$], and acetone (CH_3COCH_3) in order of increasing boiling points. Their structures are as follows:



Strategy:

Compare the molar masses and the polarities of the compounds. Compounds with higher molar masses and that are polar will have the highest boiling points.

Solution:

The three compounds have essentially the same molar mass (58–60 g/mol), so we must look at differences in polarity to predict the strength of the intermolecular dipole–dipole interactions and thus the boiling points of the compounds. The first compound, 2-methylpropane, contains only C–H bonds, which are not very polar because C and H have similar electronegativity values. It should therefore have a very small (but nonzero) dipole moment and a very low boiling point. Ethyl methyl ether has a structure similar to H_2O; it contains two polar C–O single bonds oriented at about a 109° angle to each other, in addition to relatively nonpolar C–H bonds. As a result, the C–O bond dipoles partially reinforce one another and generate a significant dipole moment that should give a moderately high boiling point. Acetone contains a polar C=O double bond oriented at about 120° to two methyl groups with nonpolar C–H bonds. The C–O bond dipole therefore corresponds to the molecular dipole, which should result in both a rather large dipole moment and a high boiling point. Thus we predict the following order of boiling points: 2-methylpropane < ethyl methyl ether < acetone. This result is in good agreement with the actual data: 2-methylpropane, boiling point = −11.7°C, and the dipole moment (μ) = 0.13 D; methyl ethyl ether, boiling point = 7.4°C and μ = 1.17 D; acetone, boiling point = 56.1°C and μ = 2.88 D.

EXERCISE 2.11.1

Arrange carbon tetrafluoride (CF_4), ethyl methyl sulfide ($CH_3SC_2H_5$), dimethyl sulfoxide [$(CH_3)_2S{=}O$], and 2-methylbutane [isopentane, $(CH_3)_2CHCH_2CH_3$] in order of decreasing boiling points.

Answer

dimethyl sulfoxide (boiling point = 189.9°C) > ethyl methyl sulfide (boiling point = 67°C) > 2-methylbutane (boiling point = 27.8°C) > carbon tetrafluoride (boiling point = −128°C)

LONDON DISPERSION FORCES

Thus far we have considered only interactions between polar molecules, but other factors must be considered to explain why many nonpolar molecules, such as bromine, benzene, and hexane, are liquids at room temperature, and others, such as iodine and naphthalene, are solids. Even the noble gases can be liquefied or solidified at low temperatures, high pressures, or both.

What kind of attractive forces can exist between nonpolar molecules or atoms? This question was answered by Fritz London (1900–1954), a German physicist who later worked in the United States. In 1930, London proposed that temporary fluctuations in the electron distributions within atoms and nonpolar molecules could result in the formation of short-lived instantaneous dipole moments, which produce attractive forces called London dispersion forces between otherwise nonpolar substances.

Table 2.12.2: Normal Melting and Boiling Points of Some Elements and Nonpolar Compounds

Substance	Molar Mass (g/mol)	Melting Point (°C)	Boiling Point (°C)
Ar	40	−189.4	−185.9
Xe	131	−111.8	−108.1
N_2	28	−210	−195.8
O_2	32	−218.8	−183.0
F_2	38	−219.7	−188.1
I_2	254	113.7	184.4
CH_4	16	−182.5	−161.5

Consider a pair of adjacent He atoms, for example. On average, the two electrons in each He atom are uniformly distributed around the nucleus. Because the electrons are in constant motion, however, their distribution in one atom is likely to be asymmetrical at any given instant, resulting in an instantaneous dipole moment. As shown in part (a) in Figure 2.12.3, the instantaneous dipole moment on one atom can interact with the electrons in an adjacent atom, pulling them toward the positive end of the instantaneous dipole or repelling them from the negative end. The net effect is that the first atom causes the temporary formation of a dipole, called an induced dipole, in the second. Interactions between these temporary dipoles cause atoms to be attracted to one another. These attractive interactions are weak and fall off rapidly with increasing distance. London was able to show with quantum mechanics that the attractive energy between molecules due to temporary dipole–induced dipole interactions falls off as $1/r^6$. Doubling the distance therefore decreases the attractive energy by 2^6, or 64-fold.

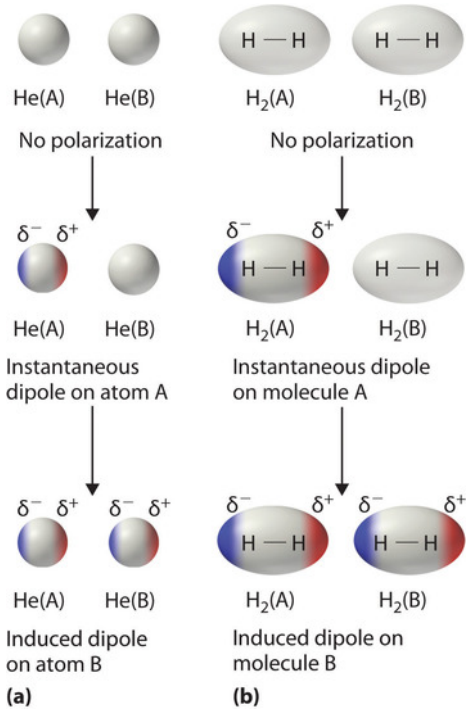


Figure 2.12.3 Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

Instantaneous dipole–induced dipole interactions between nonpolar molecules can produce intermolecular attractions just as they produce interatomic attractions in monatomic substances like Xe. This effect, illustrated for two H_2 molecules in part (b) in Figure 2.12.3, tends to become more pronounced as atomic and molecular masses increase (Table 2.12.3). For example, Xe boils at −108.1°C, whereas He boils at −269°C. The reason for this trend is that the strength of London dispersion forces is related to the ease with which the electron distribution in a given atom can be perturbed. In small atoms such as He, the two 1*s* electrons are held close to the nucleus in a very small volume, and electron–electron repulsions are strong enough to prevent significant asymmetry in their distribution. In larger atoms such as Xe, however, the outer electrons are much less strongly attracted to the nucleus because of filled intervening shells. As a result, it is relatively easy to temporarily deform the electron distribution to generate an instantaneous or induced dipole. The ease of deformation of the electron distribution in an atom or molecule is called its polarizability. Because the electron distribution is more easily perturbed in large, heavy species than in small, light species, we say that heavier substances tend to be much more *polarizable* than lighter ones.

NOTE

For similar substances, London dispersion forces get stronger with increasing molecular size.

The polarizability of a substance also determines how it interacts with ions and species that possess permanent dipoles. Thus London dispersion forces are responsible for the general trend toward higher boiling points with increased molecular mass and greater surface area in a homologous series of compounds, such as the alkanes (part (a) in Figure 2.12.4). The strengths of London dispersion forces also depend significantly on molecular shape because shape determines how much of one molecule can interact with its neighboring molecules at any given time. For example, part (b) in Figure 2.12.4 shows 2,2-dimethylpropane (neopentane) and *n*-pentane, both of which have the empirical formula C_5H_{12}. Neopentane is almost spherical, with a small surface area for intermolecular interactions, whereas *n*-pentane has an extended conformation that enables it to come into close contact with other *n*-pentane molecules. As a result, the boiling point of neopentane (9.5°C) is more than 25°C lower than the boiling point of *n*-pentane (36.1°C).

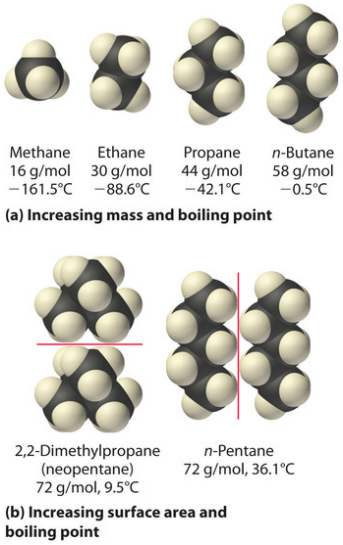


Figure 2.12.4 Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules and consequently higher boiling points. (b) Linear *n*-pentane molecules have a larger surface area and stronger intermolecular forces than spherical neopentane molecules. As a result, neopentane is a gas at room temperature, whereas *n*-pentane is a volatile liquid.

All molecules, whether polar or nonpolar, are attracted to one another by London dispersion forces in addition to any other attractive forces that may be present. In general, however, dipole–dipole interactions in small polar molecules are significantly stronger than London dispersion forces, so the former predominate.

✔ EXAMPLE 2.12.2

Arrange *n*-butane, propane, 2-methylpropane [isobutane], and *n*-pentane in order of increasing boiling points.

Strategy:

Determine the intermolecular forces in the compounds and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

The four compounds are alkanes and nonpolar, so London dispersion forces are the only important intermolecular forces. These forces are generally stronger with increasing molecular mass, so propane should have the lowest boiling point and *n*-pentane should have the highest, with the two butane isomers falling in between. Of the two butane isomers, 2-methylpropane is more compact, and *n*-butane has the more extended shape. Consequently, we expect intermolecular interactions for *n*-butane to be stronger due to its larger surface area, resulting in a higher boiling point. The overall order is thus as follows, with actual boiling points in parentheses: propane (−42.1°C) < 2-methylpropane (−11.7°C) < *n*-butane (−0.5°C) < *n*-pentane (36.1°C).

? EXERCISE 2.11.2

Arrange GeH_4, $SiCl_4$, SiH_4, CH_4, and $GeCl_4$ in order of decreasing boiling points.

Answer

$GeCl_4$ (87°C) > $SiCl_4$ (57.6°C) > GeH_4 (−88.5°C) > SiH_4 (−111.8°C) > CH_4 (−161°C)

HYDROGEN BONDS

Molecules with hydrogen atoms bonded to electronegative atoms such as O, N, and F (and to a much lesser extent Cl and S) tend to exhibit unusually strong intermolecular interactions. These result in much higher boiling points than are observed for substances in which London dispersion forces dominate, as illustrated for the covalent hydrides of elements of groups 14–17 in Figure 2.12.5. Methane and its heavier congeners in group 14 form a series whose boiling points increase smoothly with increasing molar mass. This is the expected trend in nonpolar molecules, for which London dispersion forces are the exclusive intermolecular forces. In contrast, the hydrides of the lightest members of groups 15–17 have boiling points that are more than 100°C greater than predicted on the basis of their molar masses. The effect

is most dramatic for water: if we extend the straight line connecting the points for H_2Te and H_2Se to the line for period 2, we obtain an estimated boiling point of −130°C for water! Imagine the implications for life on Earth if water boiled at −130°C rather than 100°C.

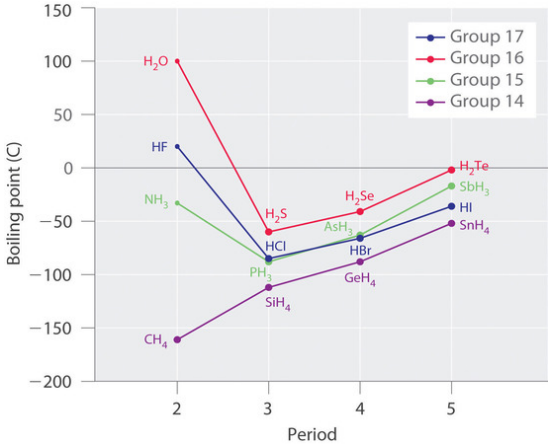


Figure 2.12.5: The Effects of Hydrogen Bonding on Boiling Points. These plots of the boiling points of the covalent hydrides of the elements of groups 14–17 show that the boiling points of the lightest members of each series for which hydrogen bonding is possible (HF, NH_3, and H_2O) are anomalously high for compounds with such low molecular masses.

Why do strong intermolecular forces produce such anomalously high boiling points and other unusual properties, such as high enthalpies of vaporization and high melting points? The answer lies in the highly polar nature of the bonds between hydrogen and very electronegative elements such as O, N, and F. The large difference in electronegativity results in a large partial positive charge on hydrogen and a correspondingly large partial negative charge on the O, N, or F atom. Consequently, H–O, H–N, and H–F bonds have very large bond dipoles that can interact strongly with one another. Because a hydrogen atom is so small, these dipoles can also approach one another more closely than most other dipoles. The combination of large bond dipoles and short dipole–dipole distances results in very strong dipole–dipole interactions called hydrogen bonds, as shown for ice in Figure 2.12.6.

A hydrogen bond is usually indicated by a dotted line between the hydrogen atom attached to O, N, or F (the *hydrogen bond donor*) and the atom that has the lone pair of electrons (the *hydrogen bond acceptor*). Because each water molecule contains two hydrogen atoms and two lone pairs, a tetrahedral arrangement maximizes the number of hydrogen bonds that can be formed. In the structure of ice, each oxygen atom is surrounded by a distorted tetrahedron of hydrogen atoms that form bridges to the oxygen atoms of adjacent water molecules. The bridging hydrogen atoms are *not* equidistant from the two oxygen atoms they connect, however. Instead, each hydrogen atom is 101 pm from one oxygen and 174 pm from the other. In contrast, each oxygen atom is bonded to two H atoms at the shorter distance and two at the longer distance, corresponding to two O–H covalent bonds and two O···H hydrogen bonds from adjacent water molecules, respectively. The resulting open, cagelike structure of ice means that the solid is actually slightly less dense than the liquid, which explains why ice floats on water rather than sinks.

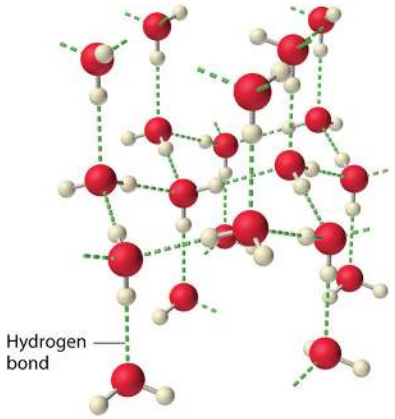


Figure 2.12.6: The Hydrogen-Bonded Structure of Ice

Each water molecule accepts two hydrogen bonds from two other water molecules and donates two hydrogen atoms to form hydrogen bonds with two more water molecules, producing an open, cage-like structure. The structure of liquid water is very similar, but in the liquid, the hydrogen bonds are continually broken and formed because of rapid molecular motion.

NOTE

Hydrogen bond formation requires *both* a hydrogen bond donor *and* a hydrogen bond acceptor.

Because ice is less dense than liquid water, rivers, lakes, and oceans freeze from the top down. In fact, the ice forms a protective surface layer that insulates the rest of the water, allowing fish and other organisms to survive in the lower levels of a frozen lake or sea. If ice were denser than the liquid, the ice formed at the surface in cold weather would sink as fast as it formed. Bodies of water would freeze from the bottom up, which would be lethal for most aquatic creatures. The expansion of water when freezing also explains why automobile or boat engines must be protected by “antifreeze” and why unprotected pipes in houses break if they are allowed to freeze.

Although hydrogen bonds are significantly weaker than covalent bonds, with typical dissociation energies of only 15–25 kJ/mol, they have a significant influence on the physical properties of a compound. Compounds such as HF can form only two hydrogen bonds at a time as can, on average, pure liquid NH_3. Consequently, even though their molecular masses are similar to that of water, their boiling points are significantly lower than the boiling point of water, which forms *four* hydrogen bonds at a time.

EXAMPLE 2.12.3

Considering CH_3OH, C_2H_6, Xe, and $(CH_3)_3N$, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Strategy:

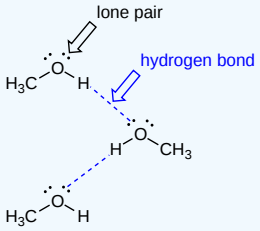
A. Identify the compounds with a hydrogen atom attached to O, N, or F. These are likely to be able to act as hydrogen bond donors.

B. Of the compounds that can act as hydrogen bond donors, identify those that also contain lone pairs of electrons, which allow them to be hydrogen bond acceptors. If a substance is both a hydrogen donor and a hydrogen bond acceptor, draw a structure showing the hydrogen bonding.

Solution:

A Of the species listed, xenon (Xe), ethane (C_2H_6), and trimethylamine [$(CH_3)_3N$] do not contain a hydrogen atom attached to O, N, or F; hence they cannot act as hydrogen bond donors.

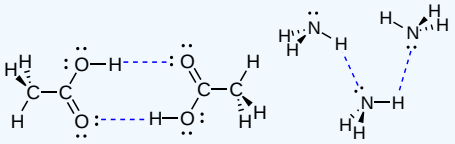
B The one compound that can act as a hydrogen bond donor, methanol (CH_3OH), contains both a hydrogen atom attached to O (making it a hydrogen bond donor) and two lone pairs of electrons on O (making it a hydrogen bond acceptor); methanol can thus form hydrogen bonds by acting as either a hydrogen bond donor or a hydrogen bond acceptor. The hydrogen-bonded structure of methanol is as follows:



EXERCISE 2.12.3

Considering CH_3CO_2H, $(CH_3)_3N$, NH_3, and CH_3F, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Answer: CH_3CO_2H and NH_3;



EXAMPLE 2.12.4

Arrange C_{60} (buckminsterfullerene, which has a cage structure), NaCl, He, Ar, and N_2O in order of increasing boiling points.

Given: compounds

Asked for: order of increasing boiling points

Strategy:

Identify the intermolecular forces in each compound and then arrange the compounds according to the strength of those forces. The substance with the weakest forces will have the lowest boiling point.

Solution:

Electrostatic interactions are strongest for an ionic compound, so we expect NaCl to have the highest boiling point. To predict the relative boiling points of the other compounds, we must consider their polarity (for dipole–dipole interactions), their ability to form hydrogen bonds, and their molar mass (for London dispersion forces). Helium is nonpolar and by far the lightest, so it should have the lowest boiling point. Argon and N_2O have very similar molar masses (40 and 44 g/mol, respectively), but N_2O is polar while Ar is not. Consequently, N_2O should have a higher boiling point. A C_{60} molecule is nonpolar, but its molar mass is 720 g/mol, much greater than that of Ar or N_2O. Because the boiling points of nonpolar substances increase rapidly with molecular mass, C_{60} should boil at a higher temperature than the other nonionic substances. The predicted order is thus as follows, with actual boiling points in parentheses: He (−269°C) < Ar (−185.7°C) < N_2O (−88.5°C) < C_{60} (>280°C) < NaCl (1465°C).

EXERCISE 2.12.4

Arrange 2,4-dimethylheptane, Ne, CS_2, Cl_2, and KBr in order of decreasing boiling points.

Answer: KBr (1435°C) > 2,4-dimethylheptane (132.9°C) > CS_2 (46.6°C) > Cl_2 (−34.6°C) > Ne (−246°C)

SUMMARY

Molecules in liquids are held to other molecules by intermolecular interactions, which are weaker than the intramolecular interactions that hold the atoms together within molecules and polyatomic ions. Transitions between the solid and liquid or the liquid and gas phases are due to changes in intermolecular interactions but do not affect intramolecular interactions. The three major types of intermolecular interactions are dipole–dipole interactions, London dispersion forces (these two are often referred to collectively as **van der Waals forces**), and hydrogen bonds. **Dipole–dipole interactions** arise from the electrostatic interactions of the positive and negative ends of molecules with permanent dipole moments; their strength is proportional to the magnitude of the dipole moment and to $1/r^6$, where r is the distance between dipoles. **London dispersion forces** are due to the formation of **instantaneous dipole moments** in polar or nonpolar molecules as a result of short-lived fluctuations of electron charge distribution, which in turn cause the temporary formation of an **induced dipole** in adjacent molecules. Like dipole–dipole interactions, their energy falls off as $1/r^6$. Larger atoms tend to be more **polarizable** than smaller ones because their outer electrons are less tightly bound and are therefore more easily perturbed. **Hydrogen bonds** are especially strong dipole–dipole interactions between molecules that have hydrogen bonded to a highly electronegative atom, such as O, N, or F. The resulting partially positively charged H atom on one molecule (the *hydrogen bond donor*) can interact strongly with a lone pair of electrons of a partially negatively charged O, N, or F atom on adjacent molecules (the *hydrogen bond acceptor*). Because of strong O · · · Hhydrogen bonding between water molecules, water has an unusually high boiling point, and ice has an open, cagelike structure that is less dense than liquid water.

KEY TAKEAWAY

- Intermolecular forces are electrostatic in nature and include van der Waals forces and hydrogen bonds.

PROBLEMS

1. Which are stronger—dipole–dipole interactions or London dispersion forces? Which are likely to be more important in a molecule with heavy atoms? Explain your answers.
2. Liquid water is essential for life as we know it, but based on its molecular mass, water should be a gas under standard conditions. Why is water a liquid rather than a gas under standard conditions?
3. Why are intermolecular interactions more important for liquids and solids than for gases? Under what conditions must these interactions be considered for gases?
4. In group 17, elemental fluorine and chlorine are gases, whereas bromine is a liquid and iodine is a solid. Why?

5. Identify the most important intermolecular interaction in each of the following.
   a) SO_2
   b) HF
   c) CO_2
   d) CCl_4
   e) CH_2Cl_2
6. Both water and methanol have anomalously high boiling points due to hydrogen bonding, but the boiling point of water is greater than that of methanol despite its lower molecular mass. Why? Draw the structures of these two compounds, including any lone pairs, and indicate potential hydrogen bonds.
7. Do you expect the boiling point of H_2S to be higher or lower than that of H_2O? Justify your answer.
8. Some recipes call for vigorous boiling, while others call for gentle simmering. What is the difference in the temperature of the cooking liquid between boiling and simmering? What is the difference in energy input?

SOLUTIONS

1. Dipole-Diple interactions are stronger because molecules polarity is permanent. Molecules involved in London dispersion forces are only temporarily polar

2. Water is a liquid under standard conditions because of its unique ability to form four strong hydrogen bonds per molecule.
3. In solids and liquids the molecules are in direct contact. In gases the molecules only contact during collisions. Intermolecules forces become inmportant when gases are cooled to the point where they form a liquid. 4. As the atomic mass of the halogens increases, so does the number of electrons and the average distance of those electrons from the nucleus. Larger atoms with more electrons are more easily polarized than smaller atoms, and the increase in polarizability with atomic number increases the strength of London dispersion forces. These intermolecular interactions are strong enough to favor the condensed states for bromine and iodine under normal conditions of temperature and pressure. 5. a) The V-shaped SO2 molecule has a large dipole moment due to the polar S=O bonds, so dipole–dipole interactions will be most important.

b) The H–F bond is highly polar, and the fluorine atom has three lone pairs of electrons to act as hydrogen bond acceptors; hydrogen bonding will be most important.

c) Although the C=O bonds are polar, this linear molecule has no net dipole moment; hence, London dispersion forces are most important.

d) This is a symmetrical molecule that has no net dipole moment, and the Cl atoms are relatively polarizable; thus, London dispersion forces will dominate.

e) This molecule has a small dipole moment, as well as polarizable Cl atoms. In such a case, dipole–dipole interactions and London dispersion forces are often comparable in magnitude.

6) Water has two polar O–H bonds with H atoms that can act as hydrogen bond donors, plus two lone pairs of electrons that can act as hydrogen bond acceptors, giving a net of four hydrogen bonds per H2O molecule. Although methanol also has two lone pairs of electrons on oxygen that can act as hydrogen bond acceptors, it only has one O–H bond with an H atom that can act as a hydrogen bond donor. Consequently, methanol can only form two hydrogen bonds per molecule on average, versus four for water. Hydrogen bonding therefore has a much greater effect on the boiling point of water.

7) H2O would have the higher boiling point because it can form the stronger hydrogen bonding intermolecular force. 8) Vigorous boiling causes more water molecule to escape into the vapor phase, but does not affect the temperature of the liquid. Vigorous boiling requires a higher energy input than does gentle simmering.

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2.MM: MOLECULAR MODELS

OBJECTIVE

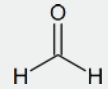
After completing this section, you should be able to

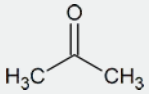
- use ball-and-stick molecular models to make models of simple organic compounds (e.g., ethane, ethylene, acetylene, ethanol, formaldehyde, acetone, acetic acid), given their Kekulé structures or molecular formulas.

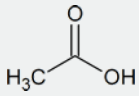
STUDY NOTES

You will have noticed that we have given two names for most of the compounds discussed up to this point. In general we shall be using systematic (i.e., IUPAC—International Union of Pure and Applied Chemistry) names throughout the course. However, simple compounds are often known by their common names, which may be more familiar than their IUPAC counterparts. We shall address the subject of nomenclature (naming) in Chapter 3.

ethanol 

formaldehyde (methanal), 

acetone (propanone), 

acetic (ethanoic) acid, 

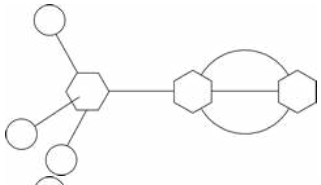
If your instructor is having you work with molecular models in class, they may use this section for you to practice creating specific structures.

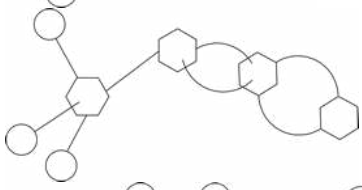
EXERCISES

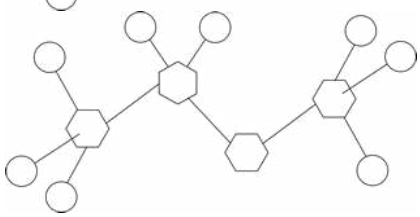
1. Construct a molecular model of each of the compounds listed below.
   a. $\ce{\sf{CH3-CN}}$
   b. $\ce{\sf{CH3-N=C=O}}$
   c. $\ce{\sf{CH3-CH2-O-CH3}}$

   Hint: Use the curved sticks to form the multiple bonds and the straight sticks for single bonds.

ANSWERS:

A. 

B. 

C. 

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2.S: POLAR COVALENT BONDS; ACIDS AND BASES (SUMMARY)

CONCEPTS & VOCABULARY

2.1 Polar Covalent Bonds: Electronegativity

- The difference in electronegativity values of two atoms determines whether the bond between those atoms is classified as either **ionic**, **polar covalent**, or **non-polar covalent**.
- **Ionic bonds** result from large differences in electronegativity values, such as that between a metal and non-metal atom (Na and Cl).
- Covalent bonding generally results when both atoms are non-metals, like C, H, O, N and the halides.
- When both atoms the same and/or have the same electronegativity value, then the bonding electrons are shared equally and the bond is classified as **non-polar covalent**.
- **Polar covalent** bonds occur when the difference in electronegativity values is small, and the bonding electrons are not shared equally.

2.2 Polar Covalent Bonds: Dipole Moments

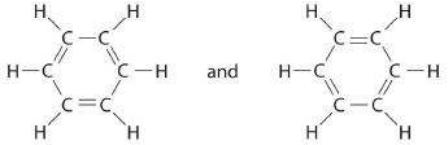
- The **molecular dipole moment** is the sum of all the bond dipoles within a molecule and depends on both the molecular geometry and the bond polarity.
- Molecules that contain no polar bonds, like CH_4, and/or completely symmetrical molecules, like CO_2, generally have no net dipole moment.
- Asymmetrical molecules that contain bonds of different polarities or non-bonding lone pairs typically have a molecular dipole moment.

2.3 Formal Charges

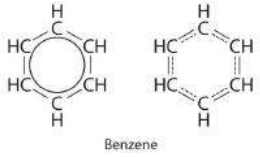
- Formal Charge compares how many valence electrons surround a free atom versus how many surround that same type of atom bonded with a molecule or ion.
- **Formal Charge = (# of valence electrons in free atom) - (# of lone-pair electrons) - (1/2 # of bond pair electrons)** *Eqn. 2.3.1*
- Formal charges of zero generally represent the most stable structures.
- These bonding patterns for the atoms commonly found in organic molecules result in a formal charge of zero
  - Carbon - 4 bonds, no lone pairs
  - Hydrogen - 1 bond, no lone pairs
  - Nitrogen - 3 bonds, 1 lone pair
  - Oxygen - 2 bonds, 2 lone pairs
  - Halogens - 1 bond, 3 lone pairs.

2.4 Resonance

- Resonance Theory is often used when the observed chemical and physical properties of a molecule or ion cannot be adequately described by a single Lewis Structure. A classic example is the benzene molecule, C_6H_6. The Lewis Structure of benzene could be drawn in two different ways. Both structures have alternating double bond and single bonds between the carbons. The only difference is the location of the pi bonds.



If these structures are correct, then the benzene molecule should have two different C-C bond lengths and bond energies, corresponding to a C-C single bond and to a C=C double bond. However, analysis shows that benzene contains only one type of carbon-carbon bond and it's bond length and energy are half between those of a single bond and double bond. Resonance theory states that benzene exists as the "average" of the two structures called a **resonance hybrid**, in which the six pi electrons **delocalized** over all six carbon atoms. Each C-C bond in benzene would be the average of a single bond and double bond or a "bond and a half". Dashed lines are often used to show type of "partial" bonding in a resonance hybrid of benzene

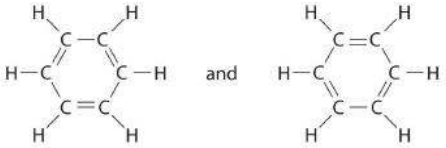


2.5 Rules for Resonance Forms

- The rules for estimating stability of resonance structures are
  - The resonance form in which all atoms have complete valence shells is more stable.

- The **greater the number of covalent bonds**, the greater the stability since more atoms will have complete octets
- The structure with the **least number of formal charges** is more stable
- The structure with the **least separation of formal charges** is more stable
- A structure with a **negative charge on the more electronegative atom** will be more stable
- **Positive charges on the least electronegative atom** (most electropositive) is more stable
- **Resonance forms that are equivalent have no difference in stability and contribute equally.** (eg. benzene)

- If these rules are applied to the two Lewis Structures of benzene, the result would be that both structures will have the same relative stability and will both contribute equally to the character of the resonance hybrid.



2.6 Drawing Resonance Forms

- In resonance structures, the electrons are able to move to help stabilize the molecule. This movement of the electrons is called delocalization.
- The rules for drawing resonance structures are:
  - Resonance structures should have the same number of electrons, do not add or subtract any electrons. (You can check the number of electrons by counting them)
  - All resonance structures must follow the rules of writing Lewis Structures.
  - The hybridization of the structure must stay the same.
  - The skeleton of the structure can not be changed (only the electrons move).
  - Resonance structures must also have the same amount of lone pairs.

2.7 Acids and Bases - The Brønsted-Lowry Definition

- A Brønsted-Lowry acid is a proton (H^+) donor and a Brønsted-Lowry base is a proton acceptor.

2.8 Acid and Base Strength

- The strength of Brønsted-Lowry acids is measured indicated by its pKa value. The lower the pKa - the stronger the acid.
- A strong acid will have a weak conjugate base. A strong base will have a weak conjugate acid.

2.9 Predicting Acid-Base Reactions from pKa Values

- The equilibrium of an acid-base reaction favors the formation of weaker acids from stronger acids. To predict the direction of the equilibrium, identify Brønsted-Lowry acid on each side of the reaction. Assign/look up pKa values for each acid. The equilibrium will favor the side that has the weakest acid (the highest pKa).

2.10 Organic Acids and Organic Bases

- Organic acids are stronger when the conjugate base that is formed upon loss of a proton is more stable.
- Some factors that effect the stability of the conjugate base (often an anion) are the anionic atom's size and electronegativity, resonance effects, inductive effects, and solvation.

2.11: Acids and Bases - The Lewis Definition

- A Lewis acid is a lone pair acceptor and a Lewis base is a lone pair donor.

2.12: Non-covalent Interactions between Molecules

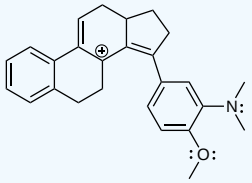
- Non-covalent Interactions, also known as Intermolecular Forces, significantly effect the physical properties of organic molecules. Hydrogen bonding is the most important of these interactions, but others include ion-dipole, dipole-dipole, and London Dispersion Forces.

2.MM: Molecular Models

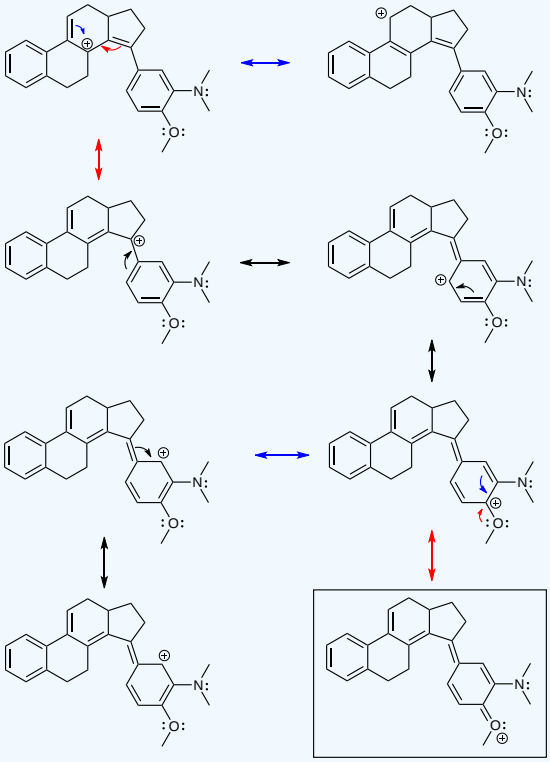
SUMMARY PROBLEMS

EXERCISE 2.S.1

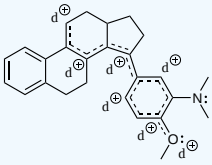
Draw all possible resonance structures to demonstrate delocalization of the positive charge in the following molecule. Circle the most stable resonance structure and explain your answer. Also, draw the resonance hybrid.



Answer



Most stable resonance structure



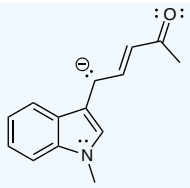
Resonance Hybrid

The circled structure is the most stable because it is the only structure with a full octet on all atoms. (Remember that carbocations must have an incomplete octet, and an oxygen with a positive charge and a full octet is more stable than a carbocation.)

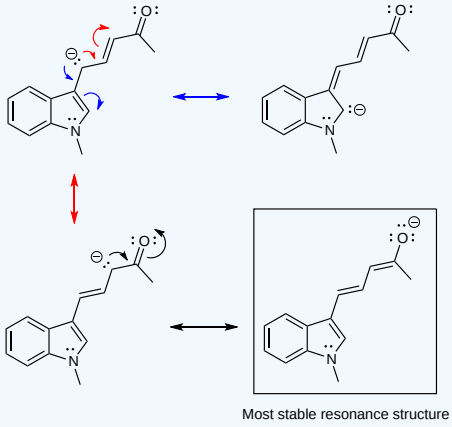
As a reminder, the resonance hybrid structure is a combination of all of your resonance structure showing partial pi bonds and partial formal charges.

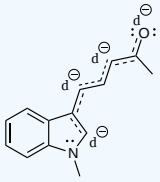
EXERCISE 2.S.2

Draw all possible resonance structures to demonstrate delocalization of the negative charge in the following molecule. Also, draw the resonance hybrid and circle the most stable resonance contributor among all of your resonance structures.



Answer

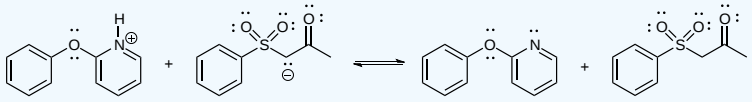




The circled structure is the most stable because the negative charge is on oxygen, the most electronegative element sharing the negative charge. As a reminder, in resonance structures with negative charges, all of the atoms have octets, so you only need to focus on electronegativity differences to find the most stable structure.

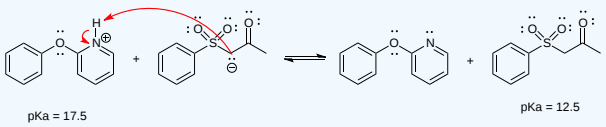
? EXERCISE 2.S.3

For the equilibrium shown below, answer the following questions: a) Draw curved arrows to illustrate bond breakage and formation in the reaction. b) At equilibrium, are the products or reactants favored? Explain. c) What percent reactants and percent products are present at equilibrium? d) Use resonance structures to explain why N is the most basic atom in the conjugate base. e) Use resonance structures to explain why the hydrogen that is removed from the conjugate acid is the most acidic proton.



Answer

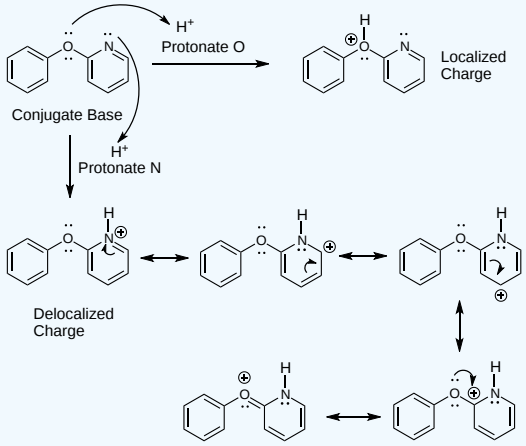
a)



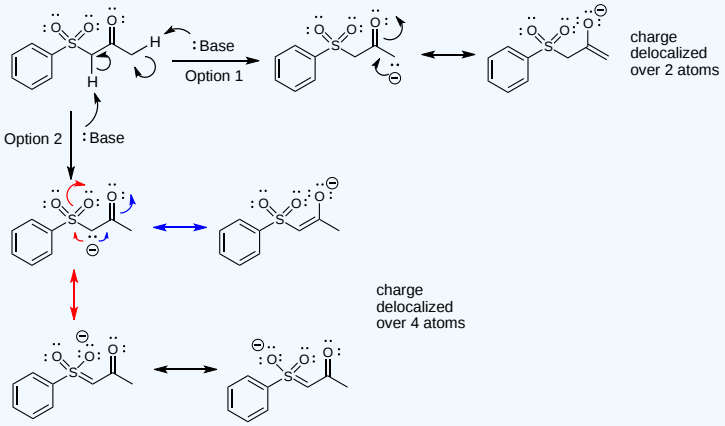
b) The lower pKa is the stronger acid, and the equilibrium will always favor the weak acid (higher pKa), so this reaction favors the reactants. Note: It's normal to assume that the neutral products would be favored, but this is a good example that shows our chemical intuition isn't always right. To make sure we understand the equilibrium, we need to have pKa values to compare.

c) Keq = $10^{12.5-17.5}$ = 10^{-5} = 0.00001 So, the ratio of reactants to products is 1:0.00001. The percent reactants is 99.999% and the percent products is 0.001%.

d) There are two atoms with lone pairs in the conjugate base, O and N, so we should evaluate both to show that N is the most basic atom. Protonating O yields a positive charge localized on O. Protonating N yields a charge delocalized over 3 Cs, 1 N, and 1 O. The N is most basic because the charge in the acid is delocalized and there are two structures with full octets (positive charge on N and O).

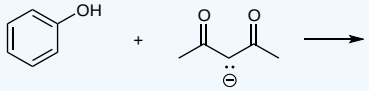


e) To find the most acidic proton, we should focus on Hs on atoms next to (not on) double bonds. This will yield a delocalized negative charge when the H is removed. In the conjugate acid, we have two options. Option 1 yields a compound with a negative charge delocalized over 2 atoms, O and C. Option 2 yields the base from the original reaction because the charge is delocalized over 4 atoms, C and 3 Os. This is very stable because it is spread over 3 electronegative oxygen atoms.



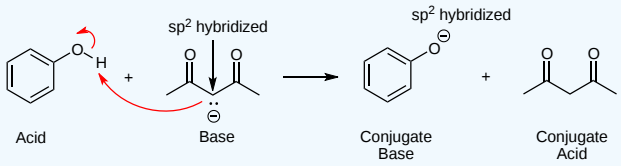
? EXERCISE 2.S.4

This question focuses on the reaction of the two molecules shown below. a) Draw an acid-base reaction of these molecules. Clearly label the acid, the base, the conjugate acid, and the conjugate base. Draw curved arrows to clearly indicate electron movement involved in bond formation and bond cleavage. For the base and the conjugate base, label the hybridization of the charged atoms. b) If you drew the reaction correctly, the pKa of the conjugate acid is 9. Use the table in Section 2.8 to determine the pKa of the acid. Are the reactants or products favored at equilibrium? What is the approximate ratio of reactants to products? What is the approximate percentage of reactants and products? c) Draw the structures of the two charged molecules in the reaction. Draw resonance structures to illustrate charge delocalization in these molecules. Based on your analysis in part b, which charged molecule is more stable? Briefly explain this result.



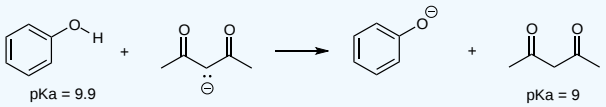
Answer

a)



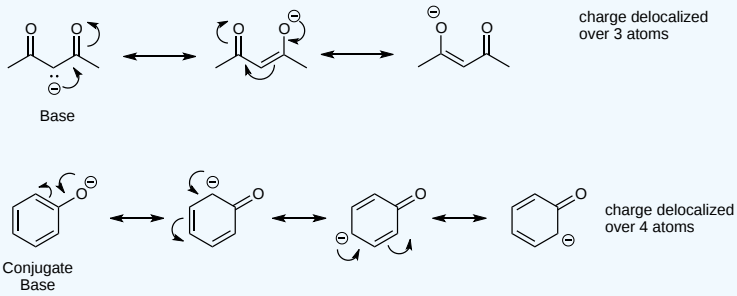
Don't forget that the charged atoms in the base and conjugate base are sp^2 hybridized so that the lone pair can be in a p orbital and then delocalized by resonance. For negative charges to be delocalized, the lone pair must be in a p orbital so that electrons can flow to adjacent pi bonds by resonance.

b)



The acid has the larger pKa, so it is the weaker acid and the reactants are favored. The approximate difference in pKa values is 1. So, Keq is 10^{-1} and for every 1 product molecule there are 10 reactant molecules. (Remember, since the reactants are favored, there are more reactants and the Keq must be less than 1.) The approximate percentage of reactants is 90% and products is 10%. (10/(10+1) is approximately 90% and 1/(10+1) is approximately 10%)

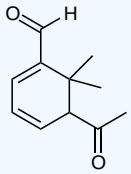
c)



We know that the equilibrium favors the reactants. We also know that in acid base reactions, the stronger acid reacts with the stronger base to yield the weaker base and the weaker acid. In this reaction, the products are the stronger acid-base pair. We also know that "stronger" means more reactive and less stable, while "weaker" means less reactive and more stable. So, since the reactants are favored, that means the base (as labeled above) is more stable than the conjugate base. This seems strange since the charge is more delocalized in the conjugate base. This comparison highlights the importance of quality of resonance structures versus quantity of resonance structures. The charge is more stable in the base since in two of the resonance structures, the negative charge is on O. In the conjugate base, only one of the structures has the negative charge on O.

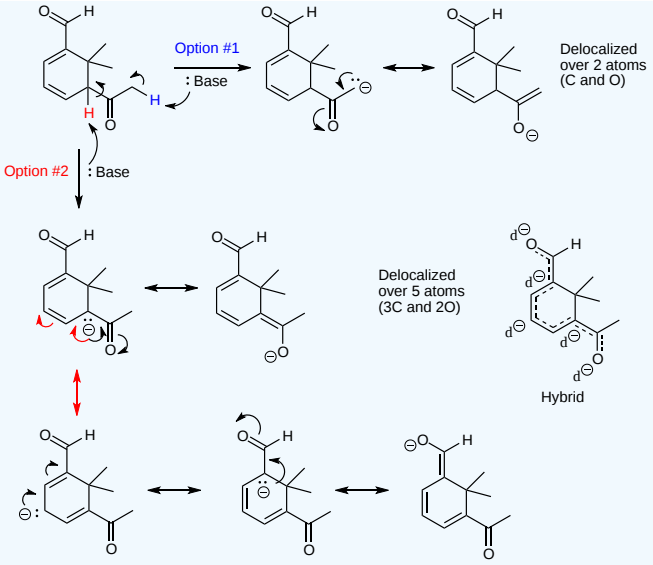
? EXERCISE 2.S.5

Determine the position of the most acidic proton in the following molecule. You should draw resonance structures and a resonance hybrid to justify your answer.



Answer

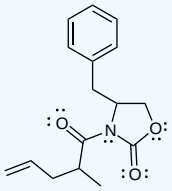
Donation of the most acidic proton (H^+) yields the most stable conjugate base; the one that has the charge on the most electronegative element and/or the most delocalized charge. You should focus on protons attached to electronegative elements (e.g., O or N) and protons on atoms next to pi bonds, but not attached to atoms with pi bonds. In this molecule, all Hs are attached to carbon. So, we should focus on the Hs next to pi bonds. These are Hs on sp^3 hybridized carbons next to sp^2 hybridized carbons. Loss of these protons will yield a negative charge that can be delocalized by resonance.



Option #1 yields a conjugate base with the charge delocalized over 1 carbon and 1 oxygen. Option #2 yields a conjugate base with a charge delocalized over 3 carbons and 2 oxygens. This is the most stable conjugate base, so the most acidic proton is the red proton (removed in option #2).

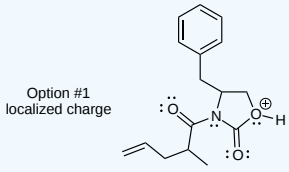
? EXERCISE 2.S.6

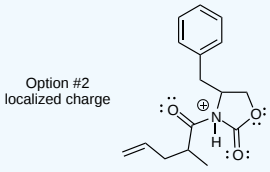
Determine the position of the most basic atom in the following molecule. You should draw resonance structures and a resonance hybrid to justify your answer.

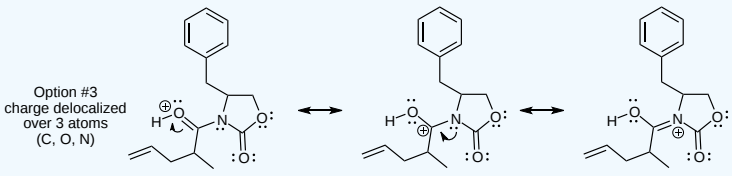


Answer

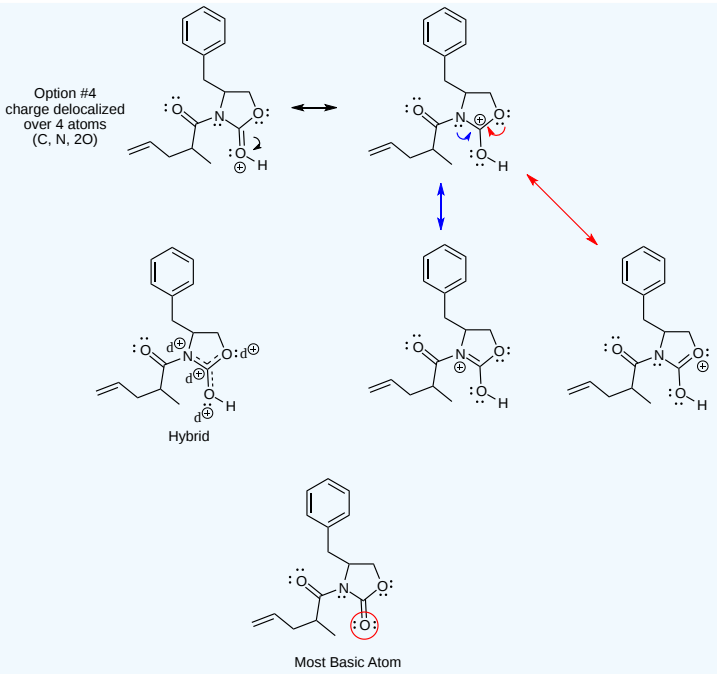
There are four basic atoms (atoms with lone pair electrons) in this molecule. The strongest base will yield the most stable conjugate acid (the one with the most delocalized positive charge and/or the charge on the least electronegative atom).







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Options #1 and #2 yield conjugate acids with localized charges. Options #3 and #4 yield conjugate acids with delocalized charges.This illustrates a key point: For atoms that can't have an expanded octet, atoms with a lone pair and no pi bond will accept a proton and yield a localized charge in the conjugate acid while atoms with both a lone pair and a pi bond will accept a proton and yield a delocalized charge in the conjugate acid. So, we should focus our energy on the latter atoms. In this problem, that means Options #3 and #4. In option #3, the charge is delocalized over 3 atoms, 2 that have full octets on all atoms (positive charge on N and O). In option #4, the charge is delocalized over 4 atoms, 3 that have full octets on all atoms (positive charge on N and 2 Os). So, Option #4 has more total resonance structures and more structures that have a full octet. This is the most stable conjugate acid which means the circled O is the most basic atom.

SKILLS TO MASTER

- Skill 2.1 Predict whether a bond is ionic, polar covalent, or non-polar covalent based on the position of the atoms in the periodic table.
- Skill 2.2 Identify the partial positive and partial negative atoms of a polar covalent bond based on relative electronegativity.
- Skill 2.3 Determine the dipole moment of a molecule based on molecular geometry and bond polarity.
- Skill 2.4 Identify the chemicals in a reaction as Brønsted-Lowry acids or bases, and conjugate acids and bases.
- Skill 2.5 Predict the products of an acid-base reaction.
- Skill 2.6 Use pKa values to predict the equilibrium direction of an acid-base reaction.
- Skill 2.7 Predict the relative strength of an organic acid by examining the stability of the conjugate base.
- Skill 2.8 Use molecular structure and analysis of intermolecular forces to rank a series of organic molecules with respect to physical properties like melting point and boiling point.
- Skill 2.9 Identify the chemicals in a reaction as Lewis acids or bases.

MEMORIZATION TASKS (MT)

- MT 2.1 Memorize that the C-H bond is considered to be non-polar.
- MT 2.2 Memorize the common bonding patterns for C, H, N, O and the halogens that have a zero formal charge.
- MT 2.3 Memorize the factors that affect the relativity stability of conjugate bases.

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CHAPTER OVERVIEW

3: ORGANIC COMPOUNDS- ALKANES AND THEIR STEREOCHEMISTRY

LEARNING OBJECTIVES

After you have completed Chapter 3, you should be able to

1. fulfill the detailed objectives listed under each section.
2. identify some of the commonest functional groups.
3. write the structures and names of the first ten straight-chain alkanes.
4. recognize and name the simple alkyl substituents, and give the systematic names for branched-chain alkanes.
5. briefly describe some of the processes used during the refining of petroleum.
6. briefly describe the physical properties of alkanes.
7. draw a number of possible conformations of some simple alkanes and alkane-like compounds, and represent the energies of such conformations on energy versus rotation diagrams.
8. define, and use in context, the key terms introduced in this chapter.

This chapter begins with an introduction to the concept of the functional group, a concept that facilitates the systematic study of organic chemistry. Next, we introduce the fundamentals of organic nomenclature (i.e., the naming of organic chemicals) through examination of the alkane family of compounds. We then discuss, briefly, the occurrence and properties of alkanes, and end with a description of *cis-trans* isomerism in cycloalkanes.

3.0: Chapter Objectives
3.1: Functional Groups
3.2: Alkanes and Alkane Isomers
3.3: Alkyl Groups
3.4: Naming Alkanes
3.5: Properties of Alkanes
3.6: Conformations of Ethane
3.7: Conformations of Other Alkanes
3.8: Gasoline - A Deeper Look
3.S: Organic Compounds- Alkanes and Their Stereochemistry (Summary)

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3.0: CHAPTER OBJECTIVES

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3.1: FUNCTIONAL GROUPS

OBJECTIVES

After completing this section, you should be able to

1. explain why the properties of a given organic compound are largely dependent on the functional group or groups present in the compound.
2. identify the functional groups present in each of the following compound types: alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, (carboxylic) acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.
3. identify the functional groups present in an organic compound, given its structure.
4. Given the structure of an organic compound containing a single functional group, identify which of the compound types listed under Objective 2, above, it belongs to.
5. draw the structure of a simple example of each of the compound types listed in Objective 2.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- functional group

STUDY NOTES

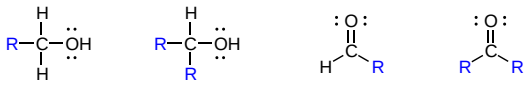
The concept of functional groups is a very important one. We expect that you will need to refer back to tables at the end of Section 3.1 quite frequently at first, as it is not really feasible to learn the names and structures of all the functional groups and compound types at one sitting. Gradually they will become familiar, and eventually you will recognize them automatically.

Functional groups are small groups of atoms that exhibit a characteristic reactivity. A particular functional group will almost always display its distinctive chemical behavior when it is present in a compound. Because of their importance in understanding organic chemistry, functional groups have specific names that often carry over in the naming of individual compounds incorporating the groups.

As we progress in our study of organic chemistry, it will become extremely important to be able to quickly recognize the most common functional groups, because they are the key structural elements that define how organic molecules react. For now, we will only worry about drawing and recognizing each functional group, as depicted by Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups tend to behave in organic reactions.

DRAWING ABBREVIATED ORGANIC STRUCTURES

Often when drawing organic structures, chemists find it convenient to use the letter 'R' to designate part of a molecule outside of the region of interest. If we just want to refer in general to a functional group without drawing a specific molecule, for example, we can use 'R groups' to focus attention on the group of interest:



a primary alcohol | a secondary alcohol | an aldehyde | a ketone

The 'R' group is a convenient way to abbreviate the structures of large biological molecules, especially when we are interested in something that is occurring specifically at one location on the molecule.

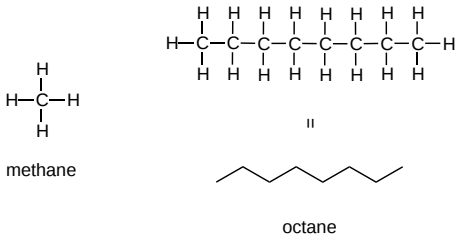
COMMON FUNCTIONAL GROUPS

In the following sections, many of the common functional groups found in organic chemistry will be described. Tables of these functional groups can be found at the bottom of the page.

HYDROCARBONS

The simplest functional group in organic chemistry (which is often ignored when listing functional groups) is called an **alkane**, characterized by single bonds between two carbons and between carbon and hydrogen. Some examples of alkanes include methane, CH_4, is the natural gas you may burn in your furnace or on a stove. Octane, C_8H_{18}, is a component of gasoline.

Alkanes

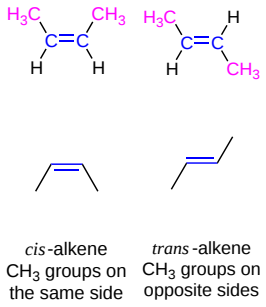


Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along with an apple - the apple emits ethene gas, setting off the ripening process in the bananas). Ethyne, commonly called acetylene, is used as a fuel in welding blow torches.

Alkenes and alkynes



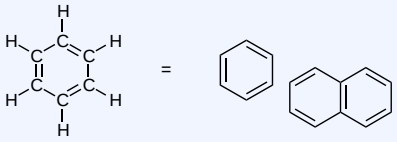
Alkenes have trigonal planar electron geometry (due to sp^2 hybrid orbitals at the alkene carbons) while alkynes have linear geometry (due to sp hybrid orbitals at the alkyne carbons). Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans*** *(or Z and E which will be explained in detail in Chapter 7)*. The *cis* and *trans* forms of a given alkene are different molecules with different physical properties there is a very high energy barrier to rotation about a double bond. In the example below, the difference between *cis* and *trans* alkenes is readily apparent.



Alkanes, alkenes, and alkynes are all classified as **hydrocarbons**, because they are composed solely of carbon and hydrogen atoms. Alkanes are said to be **saturated hydrocarbons**, because the carbons are bonded to the maximum possible number of hydrogens - in other words, they are *saturated* with hydrogen atoms. The double and triple-bonded carbons in alkenes and alkynes have fewer hydrogen atoms bonded to them - they are thus referred to as **unsaturated hydrocarbons**. As we will see in Chapter 7, hydrogen can be added to double and triple bonds, in a type of reaction called 'hydrogenation'.

The **aromatic** group is exemplified by benzene (which used to be a commonly used solvent on the organic lab, but which was shown to be carcinogenic), and naphthalene, a compound with a distinctive 'mothball' smell. Aromatic groups are planar (flat) ring structures, and are widespread in nature. We will learn more about the structure and reactions of aromatic groups in Chapter 15.

AROMATICS

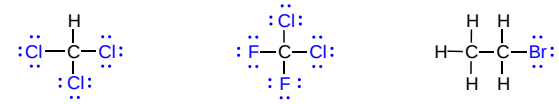


benzene = naphthalene

FUNCTIONAL GROUPS WITH CARBON SINGLE BONDS TO OTHER ATOMS

HALIDES

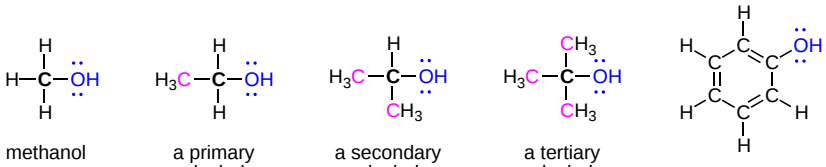
When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. The presence of a halogen atom (F, Cl, Br, or I), is often represented by X due to the similar chemistry of halogens. Chloroform is a useful solvent in the laboratory, and was one of the earlier anesthetic drugs used in surgery. Chlorodifluoromethane was used as a refrigerant and in aerosol sprays until the late twentieth century, but its use was discontinued after it was found to have harmful effects on the ozone layer. Bromoethane is a simple alkyl halide often used in organic synthesis. Alkyl halides groups are quite rare in biomolecules.



trichloromethane (chloroform) | dichlorodifluoromethane (Freon-12) | bromoethane

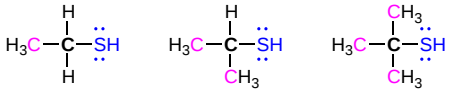
ALCOHOLS AND THIOLS

In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded to only one other carbon. In a **secondary alcohol** and **tertiary alcohol,** the carbon is bonded to two or three other carbons, respectively. When the hydroxyl group is *directly* attached to an aromatic ring, the resulting group is called a **phenol**.



methanol | a primary alcohol | a secondary alcohol | a tertiary alcohol | a phenol

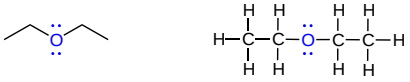
The sulfur analog of an alcohol is called a **thiol** (the prefix *thio*, derived from the Greek, refers to sulfur).



a primary thiol | a secondary thiol | a tertiary thiol

ETHERS AND SULFIDES

In an **ether** functional group, a central oxygen is bonded to two carbons. Below are the line and Lewis structures of diethyl ether, a common laboratory solvent and also one of the first medical anaesthesia agents.

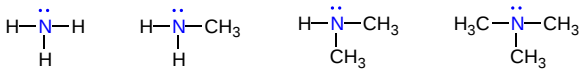


In **sulfides**, the oxygen atom of an ether has been replaced by a sulfur atom.



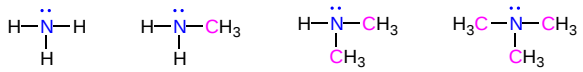
AMINES

Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

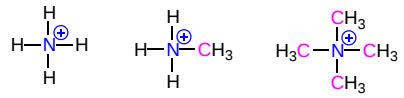


ammonia | a primary amine | a secondary amine | a tertiary amine

One of the most important properties of amines is that they are basic, and are readily protonated to form **ammonium** cations. In the case where a nitrogen has four bonds to carbon (which is somewhat unusual in biomolecules), it is called a quaternary ammonium ion.

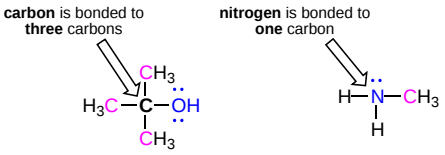


ammonia | a primary amine | a secondary amine | a tertiary amine



ammonium ion | a primary ammonium ion | a quaternary ammonium ion

> **CAUTION**
>
> Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols and amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.

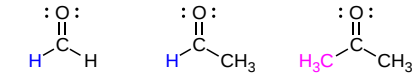


a tertiary alcohol | a primary amine

CARBONYL CONTAINING FUNCTIONAL GROUPS

ALDEHYDES AND KETONES

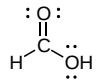
There are a number of functional groups that contain a carbon-oxygen double bond, which is commonly referred to as a **carbonyl**. **Ketones** and **aldehydes** are two closely related carbonyl-based functional groups that react in very similar ways. In a ketone, the carbon atom of a carbonyl is bonded to two other carbons. In an aldehyde, the carbonyl carbon is bonded on one side to a hydrogen, and on the other side to a carbon. The exception to this definition is formaldehyde, in which the carbonyl carbon has bonds to two hydrogens.



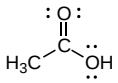
formaldehyde | an aldehyde | a ketone

CARBOXYLIC ACIDS AND ACID DERIVATIVES

If a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to a **heteroatom** (in organic chemistry, this term generally refers to oxygen, nitrogen, sulfur, or one of the halogens), the functional group is considered to be one of the '**carboxylic acid derivatives'**, a designation that describes a grouping of several functional groups. The eponymous member of this grouping is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl (OH) group.



formic acid

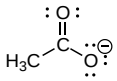


acetic acid
(vinegar)

As the name implies, carboxylic acids are acidic, meaning that they are readily deprotonated to form the conjugate base form, called a **carboxylate** (much more about carboxylic acids in Chapter 20).

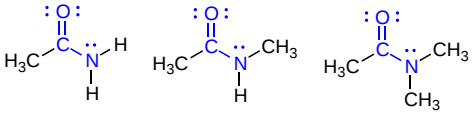


formate

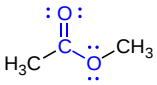


acetate

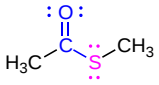
In **amides**, the carbonyl carbon is bonded to a nitrogen. The nitrogen in an amide can be bonded either to hydrogens, to carbons, or to both. Another way of thinking of an amide is that it is a carbonyl bonded to an amine.



In **esters**, the carbonyl carbon is bonded to an oxygen which is itself bonded to another carbon. Another way of thinking of an ester is that it is a carbonyl bonded to an alcohol. **Thioesters** are similar to esters, except a sulfur is in place of the oxygen.

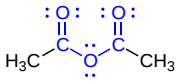


an ester



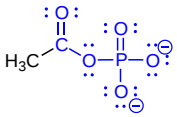
a thioester

In an **acid anhydride**, there are two carbonyl carbons with an oxygen in between. An acid anhydride is formed from combination of two carboxylic acids with the loss of water (anhydride).

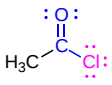


an anhydride

In an **acyl phosphate**, the carbonyl carbon is bonded to the oxygen of a phosphate, and in an **acid chloride**, the carbonyl carbon is bonded to a chlorine.



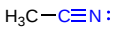
an acyl
phosphate



an acid
chloride

NITRILES AND IMINES

In a **nitrile** group, a carbon is triple-bonded to a nitrogen. Nitriles are also often referred to as **cyano** groups.



a nitrile

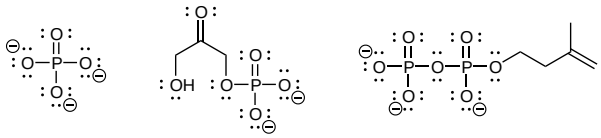
Molecules with carbon-nitrogen double bonds are called **imines**, or **Schiff bases**.



imines

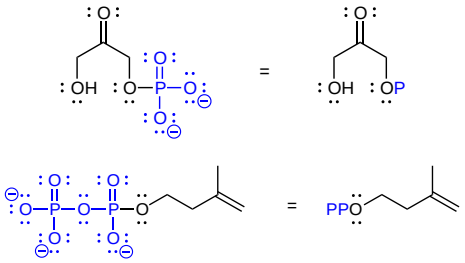
PHOSPHATES

Phosphorus is a very important element in biological organic chemistry, and is found as the central atom in the **phosphate** group. Many biological organic molecules contain phosphate, diphosphate, and triphosphate groups, which are linked to a carbon atom by the **phosphate ester** functionality.



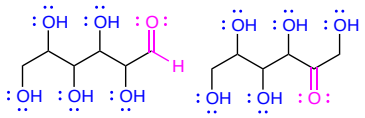
inorganic phosphate | an organic phosphate ester | an organic diphosphate ester

Because phosphates are so abundant in biological organic chemistry, it is convenient to depict them with the abbreviation 'P'. Notice that this 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.



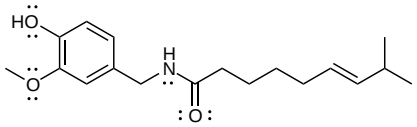
MOLECULES WITH MULTIPLE FUNCTIONAL GROUPS

A single compound may contain several different functional groups. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').



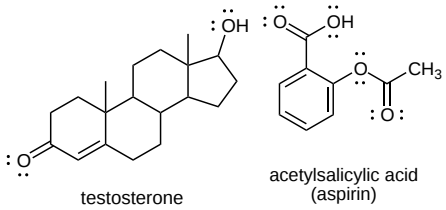
glucose | fructose

Capsaicin, the compound responsible for the heat in hot peppers, contains phenol, ether, amide, and alkene functional groups.



capsaicin

The male sex hormone testosterone contains ketone, alkene, and secondary alcohol groups, while acetylsalicylic acid (aspirin) contains aromatic, carboxylic acid, and ester groups.

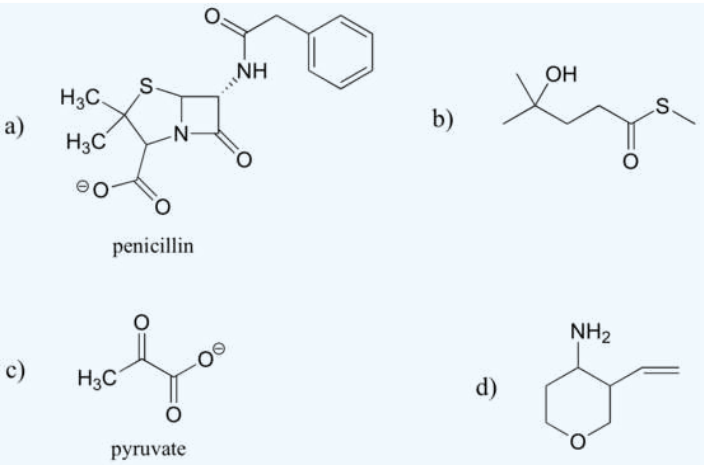


testosterone | acetylsalicylic acid (aspirin)

While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological and laboratory organic chemistry. The table found below provides a summary of all of the groups listed in this section, plus a few more that will be introduced later in the text.

? EXERCISE 3.1.1

Identify the functional groups in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.



Answer

a) carboxylate, sulfide, aromatic, two amide groups (one of which is cyclic)

b) tertiary alcohol, thioester

c) carboxylate, ketone

d) ether, primary amine, alkene

2: Draw one example each (there are many possible correct answers) of compounds fitting the descriptions below, using line structures. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule).

a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

FUNCTIONAL GROUP TABLES

EXCLUSIVELY CARBON FUNCTIONAL GROUPS

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	alkene	$H_2C{=}CH_2$	ethene	ethylene
	alkyne	HC≡CH	ethyne	acetylene
	arene	C_6H_6	benzene	benzene

FUNCTIONAL GROUPS WITH SINGLE BONDS TO HETEROATOMS

Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	halide	H_3C-I	iodomethane	methyl iodide
	alcohol	CH_3CH_2OH	ethanol	ethyl alcohol
	ether	$CH_3CH_2OCH_2CH_3$	diethyl ether	ether
	amine	H_3C-NH_2	aminomethane	methylamine
	nitro compound	H_3C-NO_2	nitromethane	
	thiol	H_3C-SH	methanethiol	methyl mercaptan
	sulfide	H_3C-S-CH_3	dimethyl sulfide	

Functional Groups with Multiple Bonds to Heteroatoms

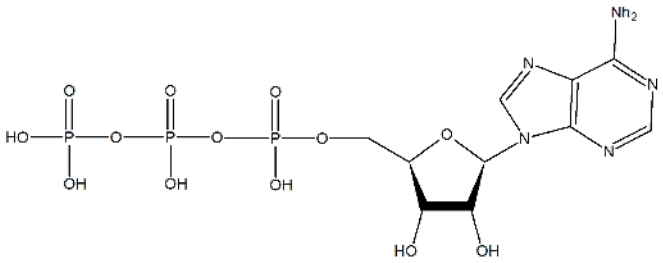
Group Formula	Class Name	Specific Example	IUPAC Name	Common Name
	nitrile	H_3C-CN	ethanenitrile	acetonitrile
	aldehyde	H_3CCHO	ethanal	acetaldehyde
	ketone	H_3CCOCH_3	propanone	acetone
	carboxylic acid	H_3CCO_2H	ethanoic Acid	acetic acid
	ester	$H_3CCO_2CH_2CH_3$	ethyl ethanoate	ethyl acetate
	acid halide	H_3CCOCl	ethanoyl chloride	acetyl chloride
	amide	$H_3CCON(CH_3)_2$	N,N-dimethylethanamide	N,N-dimethylacetamide
	acid Anhydride	$(H_3CCO)_2O$	ethanoic anhydride	acetic anhydride

EXERCISES

QUESTIONS

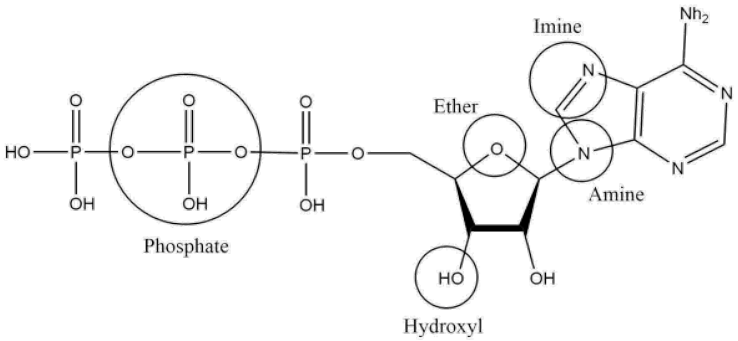
Q3.1.1

The following is the molecule for ATP, or the molecule responsible for energy in human cells. Identify the functional groups for ATP.



SOLUTIONS

S3.1.1



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3.2: ALKANES AND ALKANE ISOMERS

OBJECTIVES

After completing this section, you should be able to

1. draw the Kekulé structure, condensed structure and shorthand structure of each of the first ten straight-chain alkanes.
2. name each of the first ten straight-chain alkanes, given its molecular formula, Kekulé structure, condensed structure or shorthand structure.
3. explain the difference in structure between a straight- and a branched-chain alkane, and illustrate the difference using a suitable example.
4. explain why the number of possible isomers for a given molecular formula increases as the number of carbon atoms increases.
5. draw all the possible isomers that correspond to a given molecular formula of the type $C_n H_{2n+2}$, where n is ≤ 7.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- branched-chain alkane
- constitutional or structural isomer
- homologous series
- isomer
- saturated hydrocarbon
- straight-chain alkane (or normal alkane)

STUDY NOTES

A series of compounds in which successive members differ from one another by a CH_2 unit is called a homologous series. Thus, the series CH_4, C_2H_6, C_3H_8 . . . C_nH_{2n+2}, is an example of a homologous series.

It is important that you commit to memory the names of the first 10 straight-chain alkanes (i.e., from CH_4 to $C_{10}H_{22}$). You will use these names repeatedly when you begin to learn how to derive the systematic names of a large variety of organic compounds. You need not remember the number of isomers possible for alkanes containing more than seven carbon atoms. Such information is available in reference books when it is needed. When drawing isomers, be careful not to deceive yourself into thinking that you can draw more isomers than you are supposed to be able to. Remember that it is possible to draw each isomer in several different ways and you may inadvertently count the same isomer more than once.

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes are often called saturated hydrocarbons because they have the maximum possible number of hydrogens per carbon. In Section 1.7, thealkane molecule, ethane, was shown to contain a C-C sigma bond. By adding more C-C sigma bond larger and more complexed alkanes can be formed. Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

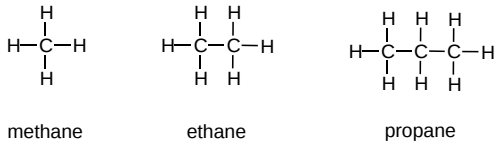


Figure 25.3.1 : The Three Simplest Alkanes

Methane (CH_4), ethane (C_2H_6), and propane (C_3H_8) are the beginning of a series of compounds in which any two members in a sequence differ by one carbon atom and two hydrogen atoms—namely, a CH_2 unit. Consider the series in Figure 25.3.3. The sequence starts with C_3H_8, and a CH_2 unit is added in each step moving up the series. Any family of compounds in which adjacent members differ from each other by a definite factor (here a CH_2 group) is called a homologous series. The members of such a series, called *homologs*, have properties that vary in a regular and predictable manner.

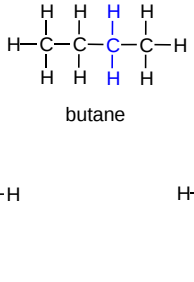


Figure 25.3.2: Members of a Homologous Series. Each succeeding formula incorporates one carbon atom and two hydrogen atoms more than the previous formula.

The homologous series allows us to write a general formula for alkanes: $C_nH_{2n\,+\,2}$. Using this formula, we can write a molecular formula for any alkane with a given number of carbon atoms. For example, an alkane with eight carbon atoms has the molecular formula $C_8H_{(2\,\times\,8)\,+\,2} = C_8H_{18}$.

MOLECULAR FORMULAS

Alkanes are the simplest family of hydrocarbons - compounds containing carbon and hydrogen only. Alkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The first six alkanes are as follows:

Table 3.2.1: Molecular formulas for small alkanes

methane	CH_4
ethane	C_2H_6
propane	C_3H_8
butane	C_4H_{10}
pentane	C_5H_{12}
hexane	C_6H_{14}

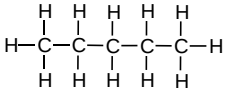
You can work out the formula of any of the alkanes using the general formula C_nH_{2n+2}

ISOMERISM

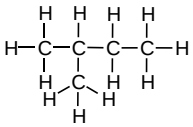
All of the alkanes containing 4 or more carbon atoms show structural isomerism, meaning that there are two or more different structural formulas that you can draw for each molecular formula. Isomers (from the Greek *isos* + *meros*, meaning "made of the same parts") are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. Alkanes with 1-3 carbons, methane (CH_4), ethane (C_2H_6), and propane (C_3H_8,) do not exist in isomeric forms because there is only one way to arrange the atoms in each formula so that each carbon atom has four bonds. However, C_4H_{10}, has more than possible structure. The four carbons can be drawn in a row to form butane or the can branch to form isobutane. The two compounds have different properties—for example, butane boils at −0.5°C, while isobutane boils at −11.7°C.



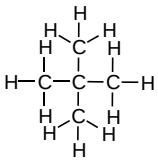
Likewise the molecular formula: C_5H_{12} has three possible isomer. The compound at the far left is pentane because it has all five carbon atoms in a continuous chain. The compound in the middle is isopentane; like isobutane, it has a one CH_3 branch off the second carbon atom of the continuous chain. The compound at the far right, discovered after the other two, was named neopentane (from the Greek *neos*, meaning “new”). Although all three have the same molecular formula, they have different properties, including boiling points: pentane, 36.1°C; isopentane, 27.7°C; and neopentane, 9.5°C.



pentane



isopentane



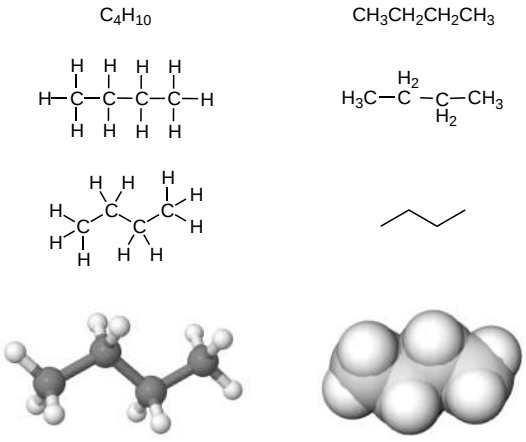
neopentane

Of the structures show above, butane and pentane are called **normal alkanes** or **straight-chain alkanes**, indicating that all contain a single continuous chain of carbon atoms and can be represented by a projection formula whose carbon atoms are in a straight line. The other structures, isobutane, isopentane, and neopentane are called called branched-chain alkanes. As the number of carbons in an akane increases the number of possible isomers also increases as shown in the table below.

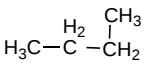
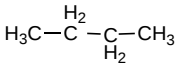
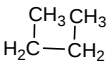
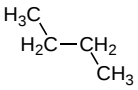
Table 3.2.2: Number of isomers for hydrocarbons

Molecular Formula	Number of Structural Isomers
CH_4	1
C_2H_6	1
C_3H_8	1
C_4H_{10}	2
C_5H_{12}	3
C_6H_{14}	5
C_7H_{16}	9
C_8H_{18}	18
C_9H_{20}	35
$C_{10}H_{22}$	75
$C_{14}H_{30}$	1858
$C_{18}H_{38}$	60,523
$C_{30}H_{62}$	4,111,846,763

Akanes can be represented in many different ways. The figure below shows some of the different ways straight-chain butane can be represented. Most often chemists refer to butane by the condensed structure $CH_3CH_2CH_2CH_3$ or *n*-C_4H_{10} where n denotes a normal straight alkane.



Note that many of these structures only imply bonding connections and do not indicate any particular geometry. The bottom two structures, referred to as "ball and stick" and "space filling" do show 3D geometry for butane. Because the four-carbon chain in butane may be bent in various ways the groups can rotate freely about the C–C bonds. However, this rotation does not change the identity of the compound. It is important to realize that bending a chain does *not* change the identity of the compound; all of the following represent the same compound, butane:

The nomenclature of straight alkanes is based on the number of carbon atoms they contain. The number of carbons are indicated by a prefix and the suffix -ane is added to indicate the molecules is an alkane. The prefix for three carbons is prop so adding -ane, the IUPAC name for C_3H_8 is propane. Likewise, the prefix for six is hex so the name for the straight chain isomer of C_6H_{14} is called hexane. The first ten prefixes should be memorized, because these alkane names from the basis for naming many other organic compounds.

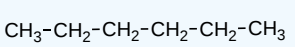
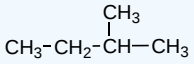
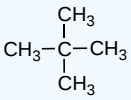
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Table **3.2.3**: The First 10 Straight-Chain Alkanes

Molecular Formula	Prefix	Condensed Structural Formula	Name
CH4	Meth	CH4	methane
C2H6	Eth	CH3CH3	ethane
C3H8	Prop	CH3CH2CH3	propane
C4H10	But	CH3CH2CH2CH3	butane
C5H12	Pent	CH3CH2CH2CH2CH3	pentane
C6H14	Hex	CH3(CH2)4CH3	hexane
C7H16	Hept	CH3(CH2)5CH3	heptane
C8H18	Oct	CH3(CH2)6CH3	octane
C9H20	Non	CH3(CH2)7CH3	nonane
C10H22	Dec	CH3(CH2)8CH3	decane

EXAMPLE 3.2.1: CHAIN ISOMERS IN PENTANE

Pentane, C_5H_{12}, has three chain isomers. If you think you can find any others, they are simply twisted versions of the ones below. If in doubt make some models.

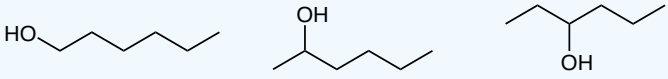




EXERCISES

EXERCISE 3.2.1

Draw all of the isomers for $C_6H_{14}O$ that contain a 6 carbon chain and an alcohol (-OH) functional group.

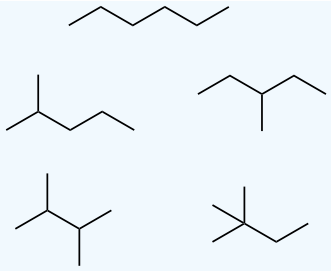
Answer



EXERCISE 3.2.2

Draw all possible isomers for C_6H_{14} (There are five total).

Answer



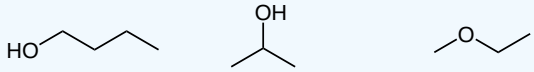
The top structure is when it is a 6 carbon chain. The middle row contains the 5 carbon chained isomers with branching at the 2nd and 3rd carbon. The bottom row contains the two 4 carbon chain isomers that can be drawn.

EXERCISE 3.2.3

Draw all possible isomers for C_3H_8.

Answer

The first structure is when an alcohol comes off the first carbon. The second structure is when the alcohol is coming off the central carbon. The third structure is the only possible ether form of C_3H_8.

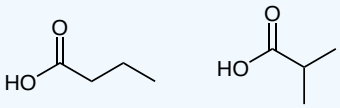


EXERCISE 3.2.4

Draw all possible isomers for $C_4H_8O_2$ that contain a carboxylic acid.

Answer

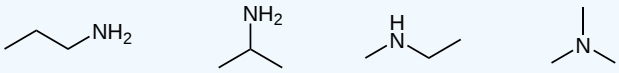
There are only 2 possibilities.



EXERCISE 3.2.5

Draw all possible isomers for C_3H_9N and indicate whether each amine is primary, secondary, or tertiary.

Answer

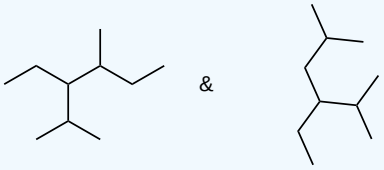


The first and second structures are primary amines. The third structure is a secondary amine. The last structure is a tertiary amine.

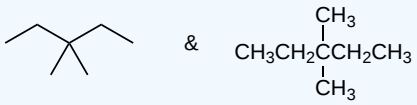
EXERCISE 3.2.6

Indicate whether each of the following sets are constitutional isomers, the same compound, or different compounds.

a)



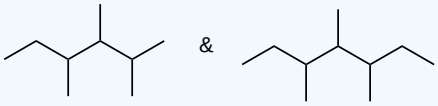
b)



c)



d)



Answer

a) Both structures have formulas of $C_{10}H_{22}$ and have different connectivity which makes these **constitutional isomers**.

b) Both structures have formulas of C_7H_{16} and have the same connectivity which makes these the **same compound**.

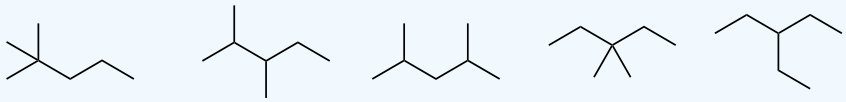
c) Both structure have formulas of C_7H_{16} and have different connectivity which makes these **constitutional isomers**.

d) The structure on the left has a formula of C_9H_{20} and the structure on the right has a formula of $C_{10}H_{22}$ so these are **different compounds**.

? EXERCISE 3.2.7

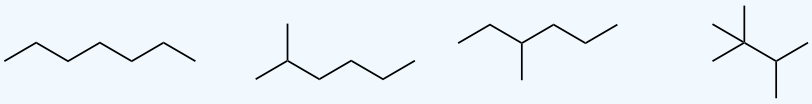
Draw the 5 constitutional isomers of C_7H_{16} (of the 9 total isomers possible) that have 5 carbons as the longest carbon chain length.

Answer



The 5 constitutional isomers with a 5 carbon chain length are shown above. Since there needs to be 7 carbons total, the 2 extra carbons are added as substituents. From left to right, the methyl group substitution pattern is 2,2, 2,3, 2,4, and 3,3, and the last one (on right) has a 3-ethyl substituent.

The other 4 possible constitutional isomers (with different length carbon chains) are shown below.



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3.3: ALKYL GROUPS

OBJECTIVES

After completing this section, you should be able to

1. recognize and name any alkyl group that can be considered to have been formed by the removal of a terminal hydrogen atom from a straight-chain alkane containing ten or fewer carbon atoms.
2. explain what is meant by a primary, secondary, tertiary or quaternary carbon atom.
3. represent the various types of organic compounds using the symbol “R” to represent any alkyl group.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alkyl group
- methyl group
- isopropyl group
- *sec*-butyl group
- isobutyl group
- *tert*-butyl group
- primary carbon
- secondary carbon
- tertiary carbon
- quaternary carbon

STUDY NOTES

The differences among primary, secondary, tertiary and quaternary carbon atoms are explained in the following discussion. A convenient way of memorizing this classification scheme is to remember that a primary carbon atom is attached directly to only one other carbon atom, a secondary carbon atom is attached directly to two carbon atoms, and so on.

The **IUPAC** system requires first that we have names for simple unbranched chains and second, that we have names for simple alkyl groups that may be attached to the chains. An **alkyl group** is formed by removing one hydrogen from the alkane chain. The removal of this hydrogen results in a stem change from **-ane** to **-yl** to indicate an alkyl group. The removal of a hydrogen from methane, CH_4, creates a methyl group $-CH_3$. Likewise, the removal of a hydrogen from ethane, CH_3CH_3, creates an ethyl group $-CH_2CH_3$. The nomenclature pattern can continue to provide a series of straight-chain alkyl groups from straight chain alkanes with a hydrogen removed from the end. Note, the letter **R** is used to designate a generic (unspecified) alkyl group.

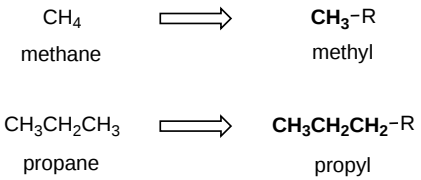


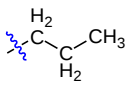
Table **3.3.2**: Straight chain alkane and alkyl group names

Alkane	Name	Alkyl Group	Name (Abbreviation)
CH_4	Methane	$-CH_3$	Methyl (Me)
CH_3CH_3	Ethane	$-CH_2CH_3$	Ethyl (Et)
$CH_3CH_2CH_3$	Propane	$-CH_2CH_2CH_3$	Propyl (Pr)
$CH_3CH_2CH_2CH_3$	Butane	$-CH_2CH_2CH_2CH_3$	Butyl (Bu)
$CH_3CH_2CH_2CH_2CH_3$	Pentane	$-CH_2CH_2CH_2CH_2CH_3$	Pentyl
$CH_3CH_2CH_2CH_2CH_2CH_3$	Hexane	$-CH_2CH_2CH_2CH_2CH_2CH_3$	Hexyl

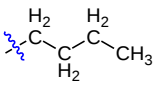
Prior to the systematic nomenclature developed for organic chemistry, prefixes were used to specify the connection point of straight-chain and branched-chain alkyl groups. Although the modern nomenclature system, discussed in the next section, is preferred these older terms are still often used, especially in solvents and reagents. Thus, an understanding of these prefixes is important to understanding organic chemistry. Notice that the total number of carbons in the alkyl subsistent is still indicated with the **prefix + yl**. For methyl and ethyl alkyl groups there is only one possible connection point so connection prefixes are not necessary. Starting with a three carbon alkyl group (propyl) the possibility of multiple connection points necessitates connection prefixes. These prefixes are often abbreviated with a letter which is italicized.

NORMAL (*N*)

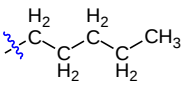
The prefix "n" is used to indicate a connection at the end of a straight-chain alkane. This prefix is not commonly used to just indicate alkyl subsistent as discussed above. However it is sometime used to indicate the connection of a functional group onto a straight alkane.



n-propyl
or propyl



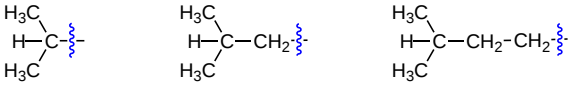
n-butyl
or butyl



n-pentyl
or pentyl

ISO (*I*)

Starting with propyl alkyl groups there is the possibility of a connection other than the very end. The prefix "iso" implies that the connection ends with a $(CH_3)_2CH$- group.



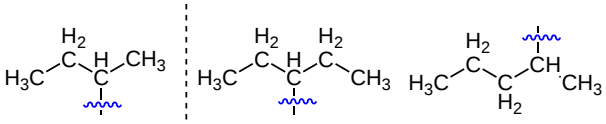
isopropyl
or *i*-propyl

isobutyl
or *i*-butyl

isopentyl
or *i*-pentyl

SECONDARY (*SEC*)

With butyl straight-chain alkyl groups there is the possibility of a connection on the second carbon from the end of the chain. These alkyl groups are given the prefix "*Sec*." This is not used for pentyl or hexyl groups because there is more than one structure that are not identical that could be named as sec-pentyl or sec-hexyl.

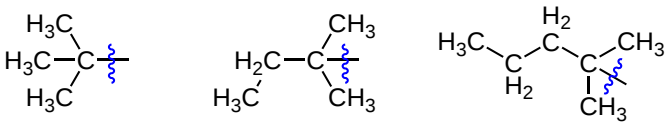


sec -butyl

NOT *sec* -pentyl

TERTIARY (*TERT* OR *T*)

Starting with four carbon alkyl groups, there is an isomer which can have a connection to a tertiary carbon. These alkyl groups get the prefix "*t*."



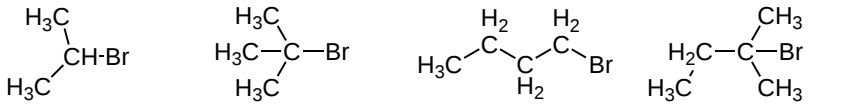
tert-butyl
or *t*-butyl

tert-pentyl
or *t*-pentyl

tert-hexyl
or *t*-hexyl

EXAMPLE:

The naming system described above is often used to describe halogens which contain only a few carbons. The halogen is shown as bonded to the connection point of the alkyl group.



isopropyl bromide

t-butyl bromide

n-butyl bromide

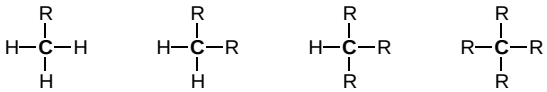
tert-pentyl bromide

CLASSIFICATION OF CARBON ATOMS

Carbons have a special terminology to describe how many other carbons they are attached to. This allows for an easy description of branching in alkanes. Also, we will find that the number of carbons attached to a given atom will have subtle effects on its chemistry.

- Primary carbons (1°) attached to one other C atom.
- Secondary carbons (2°) are attached to two other C's.
- Tertiary carbons (3°) are attached to three other C's.
- Quaternary carbons (4°) are attached to four C's.

The figure below use the group "R" to represent an alkyl group of unspecified length. R typically used to represent alkyl groups but an also represent a part of a molecule which is either unspecified or not germane to the discussion.



1° **C**

2° **C**

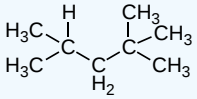
3° **C**

4° **C**

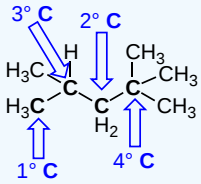
This terminology will be used repeatedly in organic chemistry to describe the number of carbons attached to a specific atom, however, the atom will not always a carbon.

EXAMPLE 3.3.1

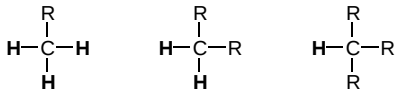
Please indicate the the number of 1°, 2°, 3°, and 4° carbons in the following molecule:



- The molecule has five Primary carbons (1°).
- The molecule has one Secondary carbon (2°).
- The molecule has one Tertiary carbon (3°).
- The molecule has one Quaternary carbon (4°)



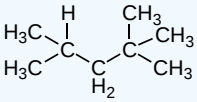
Hydrogen atoms are also classified in this manner. A hydrogen atom attached to a primary carbon atom is called a primary hydrogen ect.



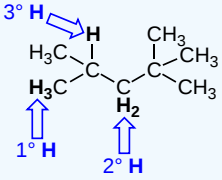
- Primary hydrogens (1°) are attached to carbons bonded to one other C atom
- Secondary hydrogens (2°) are attached to carbons bonded to two other C's
- Tertiary hydrogens (3°) are attached to carbons bonded to three other C's
- It is not possible to have a quaternary hydrogen (4°).

EXAMPLE 3.3.2

Please indicate the the number of 1°, 2°, and 3°, hydrogens are in the following molecule:



- The molecule has fifteen Primary (1°) hydrogens.
- The molecule has two Secondary (2°) hydrogens.
- The molecule has one Tertiary (3°) hydrogen.

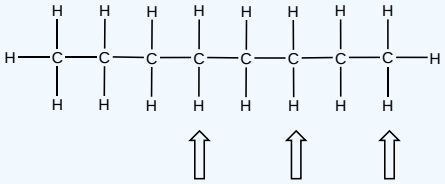


EXERCISES

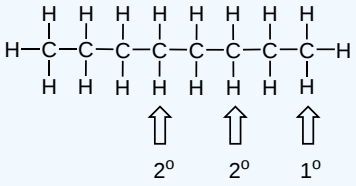
EXERCISE 3.3.1

Determine whether the H's indicated in the following structure are 1°, 2°, or 3°.

https://chem.libretexts.org/@go/page/31400

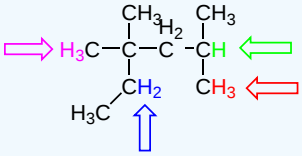


Answer

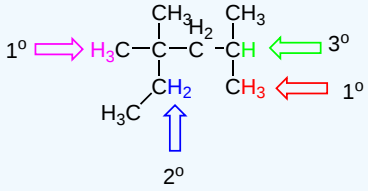


EXERCISE 3.3.2

Determine whether the H's indicated in the following structure is 1°, 2°, or 3°.

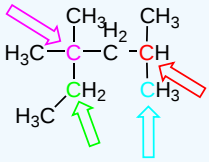


Answer

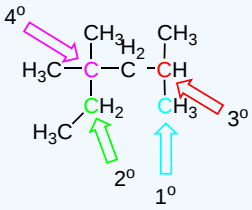


EXERCISE 3.3.3

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.



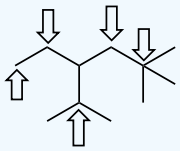
Answer



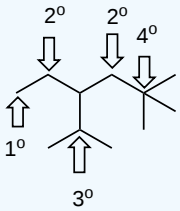
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EXERCISE 3.3.4

Determine whether the carbons indicated in the structure below are 1°, 2°, 3°, or 4°.

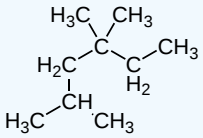


Answer



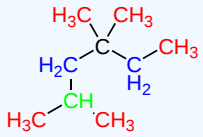
EXERCISE 3.3.5

Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



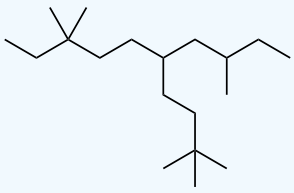
Answer

There are 5 primary (1°) C's, 2 secondary (2°) C's, 1 tertiary (3°) C and 1 quaternary (4°) C in the structure (seen color coded below).



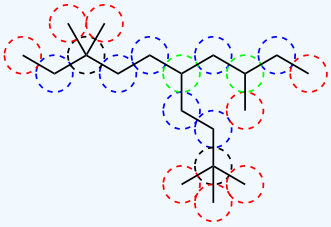
EXERCISE 3.3.6

Please indicate the total number of each type 1°, 2°, 3°, and 4° carbons in the following molecule.



Answer

There are 8 primary (1°) C's, 7 secondary (2°) C's, 2 tertiary (3°) C's and 2 quaternary (4°) C's in the structure (seen color coded below).



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3.4: NAMING ALKANES

OBJECTIVES

After completing this section, you should be able to

1. provide the correct IUPAC name for any given alkane structure (Kekulé, condensed or shorthand).
2. draw the Kekulé, condensed or shorthand structure of an alkane, given its IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- IUPAC system

STUDY NOTES

The IUPAC system of nomenclature aims to ensure

1. that every organic compound has a unique, unambiguous name.
2. that the IUPAC name of any compound conveys the structure of that compound to a person familiar with the system.

One way of checking whether the name you have given to an alkane is reasonable is to count the number of carbon atoms implied by the chosen name. For example, if you named a compound 3-ethyl-4-methylheptane, you have indicated that the compound contains a total of 10 carbon atoms—seven carbon atoms in the main chain, two carbon atoms in an ethyl group, and one carbon atom in a methyl group. If you were to check the given structure and find 11 carbon atoms, you would know that you had made a mistake. Perhaps the name you should have written was 3-ethyl-4,4-dimethylheptane!

When naming alkanes, a common error of beginning students is a failure to pick out the longest carbon chain. For example, the correct name for the compound shown below is 3-methylheptane, not 2-ethylhexane.

Remember that every substituent must have a number, and do not forget the prefixes: di, tri, tetra, etc.

You must use commas to separate numbers, and hyphens to separate numbers and substituents. Notice that 3-methylhexane is one word.

Hydrocarbons having no double or triple bond functional groups are classified as **alkanes** or **cycloalkanes**, depending on whether the carbon atoms of the molecule are arranged only in chains or also in rings. Although these hydrocarbons have no functional groups, they constitute the framework on which functional groups are located in other classes of compounds, and provide an ideal starting point for studying and naming organic compounds. The alkanes and cycloalkanes are also members of a larger class of compounds referred to as **aliphatic**. Simply put, aliphatic compounds are compounds that do not incorporate any aromatic rings in their molecular structure.

The following table lists the IUPAC names assigned to simple continuous-chain alkanes from C-1 to C-10. A common "**ane**" suffix identifies these compounds as alkanes. Longer chain alkanes are well known, and their names may be found in many reference and text books. The names **methane** through **decane** should be memorized, since they constitute the root of many IUPAC names. Fortunately, common numerical prefixes are used in naming chains of five or more carbon atoms.

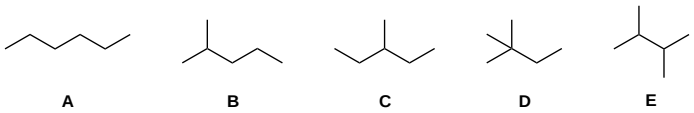
Table 3.4.1 : Simple Unbranched Alkanes

Name	Molecular Formula	Structural Formula	Isomers	Name	Molecular Formula	Structural Formula	Isomers
meth**ane**	CH_4	CH_4	1	hex**ane**	C_6H_{14}	$CH_3(CH_2)_4CH_3$	5
eth**ane**	C_2H_6	CH_3CH_3	1	hept**ane**	C_7H_{16}	$CH_3(CH_2)_5CH_3$	9
prop**ane**	C_3H_8	$CH_3CH_2CH_3$	1	oct**ane**	C_8H_{18}	$CH_3(CH_2)_6CH_3$	18
but**ane**	C_4H_{10}	$CH_3CH_2CH_2CH_3$	2	non**ane**	C_9H_{20}	$CH_3(CH_2)_7CH_3$	35
pent**ane**	C_5H_{12}	$CH_3(CH_2)_3CH_3$	3	dec**ane**	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$	75

SOME IMPORTANT BEHAVIOR TRENDS AND TERMINOLOGIES

1. The formulas and structures of these alkanes increase uniformly by a CH_2 increment.
2. A uniform variation of this kind in a series of compounds is called **homologous**.
3. These formulas all fit the $\mathbf{C_nH_{2n+2}}$ rule. This is also the highest possible H/C ratio for a stable hydrocarbon.
4. Since the H/C ratio in these compounds is at a maximum, we call them **saturated** (with hydrogen).

Beginning with butane (C_4H_{10}), and becoming more numerous with larger alkanes, we note the existence of alkane isomers. For example, there are five C_6H_{14} isomers, shown below as abbreviated line formulas (**A** through **E**):



A **B** **C** **D** **E**

Although these distinct compounds all have the same molecular formula, only one (**A**) can be called hexane. How then are we to name the others?

The **IUPAC** system requires first that we have names for simple unbranched chains, as noted above, and second that we have names for simple alkyl groups that may be attached to the chains. Examples of some common **alkyl groups** are given in the following table. Note that the "ane" suffix is replaced by "**yl**" in naming groups. The symbol **R** is used to designate a generic (unspecified) alkyl group.

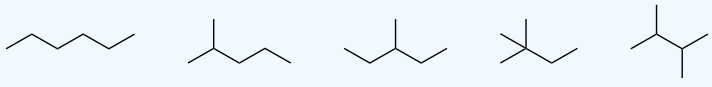
Table 3.4.2 : Alkyl Groups Names

Group	CH_3–	C_2H_5–	$CH_3CH_2CH_2$–	$(CH_3)_2CH$–	$CH_3CH_2CH_2CH_2$–	$(CH_3)_2CHCH_2$–	$CH_3CH_2CH(CH_3)$–	$(CH_3)_3C$–	R–
Name	Methyl	Ethyl	Propyl	Isopropyl	Butyl	Isobutyl	sec-Butyl	tert-Butyl	Alkyl

IUPAC RULES FOR ALKANE NOMENCLATURE

1. Find and name the longest continuous carbon chain.
2. Identify and name groups attached to this chain.
3. Number the chain consecutively, starting at the end nearest a substituent group.
4. Designate the location of each substituent group by an appropriate number and name.
5. Assemble the name, listing groups in alphabetical order.
6. The prefixes di, tri, tetra etc., used to designate several groups of the same kind, are not considered when alphabetizing.

EXAMPLE 3.4.1 : ALKANES



A **B** **C** **D** **E**

The IUPAC names of the isomers of hexane are: **A** hexane **B** 2-methylpentane **C** 3-methylpentane **D** 2,2-dimethylbutane **E** 2,3-dimethylbutane

HALOGEN GROUPS

Halogen substituents are easily accommodated, using the names: fluoro (F-), chloro (Cl-), bromo (Br-) and iodo (I-).

EXAMPLE 3.4.2 : HALOGEN SUBSTITUTION

For example, $(CH_3)_2CHCH_2CH_2Br$ would be named 1-bromo-3-methylbutane. If the halogen is bonded to a simple alkyl group an alternative "alkyl halide" name may be used. Thus, C_2H_5Cl may be named chloroethane (no locator number is needed for a two carbon chain) or ethyl chloride.

ALKYL GROUPS

Alkanes can be described by the general formula C_nH_{2n+2}. An alkyl group is formed by removing one hydrogen from the alkane chain and is described by the formula C_nH_{2n+1}. The removal of this hydrogen results in a stem change from **-ane** to **-yl**. Take a look at the following examples.

CH_4 ⟹ $\mathbf{CH_3}$–R

methane → methyl

$CH_3CH_2CH_3$ ⟹ $\mathbf{CH_3CH_2CH_2}$–R

propane → propyl

The same concept can be applied to any of the straight chain alkane names provided in the table below.

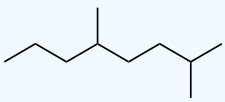
Name	Molecular Formula	Condensed Structural Formula
Methane	CH_4	CH_4
Ethane	C_2H_6	CH_3CH_3
Propane	C_3H_8	$CH_3CH_2CH_3$
Butane	C_4H_{10}	$CH_3(CH_2)_2CH_3$
Pentane	C_5H_{12}	$CH_3(CH_2)_3CH_3$
Hexane	C_6H_{14}	$CH_3(CH_2)_4CH_3$
Heptane	C_7H_{16}	$CH_3(CH_2)_5CH_3$
Octane	C_8H_{18}	$CH_3(CH_2)_6CH_3$
Nonane	C_9H_{20}	$CH_3(CH_2)_7CH_3$
Decane	$C_{10}H_{22}$	$CH_3(CH_2)_8CH_3$
Undecane	$C_{11}H_{24}$	$CH_3(CH_2)_9CH_3$
Dodecane	$C_{12}H_{26}$	$CH_3(CH_2)_{10}CH_3$
Tridecane	$C_{13}H_{28}$	$CH_3(CH_2)_{11}CH_3$
Tetradecane	$C_{14}H_{30}$	$CH_3(CH_2)_{12}CH_3$
Pentadecane	$C_{15}H_{32}$	$CH_3(CH_2)_{13}CH_3$
Hexadecane	$C_{16}H_{34}$	$CH_3(CH_2)_{14}CH_3$
Heptadecane	$C_{17}H_{36}$	$CH_3(CH_2)_{15}CH_3$
Octadecane	$C_{18}H_{38}$	$CH_3(CH_2)_{16}CH_3$
Nonadecane	$C_{19}H_{40}$	$CH_3(CH_2)_{17}CH_3$
Eicosane	$C_{20}H_{42}$	$CH_3(CH_2)_{18}CH_3$

THREE RULES FOR NAMING ALKANES

1. Choose the longest, most substituted carbon chain containing a functional group.
2. A carbon bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number.
3. Take the alphabetical order into consideration; that is, after applying the first two rules given above, make sure that your substituents and/or functional groups are written in alphabetical order.

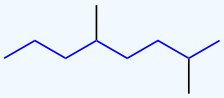
✔ EXAMPLE 3.4.3

What is the name of the follow molecule?

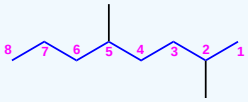


Solution

Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example does not contain any functional groups, so we only need to be concerned with choosing the longest, most substituted carbon chain. The longest carbon chain has been highlighted in blue and consists of eight carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substitute present must have the lowest possible number. Because this example does not contain any functional groups, we only need to be concerned with the two substitutes present, that is, the two methyl groups. If we begin numbering the chain from the left, the methyls would be assigned the numbers 4 and 7, respectively. If we begin numbering the chain from the right, the methyls would be assigned the numbers 2 and 5. Therefore, to satisfy the second rule, numbering begins on the right side of the carbon chain as shown below. This gives the methyl groups the lowest possible numbering.

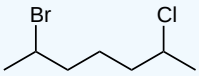


Rule 3: In this example, there is no need to utilize the third rule. Because the two substitutes are identical, neither takes alphabetical precedence with respect to numbering the carbons. This concept will become clearer in the following examples.

The name of this molecule is **2,5-dimethyloctane**

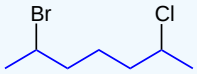
EXAMPLE 3.4.4

What is the name of the follow molecule?



Solution

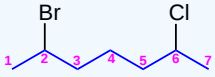
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. If there are no functional groups, then any substituent present must have the lowest possible number. In this example, numbering the chain from either the left or the right would satisfy this rule. If we number the chain from the left, bromine and chlorine would be assigned the second and sixth carbon positions, respectively. If we number the chain from the right, chlorine would be assigned the second position and bromine would be assigned the sixth position. In other words, whether we choose to number from the left or right, the functional groups occupy the second and sixth positions in the chain. To select the correct numbering scheme, we need to utilize the third rule.



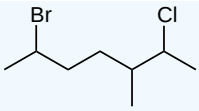
Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.



The name of this molecule is: **2-bromo-6-chloroheptane**

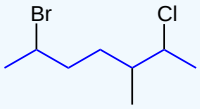
EXAMPLE 3.4.5

What is the name of the follow molecule?

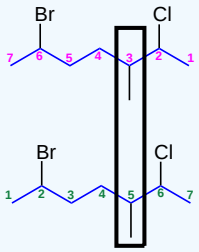


Solution

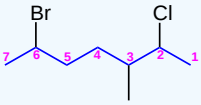
Rule #1: Choose the longest, most substituted carbon chain containing a functional group. This example contains two functional groups, bromine and chlorine, and one substitute, the methyl group. The longest carbon chain has been highlighted in blue and consists of seven carbons.



Rule #2: Carbons bonded to a functional group must have the lowest possible carbon number. After taking functional groups into consideration, any substitutes present must have the lowest possible carbon number. This particular example illustrates the **point of difference principle**. If we number the chain from the left, bromine, the methyl group and chlorine would occupy the second, fifth and sixth positions, respectively. This concept is illustrated in the second drawing below. If we number the chain from the right, chlorine, the methyl group and bromine would occupy the second, third and sixth positions, respectively, which is illustrated in the first drawing below. The position of the methyl, therefore, becomes a **point of difference**. In the first drawing, the methyl occupies the third position. In the second drawing, the methyl occupies the fifth position. To satisfy the second rule, we want to choose the numbering scheme that provides the lowest possible numbering of this substitute. Therefore, the first of the two carbon chains shown below is correct.



Therefore, the first numbering scheme is the appropriate one to use.



Once you have determined the correct numbering of the carbons, it is often useful to make a list, including the functional groups, substitutes, and the name of the parent chain.

Rule #3: After applying the first two rules, take the alphabetical order into consideration. Alphabetically, bromine comes before chlorine. Therefore, bromine is assigned the second carbon position, and chlorine is assigned the sixth carbon position.

Parent chain: heptane Substitutents: 2-chloro 3-methyl 6-bromo

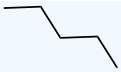
The name of this molecule is: **6-bromo-2-chloro-3-methylheptane**

EXERCISES

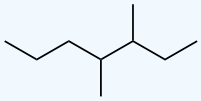
? EXERCISE 3.4.1

Give the proper IUPAC names of the following compounds.

a)



b)



c)



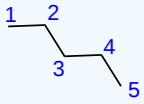
Answer

a) Since this structure is an unbranched alkane (all single bonds) with a 5 carbon chain length, its name would be **pentane**.

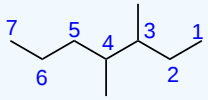
b) This alkane has a 7 carbon longest continuous chain length that we number from right to left to get the first methyl substituent we encounter to have the lowest possible number (3 versus being 4 if numbering from left to right). This causes it to have 2 methyl substituents at positions 3 & 4 so we would name it indicating those numbers and the prefix dimethyl which gives a proper IUPAC name of **3,4-dimethylheptane**.

c) This alkane has a 5 carbon longest continuous chain length (which could be numbered from left to right or right to left due to the symmetry at C-3). It has two methyl substituents off of C-3 so the proper IUPAC name is **3,3-dimethylpentane.**

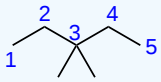
a)



b)



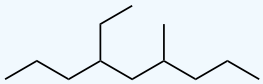
c)



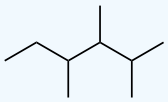
EXERCISE 3.4.2

Give the proper IUPAC names of the following compounds.

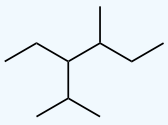
a)



b)



c)



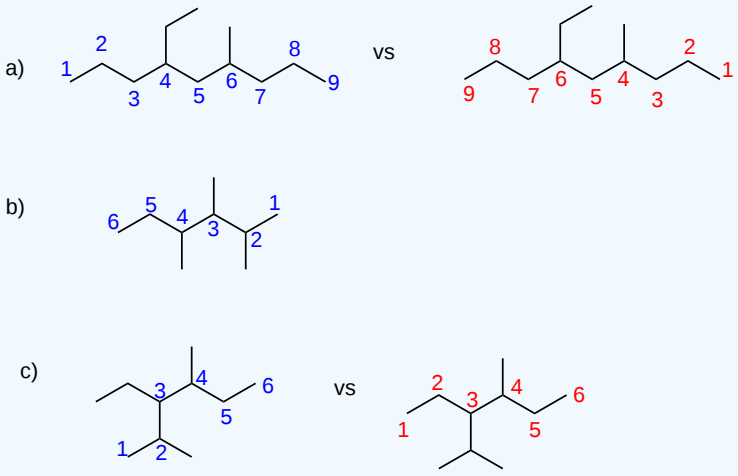
Answer

a) This alkane has a 9 carbon longest continuous chain length that we number from left to right (structure on left numbered in blue) to make the ethyl substituent be number 4. For the structure on the right (numbered in red) going from right to left, the methyl

substituent is number 4. Since ethyl is higher in the alphabetical order, you want to make it have the lower number so the structure on the left (blue numbering) takes priority and the name is **4-ethyl-6-methylnonane**.

b) This alkane has a 6 carbon longest continuous chain length that we number from right to left to make the first methyl be C-2 (versus the opposite direction which would make the first methyl C-3). Since there are 3 methyl substituents at positions 2,3, & 4, this compound would have the name **2,3,4-trimethylhexane**.

c) This 6 carbon alkane can be numbered along different chains (see below) as well as in the opposite directions. This shows the two different chains that can be drawn (making the first substituent in that chain the lowest number). The structure on the left (numbered in blue) is the correct choice since it causes more substituents to be on the longest continuous chain (3 vs 2 in the structure on the right). This would make the IUPAC name of the structure **3-ethyl-2,4-dimethylhexane**. (Notice how ethyl takes priority over methyl and the di- is not considered for alphabetizing.)



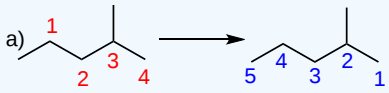
EXERCISE 3.4.3

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

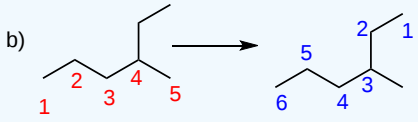
a. 1,3-dimethylbutane
b. 4-ethylpentane
c. 2-ethyl-3-methylpentane

Answer

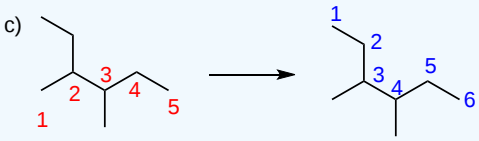
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), the correct name should be **2-methylpentane**.



b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and we start the numbering on the end to the right to make the methyl substituent come off at C-3 (instead of beong at C-4 if we numbered it the opposite direction) the correct name should be **3-methyl hexane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is 6 C's and since this molecule is symmetrical (between carbon 3 & 4), you can start the numbers from either end. In this case, we have methyl substituents coming off of carbons 3 & 4 so the proper name is **3,4-dimethyl hexane**.



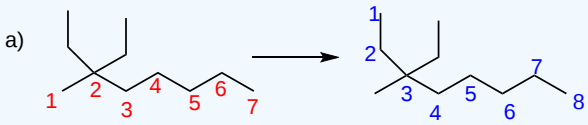
EXERCISE 3.4.4

All of the following names represent a compound that has been named improperly. Draw out the structure from the name and give the proper IUPAC name for the compounds.

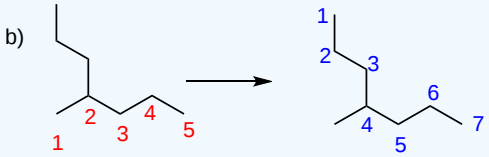
a. 2,2-diethylheptane
b. 2-propylpentane
c. 4,4-diethylbutane

Answer

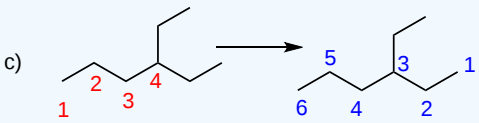
a) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 8 C's and you have an ethyl substituent at C-3 and a methyl substituent also at C-3 so the proper name is **3- ethyl-3-methyloctane**.



b) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right), notice that the longest chain is now 7 C's and since this molecule is symmetrical (at carbon 4), you can start the numbers from either end. There is a methyl substituent at C-4 so the proper name is **4-methylheptane**.



c) The structure that can be drawn for the improper name is shown below on the left. When you renumber it properly (structure on the right) going from right to left (to make the ethyl substituent have the lowest number possible), the correct name is **3-ethylhexane**



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3.5: PROPERTIES OF ALKANES

OBJECTIVES

After completing this section, you should be able to

1. arrange a number of given straight-chain alkanes in order of increasing or decreasing boiling point or melting point.
2. arrange a series of isomeric alkanes in order of increasing or decreasing boiling point.
3. explain the difference in boiling points between a given number of alkanes.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- van der Waals force (also known as London Dispersion force)

Alkanes are not very reactive and have little biological activity; all alkanes are colorless and odorless non-polar compounds. The relative weak London dispersion forces of alkanes result in gaseous substances for short carbon chains, volatile liquids with densities around 0.7 g/mL for moderate carbon chains, and solids for long carbon chains. For molecules with the same functional groups, there is a direct relationship between the size and shape of molecules and the strength of the intermolecular forces (IMFs) causing the differences in the physical states.

BOILING POINTS

Table **3.5.1** describes some of the properties of some straight-chain alkanes. There is not a significant electronegativity difference between carbon and hydrogen, thus, there is not any significant bond polarity. The molecules themselves also have very little polarity. A totally symmetrical molecule like methane is completely non-polar, meaning that the only attractions between one molecule and its neighbors will be Van der Waals dispersion forces. These forces will be very small for a molecule like methane but will increase as the molecules get bigger. Therefore, the boiling points of the alkanes increase with molecular size.

For isomers, the more branched the chain, the lower the boiling point tends to be. Van der Waals dispersion forces are smaller for shorter molecules and only operate over very short distances between one molecule and its neighbors. It is more difficult for short, fat molecules (with lots of branching) to lie as close together as long, thin molecules.

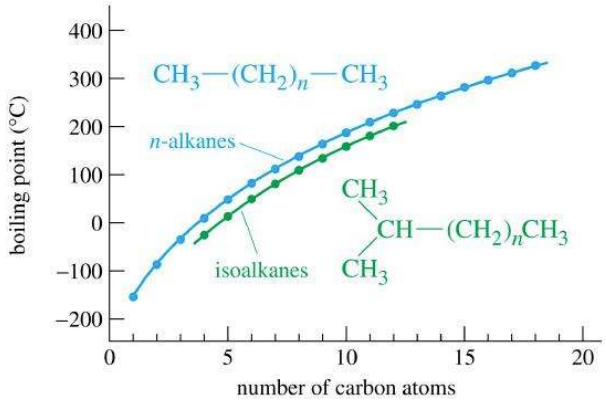
The boiling points shown are for the "straight chain" isomers of which there is more than one. The first four alkanes are gases at room temperature, and solids do not begin to appear until about $C_{17}H_{36}$, but this is imprecise because different isomers typically have different melting and boiling points.

Table **3.5.1**: Physical Properties of Some Alkanes

Molecular Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density (20°C)*	Physical State (at 20°C)
methane	CH_4	–182	–164	0.668 g/L	gas
ethane	C_2H_6	–183	–89	1.265 g/L	gas
propane	C_3H_8	–190	–42	1.867 g/L	gas
butane	C_4H_{10}	–138	–1	2.493 g/L	gas
pentane	C_5H_{12}	–130	36	0.626 g/mL	liquid
hexane	C_6H_{14}	–95	69	0.659 g/mL	liquid
octane	C_8H_{18}	–57	125	0.703 g/mL	liquid
decane	$C_{10}H_{22}$	–30	174	0.730 g mL	liquid

*Note the change in units going from gases (grams per liter) to liquids (grams per milliliter). Gas densities are at 1 atm pressure.

The boiling points for the "straight chain" isomers and isoalkanes isomers are shown to demonstrate that branching decreases the surfaces area, weakens the IMFs, and lowers the boiling point.



EXAMPLE 3.5.1: BOILING POINTS OF ALKANES

For example, the boiling points of the three isomers of C_5H_{12} are:

- pentane: 309.2 K
- 2-methylbutane: 301.0 K
- 2,2-dimethylpropane: 282.6 K

The slightly higher boiling points for the cycloalkanes are presumably because the molecules can get closer together because the ring structure makes them better able!

EXERCISE 3.5.1

For each of the following pairs of compounds, select the substance which you expect to have the higher boiling point:

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Solution

a. nonane, since it has more atoms it will have greater IMF
b. octane, since it is not branched, the molecules can pack closer together increasing IMF

SOLUBILITY

Alkanes are virtually insoluble in water, but dissolve in organic solvents. However, liquid alkanes are good solvents for many other non-ionic organic compounds.

SOLUBILITY IN WATER

When a molecular substance dissolves in water, the following must occur:

- break the intermolecular forces within the substance. In the case of the alkanes, these are the Van der Waals dispersion forces.
- break the intermolecular forces in the water so that the substance can fit between the water molecules. In water, the primary intermolecular attractions are hydrogen bonds.

Breaking either of these attractions requires energy, although the amount of energy to break the Van der Waals dispersion forces in something like methane is relatively negligible; this is not true of the hydrogen bonds in water.

As something of a simplification, a substance will dissolve if there is enough energy released when new bonds are made between the substance and the water to compensate for what is used in breaking the original attractions. The only new attractions between the alkane and the water molecules are Van der Waals forces. These forces do not release a sufficient amount of energy to compensate for the energy required to break the hydrogen bonds in water. The alkane does not dissolve.

> This is a simplification because entropic effects are important when things dissolve.

SOLUBILITY IN ORGANIC SOLVENTS

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals. Therefore, when an alkane dissolves in an organic solvent, the Van der Waals forces are broken and are replaced by new Van der Waals forces. The two processes more or less cancel each other out energetically; thus, there is no barrier to solubility.

? EXERCISE 3.5.1

For each of the following pairs of compounds, select the substance you expect to have the higher boiling point.

a. octane and nonane.
b. octane and 2,2,3,3-tetramethylbutane.

Answer

Nonane will have a higher boiling point than octane, because it has a longer carbon chain than octane. Octane will have a higher boiling point than 2,2,3,3-tetramethylbutane, because it branches less than 2,2,3,3-tetramethylbutane, and therefore has a larger "surface area" and more van der Waals forces.

Note: The actual boiling points are:

- nonane, 150.8°C
- octane, 125.7°C
- 2,2,3,3-tetramethylbutane, 106.5°C

REACTIONS OF ALKANES

Alkanes undergo very few reactions. There are two important reactions that are still possible, combustion and halogenation. The halogenation reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

COMBUSTION

Complete combustion (given sufficient oxygen) of any hydrocarbon produces carbon dioxide, water, and a significant amount of heat. Due to the exothermic nature of these combustion reactions, alkanes are commonly used as a fuel source (for example: propane for outdoor grills, butane for lighters). The hydrocarbons become harder to ignite as the molecules get bigger. This is because the larger molecules don't vaporize as easily. If the liquid is not very volatile, only those molecules on the surface can react with the oxygen. Larger molecules have greater Van der Waals attractions which makes it more difficult for them to break away from their neighbors and become a gas. An example combustion reaction is shown for propane:

$$C_3H_8 + O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + 2044\,kJ/mol$$

HALOGENATION

Halogenation is the replacement of one or more hydrogen atoms in an organic compound by a halogen (fluorine, chlorine, bromine or iodine). Unlike the complex transformations of combustion, the halogenation of an alkane appears to be a simple **substitution reaction** in which a C-H bond is broken and a new C-X bond is formed.

Since only two covalent bonds are broken (C-H & Cl-Cl) and two covalent bonds are formed (C-Cl & H-Cl), this reaction seems to be an ideal case for mechanistic investigation and speculation. However, one complication is that all the hydrogen atoms of an alkane may undergo substitution, resulting in a mixture of products, as shown in the following unbalanced equation. The relative amounts of the various products depend on the proportion of the two reactants used. In the case of methane, a large excess of the hydrocarbon favors formation of methyl chloride as the chief product; whereas, an excess of chlorine favors formation of chloroform and carbon tetrachloride.

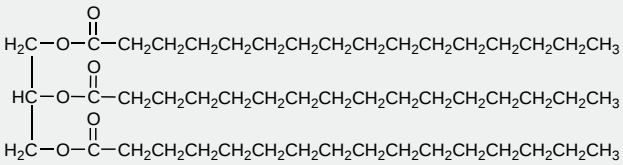
$$CH_4 + Cl_2 \rightarrow CH_3Cl + CH_2Cl + CHCl_3 + CCl_4 + HCl$$

LOOKING CLOSER: AN ALKANE BASIS FOR PROPERTIES OF OTHER COMPOUNDS

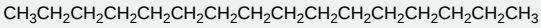
An understanding of the physical properties of alkanes is important since petroleum and natural gas and the many products derived from them—gasoline, bottled gas, solvents, plastics, and more—are composed primarily of alkanes. This understanding is also vital because it is the basis for describing the properties of other organic and biological compound families. For example, large portions of the structures of lipids consist of nonpolar alkyl groups. Lipids include the dietary fats and fat like compounds called phospholipids and sphingolipids that serve as structural components of living tissues. These compounds have both polar and nonpolar groups, enabling

them to bridge the gap between water-soluble and water-insoluble phases. This characteristic is essential for the selective permeability of cell membranes.

(a)



(b)



Tripalmitin (a), a typical fat molecule, has long hydrocarbon chains typical of most lipids. Compare these chains to hexadecane (b), an alkane with 16 carbon atoms.

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3.6: CONFORMATIONS OF ETHANE

OBJECTIVES

After completing this section, you should be able to

1. explain the concept of free rotation about a carbon-carbon single bond.
2. explain the difference between conformational isomerism and structural isomerism.
3. draw the conformers of ethane using both sawhorse representation and Newman projection.
4. sketch a graph of energy versus bond rotation for ethane, and discuss the graph in terms of torsional strain.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- conformation (conformer, conformational isomer)
- dihedral angle
- eclipsed conformation
- Newman projection
- staggered conformation
- strain energy
- torsional strain (eclipsing strain)

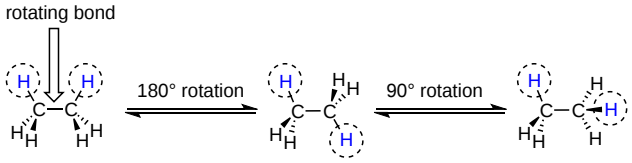
STUDY NOTES

You should be prepared to sketch various conformers using both sawhorse representations and Newman projections. Each method has its own advantages, depending upon the circumstances. Notice that when drawing the Newman projection of the eclipsed conformation of ethane, you cannot clearly draw the rear hydrogens exactly behind the front ones. This is an inherent limitation associated with representing a 3-D structure in two dimensions.

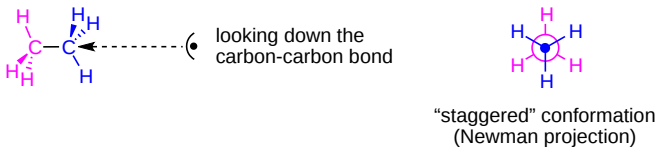
Conformational isomerism involves rotation about sigma bonds, and does not involve any differences in the connectivity of the atoms or geometry of bonding. Two or more structures that are categorized as conformational isomers, or **conformers**, are really just two of the exact same molecule that differ only in rotation of one or more sigma bonds.

ETHANE CONFORMATIONS

Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds does not result in any change in the shape of the molecule because the hydrogen atoms are essentially spherical. Rotation about the carbon-carbon bond, however, results in many different possible molecular conformations.



In order to better visualize these different conformations, it is convenient to use a drawing convention called the **Newman projection**. In a Newman projection, we look lengthwise down a specific bond of interest – in this case, the carbon-carbon bond in ethane. We depict the 'front' atom as a dot, and the 'back' atom as a larger circle.



The six carbon-hydrogen bonds are shown as solid lines protruding from the two carbons at 120°angles, which is what the actual tetrahedral geometry looks like when viewed from this perspective and flattened into two dimensions.

Figure 3.6.1: A 3D Model of Staggered Ethane.

The lowest energy conformation of ethane, shown in the figure above, is called the 'staggered' conformation. In the staggered conformation, all of the C-H bonds on the front carbon are positioned at an angle of 60° relative to the C-H bonds on the back carbon. This angle between a sigma bond on the front carbon compared to a sigma bond on the back carbon is called the dihedral angle. In this conformation, the distance between the bonds (and the electrons in them) is maximized. Maximizing the distance between the electrons decreases the electrostatic repulsion between the electrons and results in a more stable structure.

If we now rotate the front CH_3 group 60° clockwise, the molecule is in the highest energy 'eclipsed' conformation, and the hydrogens on the front carbon are as close as possible to the hydrogens on the back carbon.



"eclipsed" conformation

This is the highest energy conformation because of unfavorable electrostatic repulsion between the electrons in the front and back C-H bonds. The energy of the eclipsed conformation is approximately 3 kcal/mol (12 kJ/mol) higher than that of the staggered conformation. **Torsional strain** (or eclipsing strain) is the name give to the energy difference caused by the increased electrostatic repulsion of eclipsing bonds.

Another 60° rotation returns the molecule to a second staggared conformation. This process can be continued all around the 360° circle, with three possible eclipsed conformations and three staggered conformations, in addition to an infinite number of variations in between. We will focus on the staggered and eclipsed conformers since they are, respectively, the lowest and highest energy conformers.

UNHINDERED (FREE) ROTATIONS DO NOT EXIST IN ETHANE

The carbon-carbon bond is not *completely* free to rotate – the 3 kcal/mol torsional strain in ethane creates a barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not large enough to prevent rotation except at extremely cold temperatures. So at normal temperatures, the carbon-carbon bond is constantly rotating. However, at any given moment the molecule is more likely to be in a staggered conformation - one of the rotational 'energy valleys' - than in any other conformer. The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown in Figure 3.6.2.

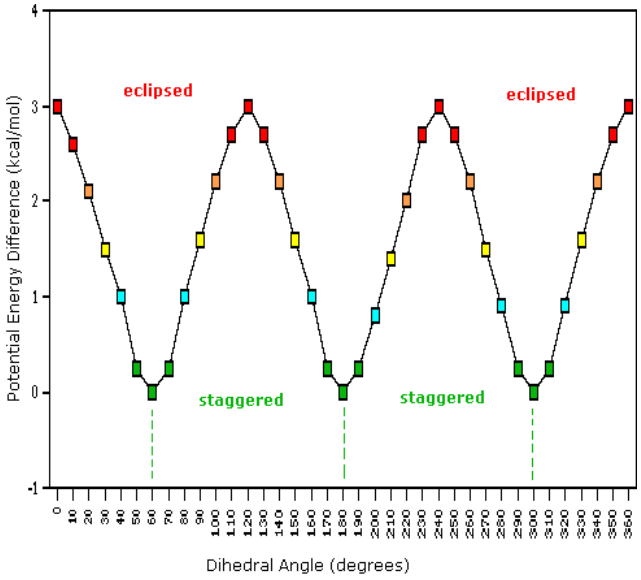


Figure 3.6.2: The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds. Valleys in the graph represent the low energy staggered conformers, while peaks represent the higher energy eclipsed conformers.

Although the conformers of ethane are in rapid equilibrium with each other, the 3 kcal/mol energy difference leads to a substantial preponderance of staggered conformers (> 99.9%) at any given time. The animation below illustrates the relationship between ethane's potential energy and its dihedral angle

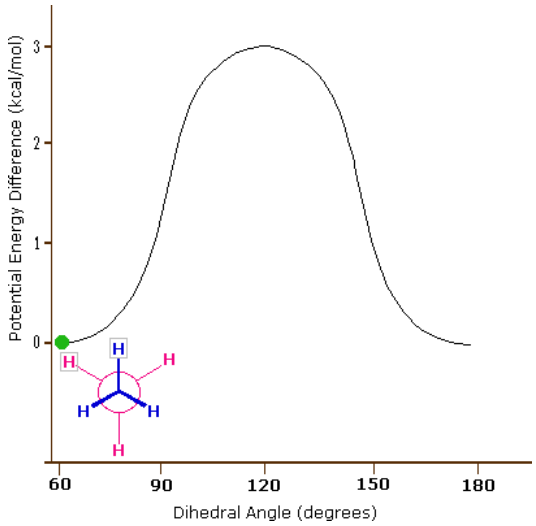


Figure 3.6.2: Animation of potential energy vs. dihedral angle in ethane

EXERCISES

1) What is the most stable rotational conformation of ethane and explain why it is preferred over the other conformation?

SOLUTIONS

1) Staggered, as there is less repulsion between the hydrogen atoms.

QUESTIONS

Q3.6.1

What is the most stable rotational conformation of ethane and explain why it is preferred over the other conformation?

SOLUTIONS

S3.6.1

Staggered, as there is less repulsion between the hydrogen atoms.

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3.7: CONFORMATIONS OF OTHER ALKANES

OBJECTIVES

After completing this section, you should be able to

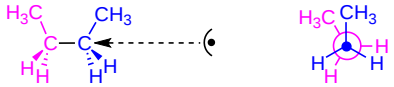
1. depict the staggered and eclipsed conformers of propane (or a similar compound) using sawhorse representations and Newman projections.
2. sketch a graph of energy versus bond rotation for propane (or a similar compound) and discuss the graph in terms of torsional strain.
3. depict the anti, gauche, eclipsed and fully eclipsed conformers of butane (or a similar compound), using sawhorse representations and Newman projections.
4. sketch a graph of energy versus C_2-C_3 bond rotation for butane (or a similar compound), and discuss it in terms of torsional and steric repulsion.
5. assess which of two (or more) conformers of a given compound is likely to predominate at room temperature from a semi-quantitative knowledge of the energy costs of the interactions involved.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- anti conformation
- gauche conformation
- eclipsed conformation
- steric repulsion (strain)

In butane, there are three rotating carbon-carbon sigma bonds to consider, but we will focus on the middle bond between C_2 and C_3. Below are two representations of butane in a conformation which puts the two CH_3 groups (C_1 and C_4) in the eclipsed position.

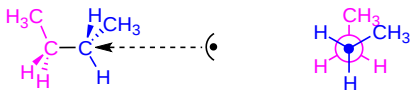


"eclipsed" (A)

Eclipsed interaction	Energy (kcal/mol)	Energy (kJ/mol)
H-H	1.0	4.0
H-CH_3	1.4	6.0
CH_3-CH_3	2.6	11.0

The CH_3-CH_3 groups create the significantly larger eclipsed interaction of 11.0 kJ/mol. There are also two H-H eclipsed interactions at 4.0 kJ/mol each to create a total of 2(4.0 kJ/mol) + 11.0 kJ/mol = 19.0 kJ/mol of strain. This is the highest energy conformation for butane, due to torsional strain caused by the electrostatic repulsion of electrons in the eclipsed bonds, but also because of another type of strain called '**steric repulsion'**, between the two rather bulky methyl groups. Steric strain comes about when two large groups, such as two methyl groups, try to occupy the same space. What results is a repulsive non-covalent interaction caused by their respective electron densities.

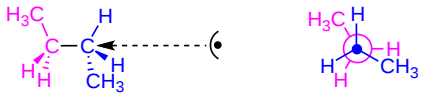
If we rotate the front, (blue) carbon by 60°clockwise, the butane molecule is now in a staggered conformation.



gauche

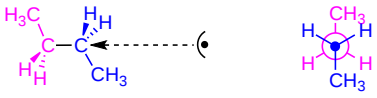
This is more specifically referred to as the '**gauche'** conformation of butane. Notice that although they are staggered, the two methyl groups are not as far apart as they could possibly be. There is still significant steric repulsion between the two bulky groups.

A further rotation of 60° gives us a second eclipsed conformation (B) in which both methyl groups are lined up with hydrogen atoms.



"eclipsed" (B)

Due to steric repulsion between methyl and hydrogen substituents, this eclipsed conformation B is higher in energy than the gauche conformation. However, because there is no methyl-to-methyl eclipsing, it is lower in energy than eclipsed conformation A. One more 60° rotation produces the **'anti'** conformation, where the two methyl groups are positioned opposite each other and steric repulsion is minimized.



anti

The anti conformation is the lowest energy conformation for butane. The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.

Figure* 3.7.1:* A 3D Structure of the Anti Butane Conformer.

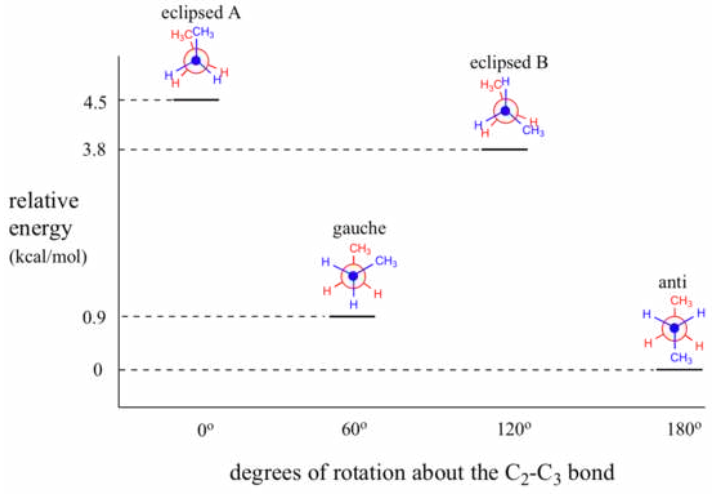


Figure 3.7.2: Potential curve vs dihedral angle of the C_2-C_3 bond of butane.

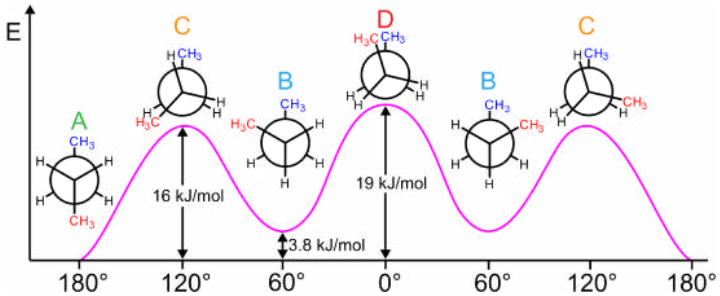
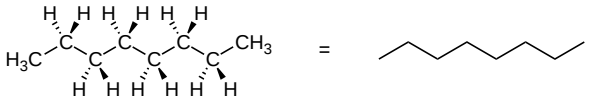


Figure 3.7.2: Newman projections of butane conformations & their relative energy differences (not total energies). Conformations form when butane rotates about one of its single covalent bond. Torsional/dihedral angle is shown on x-axis. Torsional/dihedral angle is shown on x-axis. Conformation names (according to IUPAC): **A**: anti-periplanar, anti or trans **B**: synclinal or gauche **C**: anticlinal or eclipsed **D**: syn-periplanar or cis. Source for conformation names & conformer classification: Pure & Appl. Chem., Vol. 68, No. 12, pp. 2193-2222, 1996. (Public Domain; Keministi).

At room temperature, butane is most likely to be in the lowest-energy anti conformation at any given moment in time, although the energy barrier between the anti and eclipsed conformations is not high enough to prevent constant rotation except at very low temperatures. For this reason (and also simply for ease of drawing), it is conventional to draw straight-chain alkanes in a zigzag form, which implies the anti conformation at all carbon-carbon bonds. For example octane is commonly drawn as:



octane

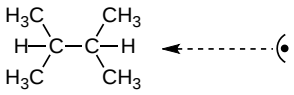
DRAWING NEWMAN PROJECTIONS

Newman projections are a valuable method for viewing the relative positions of groups within molecule. Being able to draw the Newman projection for a given molecule is a valuable skill and will be used repeatedly throughout organic chemistry. Because organic molecules often contain multiple carbon-carbon bonds it is important to precisely know which bond and which direction is being sighted for the Newman projection. The details of the Newman projection change given the molecule but for typical alkanes a full conformational analysis involves a full 360° rotation in 60° increments. This will produce three staggered conformers and three eclipsed conformers. Typically, the staggered conformers are more stable and the eclipsed conformers are less stable. The least stable conformer will have the largest groups eclipsed while the most stable conformer will have the largest groups anti (180°) to each other.

EXAMPLE

Draw the Newman projection of 2,3 dimethylbutane along the C_2-C_3 bond. Then determine the least stable conformation.

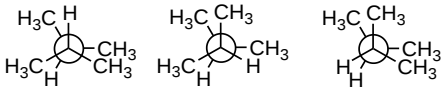
First draw the molecule and locate the indicated bond:



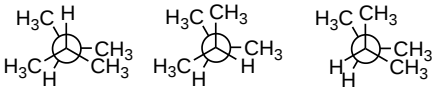
Because the question asks for the least stable conformation, focus on the three possible eclipsed Newman projections. Draw out three eclipsed Newman projections as a template. Because it is difficult to draw a true staggered Newman projection, it is common to show the bonds slightly askew.



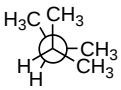
Place the substituents attached to the second carbon (C_3) on the back bonds of all three Newman projections. In this example they are 2 CH_3s and an H. Place the substituents in the same position on all three Newman projections.



Then place the substituents attached to the first carbon (C_2) on the front bonds of the Newman projection. In this example, the substituents are also 2 CH_3s and an H. Move the substituents through two 60° rotations to create the remaining two eclipsed Newman projections. Leave the substituents on the back carbon in place. Attempting to rotate the front and back carbons simultaneously is a common mistake and often leads to incorrect Newman projections.



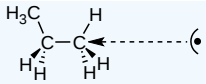
Compare the Newman projections by looking the eclipsed interactions. Remember that the order of torsional strain interactions are CH_3-CH_3 > CH_3-H > H-H. The third structure has two CH_3-CH_3 torsional interactions which will make it the least stable conformer of 2,3 dimethyl butane.



✔ EXAMPLE 3.7.1

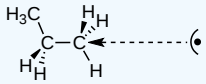
Draw Newman projections of the eclipsed and staggered conformations of propane, as if viewed down the C_1-C_2 bond.

Answer





highest energy
(eclipsed)

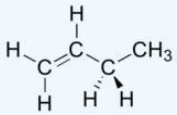




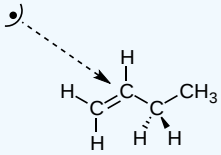
lowest energy
(staggered)

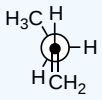
EXAMPLE 3.7.2

Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below.



Answer





EXERCISES

QUESTIONS

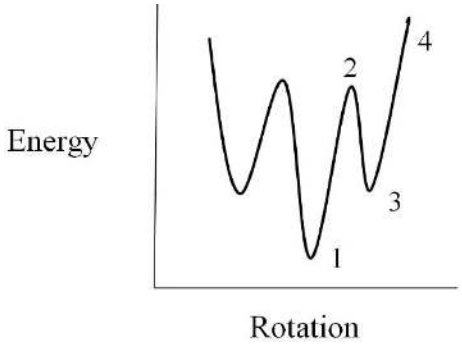
Q3.7.1

Draw the energy diagram for the rotation of the bond highlighted in pentane.

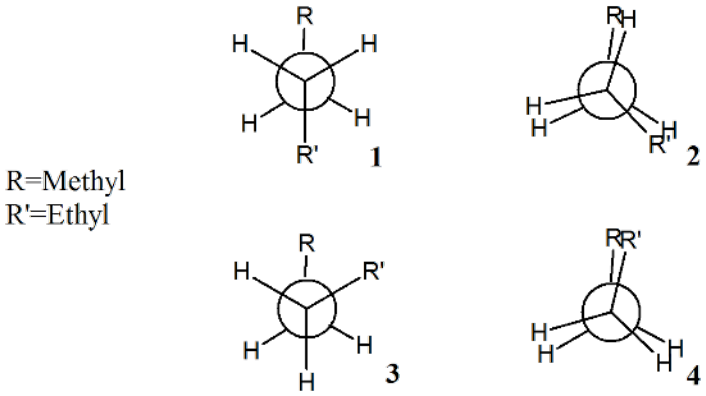


SOLUTIONS

S3.7.1



https://chem.libretexts.org/@go/page/31404



R=Methyl
R'=Ethyl

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3.8: GASOLINE - A DEEPER LOOK

OBJECTIVES

After completing this section, you should be able to

1. describe the general nature of petroleum deposits, and recognize why petroleum is such an important source of organic compounds.
2. explain, in general terms, the processes involved in the refining of petroleum.
3. define the octane number of a fuel, and relate octane number to chemical structure.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- catalytic cracking
- catalytic reforming
- fractional distillation
- octane number (octane rating)

STUDY NOTES

The refining of petroleum into usable fractions is a very important industrial process. In the laboratory component of this course, you will have the opportunity to compare this industrial process to the distillation procedure as it is performed in the student laboratory.

PETROLEUM

The petroleum that is pumped out of the ground is a complex mixture of several thousand organic compounds, including straight-chain alkanes, cycloalkanes, alkenes, and aromatic hydrocarbons with four to several hundred carbon atoms. The identities and relative abundance of the components vary depending on the source - Texas crude oil is somewhat different from Saudi Arabian crude oil. In fact, the analysis of petroleum from different deposits can produce a “fingerprint” of each, which is useful in tracking down the sources of spilled crude oil. For example, Texas crude oil is “sweet,” meaning that it contains a small amount of sulfur-containing molecules, whereas Saudi Arabian crude oil is “sour,” meaning that it contains a relatively large amount of sulfur-containing molecules.

GASOLINE

Petroleum is converted to useful products such as gasoline in three steps: distillation, cracking, and reforming. Recall from Chapter 1 that distillation separates compounds on the basis of their relative volatility, which is usually inversely proportional to their boiling points. Part (a) in Figure 3.8.1 shows a cutaway drawing of a column used in the petroleum industry for separating the components of crude oil. The petroleum is heated to approximately 400°C (750°F) and becomes a mixture of liquid and vapor. This mixture, called the feedstock, is introduced into the refining tower. The most volatile components (those with the lowest boiling points) condense at the top of the column where it is cooler, while the less volatile components condense nearer the bottom. Some materials are so nonvolatile that they collect at the bottom without evaporating at all. Thus the composition of the liquid condensing at each level is different. These different fractions, each of which usually consists of a mixture of compounds with similar numbers of carbon atoms, are drawn off separately. Part (b) in Figure 3.8.1 shows the typical fractions collected at refineries, the number of carbon atoms they contain, their boiling points, and their ultimate uses. These products range from gases used in natural and bottled gas to liquids used in fuels and lubricants to gummy solids used as tar on roads and roofs.

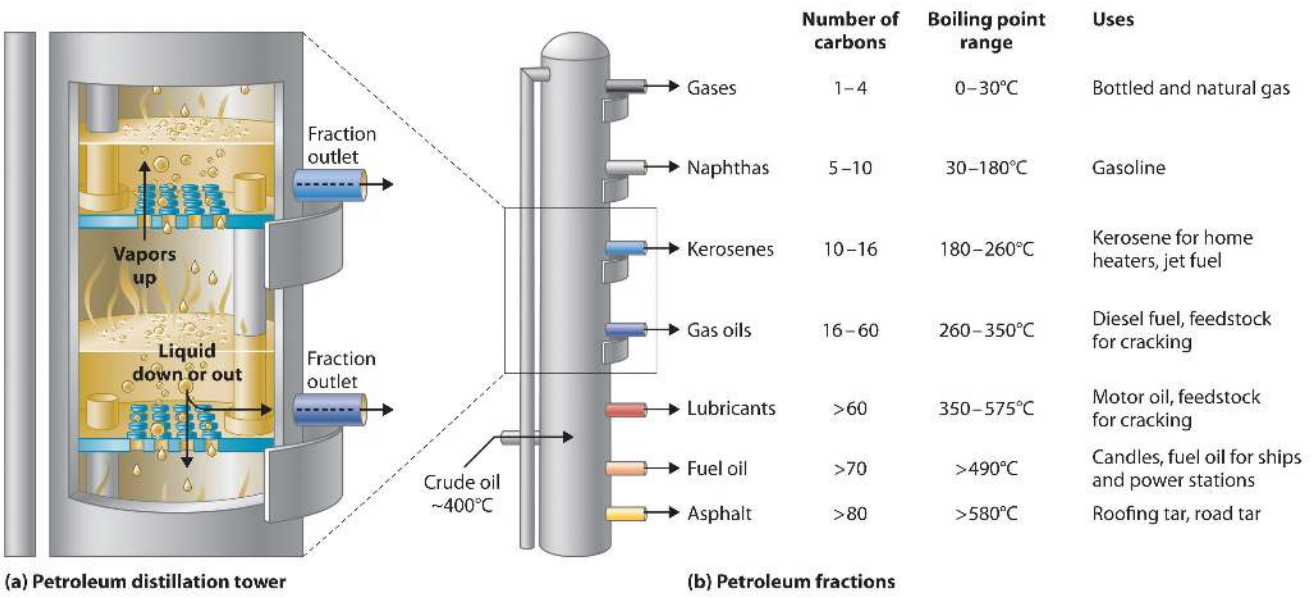


Figure 3.8.1: The Distillation of Petroleum. (a) This is a diagram of a distillation column used for separating petroleum fractions. (b) Petroleum fractions condense at different temperatures, depending on the number of carbon atoms in the molecules, and are drawn off from the column. The most volatile components (those with the lowest boiling points) condense at the top of the column, and the least volatile (those with the highest boiling points) condense at the bottom. (CC BY-NC-SA; anonymous)

The economics of petroleum refining are complex. For example, the market demand for kerosene and lubricants is much lower than the demand for gasoline, yet all three fractions are obtained from the distillation column in comparable amounts. Furthermore, most gasolines and jet fuels are blends with very carefully controlled compositions that cannot vary as their original feedstocks did. To make petroleum refining more profitable, the less volatile, lower-value fractions are converted to more volatile, higher-value mixtures that have carefully controlled formulas. The first process used to accomplish this transformation is cracking, in which the larger and heavier hydrocarbons in the kerosene and higher-boiling-point fractions are heated to temperatures as high as 900°C. High-temperature reactions cause the carbon–carbon bonds to break, which converts the compounds to lighter molecules similar to those in the gasoline fraction. Thus in cracking, a straight-chain alkane with a number of carbon atoms corresponding to the kerosene fraction is converted to a mixture of hydrocarbons with a number of carbon atoms corresponding to the lighter gasoline fraction. The second process used to increase the amount of valuable products is called reforming; it is the chemical conversion of straight-chain alkanes to either branched-chain alkanes or mixtures of aromatic hydrocarbons. Using metals such as platinum brings about the necessary chemical reactions. The mixtures of products obtained from cracking and reforming are separated by fractional distillation.

OCTANE RATINGS

The quality of a fuel is indicated by its octane rating, which is a measure of its ability to burn in a combustion engine without knocking or pinging. Knocking and pinging signal premature combustion (Figure 3.8.2), which can be caused either by an engine malfunction or by a fuel that burns too fast. In either case, the gasoline-air mixture detonates at the wrong point in the engine cycle, which reduces the power output and can damage valves, pistons, bearings, and other engine components. The various gasoline formulations are designed to provide the mix of hydrocarbons least likely to cause knocking or pinging in a given type of engine performing at a particular level.

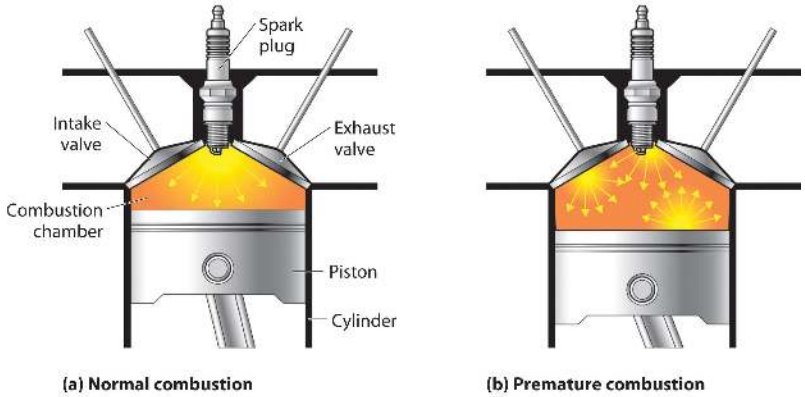


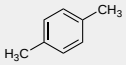
Figure 3.8.2: The Burning of Gasoline in an Internal Combustion Engine. (a) Normally, fuel is ignited by the spark plug, and combustion spreads uniformly outward. (b) Gasoline with an octane rating that is too low for the engine can ignite prematurely, resulting in uneven burning that causes knocking and pinging. (CC BY-NC-SA; anonymous)

The octane scale was established in 1927 using a standard test engine and two pure compounds: n-heptane and isooctane (2,2,4-trimethylpentane). n-Heptane, which causes a great deal of knocking on combustion, was assigned an octane rating of 0, whereas isooctane, a very smooth-burning fuel, was assigned an octane rating of 100. Chemists assign octane ratings to different blends of gasoline by burning a sample of each in a test engine and comparing the observed knocking with the amount of knocking caused by specific mixtures of n-heptane and isooctane. For example, the octane rating of a blend of 89% isooctane and 11% n-heptane is simply the average of the octane ratings of the components weighted by the relative amounts of each in the blend. Converting percentages to decimals, we obtain the octane rating of the mixture:

$$0.89(100) + 0.11(0) = 89 \tag{3.8.1}$$

As shown in Table **3.8.1**, many compounds that are now available have octane ratings greater than 100, which means they are better fuels than pure isooctane. In addition, anti-knock agents, also called octane enhancers, have been developed. One of the most widely used for many years was **tetraethyl lead** [$(C_2H_5)_4Pb$], which at approximately 3 g/gal gives a 10–15-point increase in octane rating. Since 1975, however, lead compounds have been phased out as gasoline additives because they are highly toxic. Other enhancers, such as methyl t-butyl ether (MTBE), have been developed to take their place. They combine a high octane rating with minimal corrosion to engine and fuel system parts. Unfortunately, when gasoline containing MTBE leaks from underground storage tanks, the result has been contamination of the groundwater in some locations, resulting in limitations or outright bans on the use of MTBE in certain areas. As a result, the use of alternative octane enhancers such as ethanol, which can be obtained from renewable resources such as corn, sugar cane, and, eventually, corn stalks and grasses, is increasing.

Table **3.8.1**: The Octane Ratings of Some Hydrocarbons and Common Additives

Name	Condensed Structural Formula	Octane Rating	Name	Condensed Structural Formula	Octane Rating
n-heptane	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	0	*o*-xylene	skeletal structure of o-xylene.cdxml	107
n-hexane	$CH_3CH_2CH_2CH_2CH_2CH_3$	25	ethanol	CH_3CH_2OH	108
n-pentane	$CH_3CH_2CH_2CH_2CH_3$	62	*t*-butyl alcohol	$(CH_3)_3COH$	113
isooctane	$(CH_3)_3CCH_2CH(CH_3)_2$	100	*p*-xylene		116
benzene		106	methyl *t*-butyl ether	$H_3COC(CH_3)_3$	116
methanol	CH_3OH	107	toluene		118

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3.S: ORGANIC COMPOUNDS- ALKANES AND THEIR STEREOCHEMISTRY (SUMMARY)

CONCEPTS & VOCABULARY

3.1: Functional Groups

- **Functional groups** are atoms or small groups of atoms (two to four) that exhibit a characteristic reactivity.
- Functional groups have characteristic names that often carry over into the naming of compounds.
- The most common organic functional groups that will be encountered is this course are: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.

3.2: Alkanes and Alkane Isomers

- Hydrocarbons are a common class of organic molecules that contain only carbon and hydrogen atoms.
- Alkanes are one type of hydrocarbon that contains only carbon-carbon and carbon hydrogen single bonds.
- Straight chain and branched alkanes have the generic formula C_nH_{2n+2}, where *n* is equal to the number of carbons. Cycloalkanes have the generic formula C_nH_{2n}.
- Structural isomers are molecules with the same molecular formula, but different structures.

3.3: Alkyl Groups

- Alkyl groups are small hydrocarbon chains attached to the parent alkane chain. The names of alkyl groups use the same prefixes to indicate the number of carbons (meth-, eth-, etc.), but use "-yl" as the ending, instead of "-ane".

3.4: Naming Alkanes

- The IUPAC System of nomenclature provides a set of rules for assigning every molecule a unique name.

3.5: Properties of Alkanes

- The boiling point of an alkane depends upon molecular weight and number of branches in the chain. Boiling points tend to increase with increasing molecular weight. Boiling points tend to decrease within a set of isomers as the number of branches increases.
- Alkanes and cycloalkanes are generally more soluble in organic solvents than in water.

3.6: Conformations of Ethane

- Rotation about the carbon-carbon sigma bonds in ethane results in different **rotational isomers** (also known as **conformational isomers** or **conformers**). **Newman projections** are a very common way of depicting conformers.
- The two most common conformers of ethane are called **staggered** and **eclipsed**. The staggered conformer is lower in energy (more stable) than the eclipsed conformer, because it has less **torsional strain**.

3.7: Conformations of Other Alkanes

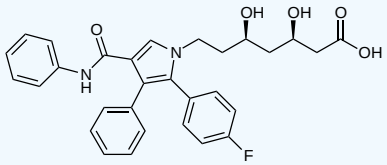
- Alkanes more complex than ethane, will have a greater variety of possible conformers. The **anti** and **gauche** conformers of butane are specific types of staggered conformations.

3.8: Gasoline - A Deeper Look

SUMMARY PROBLEMS

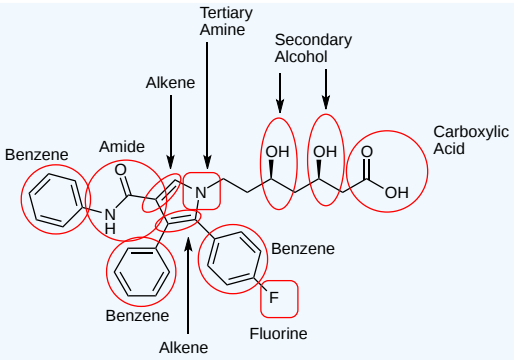
? EXERCISE 3.S.1

Atorvastatin (Lipitor) is a synthetic pharmaceutical marketed by Pfizer for lowering blood cholesterol and is one of the top selling drugs in the world. Circle and label all functional groups in Lipitor. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.)



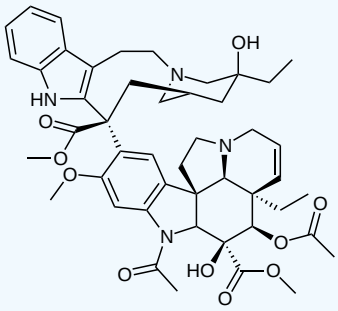
https://chem.libretexts.org/@go/page/167947

Answer

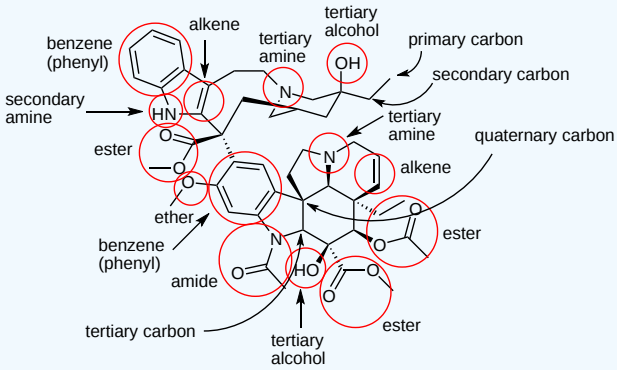


EXERCISE 3.S.2

Vincristine is a natural product that was originally isolated in 1958 and has been studied as an anticancer agent. Answer the following questions related to this molecule. a) Circle and label all functional groups. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.) b) Clearly label one primary carbon, one secondary carbon, one tertiary carbon, and one quaternary carbon.

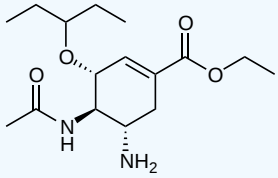


Answer

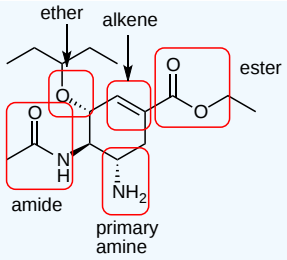


EXERCISE 3.S.3

Tamiflu (oseltamivir) is an anti-influenza medication that was discovered by Gilead Sciences and is marketed by the pharmaceutical company Genetech. Circle and label all functional groups in Tamiflu. (Be sure to label any amines or alcohols as primary, secondary, or tertiary.)



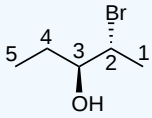
Answer



Notes: Alkanes are not functional groups, so there is no reason to circle groups like methyl or ethyl. (They are structural fragments.) Also, this molecule does not contain an aromatic ring. This is a cyclohexene ring. An aromatic ring is benzene and requires three double bonds in a six-membered ring.

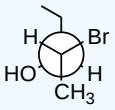
? EXERCISE 3.S.4

For the following structure, a) Draw a Newman projection looking down the C2-C3 bond. (C2 should be in front.) b) Rotate the C2-C3 bond by 180 degrees (keep 3, 4, and 5 in the same orientation as the original structure). Draw the new skeletal structure and the new Newman projection looking down the C2-C3 bond. c) Label the Newman projections from parts a and b as staggered or eclipsed.



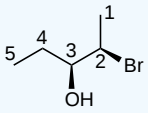
Answer

a)



staggered

b)





eclipsed

SKILLS TO MASTER

- Skill 3.1 Identify the following functional groups that are present in a given organic molecule: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, and nitro compounds.
- Skill 3.2 Name and draw structures of straight chain alkanes up to ten carbons in length.
- Skill 3.3 Name and draw structures for all the structural isomers of a given molecular formula.
- Skill 3.4 Identify methyl, primary, secondary, tertiary, and quaternary carbons in organic structures.
- Skill 3.5 Provide the IUPAC name of any given alkane or cycloalkane structure.
- Skill 3.6 Draw the structure of an alkane or cycloalkane given its IUPAC name.
- Skill 3.7 Arrange a series of alkanes in order of increasing or decreasing boiling point.
- Skill 3.8 Be able to draw Newman Projections of different conformers of alkanes.
- Skill 3.9 be able evaluate a conformer in terms of torsional and steric strain.
- Skill 3.10 Be able to identify the staggered, eclipsed, anti and gauche conformers of alkanes and to order them with respect to relative energy.

MEMORIZATION TASKS (MT)

- MT 3.1 Memorize the name and structure of each of the common functional groups listed in Skill 3.1.
- MT 3.2 Memorize the names and be able to draw the first ten straight chain alkanes.
- MT 3.3 Memorize the structures and common names of the alkyl substitutent groups - isopropyl, *sec*-butyl, isobutyl,, and *tert*-butyl.

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CHAPTER OVERVIEW

4: ORGANIC COMPOUNDS - CYCLOALKANES AND THEIR STEREOCHEMISTRY

LEARNING OBJECTIVES

After you have completed Chapter 4, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the *cis-trans* isomers of some simple disubstituted cycloalkanes, and write the IUPAC names of such compounds.
3. define, and use in context, the key terms introduced in this chapter.

This chapter deals with the concept of stereochemistry and conformational analysis in cyclic compounds. The causes of various ring strains and their effects on the overall energy level of a cycloalkane are discussed. We shall stress the stereochemistry of alicyclic compounds.

4.0: Chapter Objectives
4.1: Naming Cycloalkanes
4.2: Cis-Trans Isomerism in Cycloalkanes
4.3: Stability of Cycloalkanes - Ring Strain
4.4: Conformations of Cycloalkanes
4.5: Conformations of Cyclohexane
4.6: Axial and Equatorial Bonds in Cyclohexane
4.7: Conformations of Monosubstituted Cyclohexanes
4.8: Conformations of Disubstituted Cyclohexanes
4.9: Conformations of Polycyclic Molecules
4.S: Organic Compounds- Cycloalkanes and their Stereochemistry (Summary)

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4.0: CHAPTER OBJECTIVES

Cycloalkanes, a fundamental class of organic compounds, possess intriguing structural characteristics that distinguish them within the realm of organic chemistry. Unlike their linear counterparts, cycloalkanes form closed-ring structures composed entirely of carbon atoms, bonded together in a cyclic fashion. This unique geometry gives rise to diverse stereochemical phenomena, influencing the properties and reactivity of these compounds.

In this exploration, we embark on a journey into the world of cycloalkanes and delve into their stereochemistry. Stereochemistry examines the spatial arrangement of atoms within molecules and its impact on their behavior. For cycloalkanes, stereochemistry becomes particularly captivating due to the constraints imposed by the cyclic framework, leading to fascinating structural isomerism and conformational dynamics.

Throughout our investigation, we will uncover the principles underlying cycloalkane stereochemistry, including cis-trans isomerism, ring strain, and conformational analysis. By elucidating these concepts, we aim to unravel the complexity inherent in cycloalkane structures and shed light on their significance in various fields, from organic synthesis to medicinal chemistry.

Join us as we navigate the intricate world of cycloalkanes and explore the nuances of their stereochemistry, unveiling the secrets hidden within these remarkable molecules.

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4.1: NAMING CYCLOALKANES

OBJECTIVES

After completing this section, you should be able to:

- Name a substituted or unsubstituted cycloalkane, given its Kekulé structure, shorthand structure or condensed structure.
- Draw the Kekulé, shorthand or condensed structure for a substituted or unsubstituted cycloalkane, given its IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

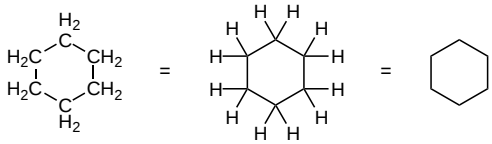
- cycloalkane

STUDY NOTES

Provided that you have mastered the IUPAC system for naming alkanes, you should find that the nomenclature of cycloalkanes does not present any particular difficulties.

Many organic compounds found in nature contain rings of carbon atoms. These compounds are known as **cycloalkanes**. Cycloalkanes only contain carbon-hydrogen bonds and carbon-carbon single bonds. The simplest examples of this class consist of a single, un-substituted carbon ring, and these form a homologous series similar to the unbranched alkanes.

Like alkanes, cycloalkane molecules are often drawn as skeletal structures in which each intersection between two lines is assumed to have a carbon atom with its corresponding number of hydrogens. Cyclohexane, one of the most common cycloalkanes is shown below as an example.



Cyclic hydrocarbons have the prefix "cyclo-". The IUPAC names, molecular formulas, and skeleton structures of the cycloalkanes with 3 to 10 carbons are given in Table **4.1.1**. Note that the general formula for a cycloalkane composed of **n** carbons is C_nH_{2n}, and not C_nH_{2n+2} as for alkanes. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so are still considered to be **saturated** with hydrogen.

Table **4.1.1**: Examples of Simple Cycloalkanes

Cycloalkane	Molecular Formula	Skeleton Structure
Cyclopropane	C_3H_6	
Cyclobutane	C_4H_8	
Cyclopentane	C_5H_{10}	
Cyclohexane	C_6H_{12}	
Cycloheptane	C_7H_{14}	
Cyclooctane	C_8H_{16}	
Cyclononane	C_9H_{18}	
Cyclodecane	$C_{10}H_{20}$	

IUPAC RULES FOR NOMENCLATURE

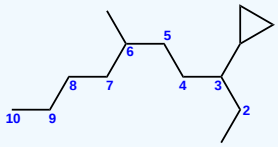
The naming of substituted cycloalkanes follows the same basic steps used in naming alkanes.

1. Determine the parent chain.
2. Number the substituents of the ring beginning at one substituent so that the nearest substituent is numbered the lowest possible. If there are multiple choices that are still the same, go to the next substituent and give it the lowest number possible.
3. Name the substituents and place them in alphabetical order.

More specific rules for naming substituted cycloalkanes with examples are given below.

1. Determine the cycloalkane to use as the parent. If there is an alkyl straight chain that has a greater number of carbons than the cycloalkane, then the alkyl chain must be used as the primary parent chain. Cycloalkanes substituents have an ending "-yl". If there are two cycloalkanes in the molecule, use the cycloalkane with the higher number of carbons as the parent.

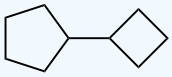
EXAMPLE 4.1.1



The longest straight chain contains 10 carbons, compared with cyclopropane, which only contains 3 carbons. The parent chain in this molecule is decane and cyclopropane is a substituent. The name of this molecule is 3-cyclopropyl-6-methyldecane.

EXAMPLE 4.1.2

Name the cycloalkane structure.

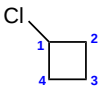


Solution

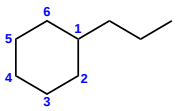
There are two different cycloalkanes in this molecule. Because it contains more carbons, the cyclopentane ring will be named as the parent chain. The smaller ring, cyclobutane, is named as a substituent on the parent chain. The name of this molecule is cyclobutylcyclopentane.

2. When there is only one substituent on the ring, the ring carbon attached to the substituent is automatically carbon #1. Indicating the number of the carbon with the substituent in the name is optional.

EXAMPLE 4.1.3



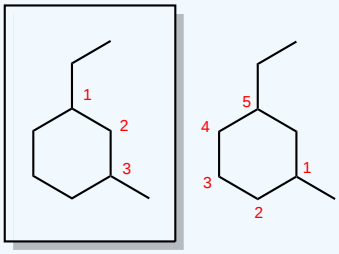
1-chlorocyclobutane or cholorocyclobutane



1-propylcyclohexane or propylcyclohexane

3. If there are multiple substituents on the ring, number the carbons of the cycloalkane so that the carbons with substituents have the lowest possible number. A carbon with multiple substituents should have a lower number than a carbon with only one substituent or functional group. One way to make sure that the lowest number possible is assigned is to number the carbons so that when the numbers corresponding to the substituents are added, their sum is the lowest possible.
4. When naming the cycloalkane, the substituents must be placed in alphabetical order. Remember the prefixes di-, tri-, etc. , are not used for alphabetization.

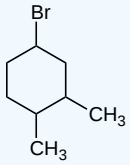
EXAMPLE 4.1.4



In this example, the ethyl or the methyl subsistent could be attached to carbon one. The ethyl group attachment is assigned carbon 1 because ethyl comes before methyl alphabetically. After assigning carbon 1 the cyclohexane ring can be numbered going clockwise or counterclockwise. When looking at the numbers produced going clockwise produces lower first substituent numbers (1,3) than when numbered counterclockwise (1,5). So the correct name is 1-ethyl-3-methylcyclohexane.

EXAMPLE 4.1.5

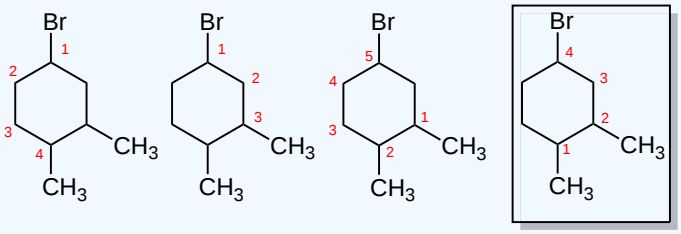
Name the following structure using IUPAC rules.



Solution

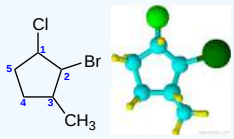
Remember when dealing with cycloalkanes with more than two substituents, finding the lowest possible 2nd substituent numbering takes precedence. Consider a numbering system with each substituent attachment point as being carbon one. Compare them and whichever produces the lowest first point of difference will be correct.

The first structure would have 1,4 for the relationship between the first two groups. The next structure would have 1,3. The final 2 structures both have 1,2 so those are preferable to the first two. Now we have to determine which is better between the final 2 structures. The 3rd substituent on structure 3 would be at the 5 position leading to 1,2,5 while in the final structure the 3rd methyl group is on carbon 4 leading to 1,2,4. This follows the rules of giving the lowest numbers at the first point of difference.



The correct name for the molecule is 4-Bromo-1,2-dimethylcyclohexane.

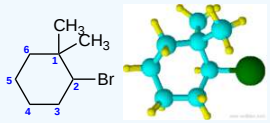
EXAMPLE 4.1.6



2-bromo-1-chloro-3-methylcyclopentane

Notice that "b" of bromo alphabetically precedes the "m" of methyl. Also, notice that the chlorine attachment point is assigned carbon 1 because it comes first alphabetically and the overall sum of numbers would be the same if the methyl attachment carbon was assigned as 1 and the chlorine attachment as 3.

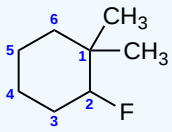
EXAMPLE 4.1.7



(2-bromo-1,1-dimethylcyclohexane)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order.

EXAMPLE 4.1.8



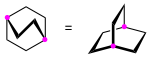
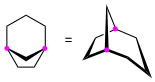
2-fluoro-1,1,-dimethylcyclohexane **NOT** 1,1-dimethyl-2-fluorocyclohexane also 2-fluoro-1,1,-dimethylcyclohexane **NOT** 1-fluoro-2,2-dimethylcyclohexane (as that would give a larger number to the first point of difference)

Although "di" alphabetically precedes "f", "di" is not used in determining the alphabetical order of the substituents. Notice that the attachment point of the two methyl groups is assigned carbon 1 despite the fact that fluorine comes first alphabetically. This is because this assignment allows for a lower overall numbering of substituents, so assigning alphabetical priority is not necessary.

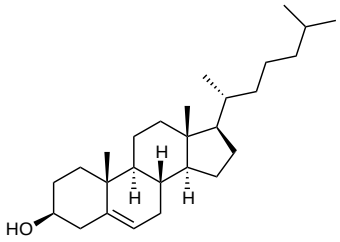
POLYCYCLIC COMPOUNDS

Hydrocarbons having more than one ring are common, and are referred to as **bicyclic** (two rings), **tricyclic** (three rings) and in general, **polycyclic compounds**. The molecular formulas of such compounds have H/C ratios that decrease with the number of rings. In general, for a hydrocarbon composed of n carbon atoms associated with m rings the formula is: $C_nH_{2n+2-2m}$. The structural relationship of rings in a polycyclic compound can vary. They may be separate and independent, or they may share one or two common atoms. Some examples of these possible arrangements are shown in the following table.

Table 4.1.2: Examples of Isomeric C_8H_{14} Bicycloalkanes

Isolated Rings	Spiro Rings	Fused Rings	Bridged Rings
No common atoms	One common atom	One common bond	Two common atoms
			
			

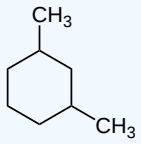
Polycyclic compounds, like cholesterol shown below, are biologically important and typically have common names accepted by IUPAC. However, the common names do not generally follow the basic IUPAC nomenclature rules, and will not be covered here.

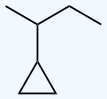


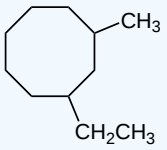
Cholesterol (polycyclic)

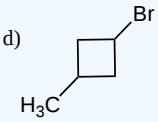
EXERCISE 4.1.1

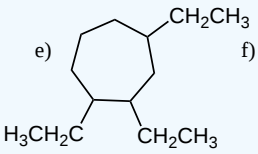
Give the IUPAC names for the following cycloalkane structures.

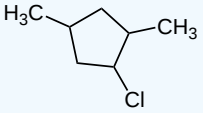
a) 

b) 

c) 

d) 

e) 

f) 

Answer

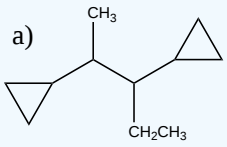
a. 1,3-Dimethylcyclohexane
b. 2-Cyclopropylbutane
c. 1-Ethyl-3-methylcyclooctane
d. 1-Bromo-3-methylcyclobutane
e. 1,2,4-Triethylcycloheptane
f. 1-Chloro-2,4-dimethylcyclopentane

EXERCISE 4.1.2

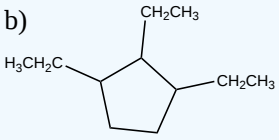
Draw the structures for the IUPAC names below.

a. 2,3-dicyclopropylpentane
b. 1,2,3-triethylcyclopentane
c. 3-cyclobutyl-2-methylhexane
d. 2-bromo-1-chloro-4-methylcyclohexane
e. 1-bromo-5-propylcyclododecane

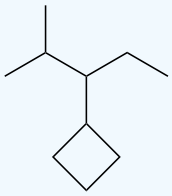
Answer

a) 

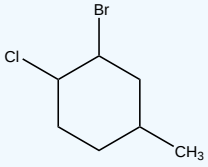
2,3-dicyclopropylpentane

b) 

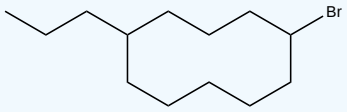
1,2,3-triethylcyclopentane

c) 

3-cyclobutyl-2-methylhexane

d) 

2-bromo-1-chloro-4-methylcyclohexane

e) 

1-bromo-5-propylcyclodecane

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4.2: CIS-TRANS ISOMERISM IN CYCLOALKANES

OBJECTIVES

After completing this section, you should be able to

- draw structural formulas that distinguish between *cis* and *trans* disubstituted cycloalkanes.
- construct models of *cis* and *trans* disubstituted cycloalkanes using ball-and-stick molecular models.

KEY TERMS

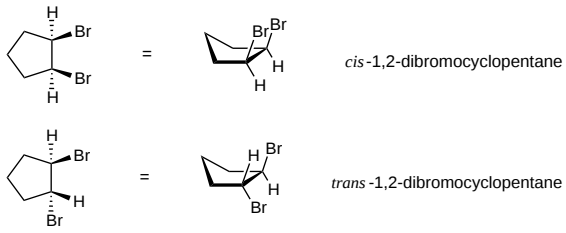
Make certain that you can define, and use in context, the key terms below.

- constitutional isomer
- stereoisomer
- *cis-trans* isomers

Previously, constitutional isomers have been defined as molecules that have the same molecular formula, but different atom connectivity. In this section, a new class of isomers, stereoisomers, will be introduced. **Stereoisomers** are molecules that have the same molecular formula, the same atom connectivity, but they differ in the relative spatial orientation of the atoms.

Cycloalkanes are similar to open-chain alkanes in many respects. They both tend to be nonpolar and relatively inert. One important difference, is that cycloalkanes have much less freedom of movement than open-chain alkanes. As discussed in Sections 3.6 and 3.7, open-chain alkanes are capable of rotation around their carbon-carbon sigma bonds. The ringed structures of cycloalkanes prevent such free rotation, causing them to be more rigid and somewhat planar.

Di-substituted cycloalkanes are one class of molecules that exhibit stereoisomerism. 1,2-dibromocyclopentane can exist as two different stereoisomers: *cis*-1,2-dibromocyclopentane and *trans*-1,2-dibromocyclopentane. The *cis*-1,2-dibromocyclopentane and *trans*-1,2-dibromocyclopentane stereoisomers of 1,2-dibromocyclopentane are shown below. Both molecules have the same molecular formula and the same atom connectivity. They differ only in the relative spatial orientation of the two bromines on the ring. In *cis*-1,2-dibromocyclopentane, both bromine atoms are on the same "face" of the cyclopentane ring, while in *trans*-1,2-dibromocyclopentane, the two bromines are on opposite faces of the ring. Stereoisomers require an additional nomenclature prefix be added to the IUPAC name in order to indicate their spatial orientation. Di-substituted cycloalkane stereoisomers are designated by the nomenclature prefixes ***cis*** (Latin, meaning on this side) and ***trans*** (Latin, meaning across).

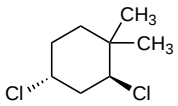


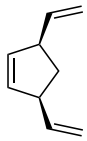
REPRESENTING 3D STRUCTURES

By convention, chemists use heavy, wedge-shaped bonds to indicate a substituent located above the plane of the ring (coming out of the page), a dashed line for bonds to atoms or groups located below the ring (going back into the page), and solid lines for bonds in the plane of the page.



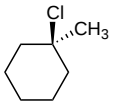
cis-1,3-dimethylcyclobutane *trans*-5-bromo-1,4,6-trimethyl-1,3-cycloheptadiene





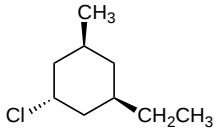
trans-2,4-dichloro-1,1-dimethylcyclohexane *cis*-3,5-divinylcyclopentene

In general, if any two sp^3 carbons in a ring have two different substituent groups (not counting other ring atoms) cis/trans stereoisomerism is possible. However, the cis/trans designations are not used if both groups are on the same carbon. For example, the chlorine and the methyl group are on the same carbon in 1-chloro-1-methylcyclohexane and the *trans* prefix should not be used.



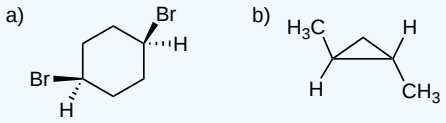
1-chloro-1-methylcyclohexane

If more than two ring carbons have substituents, the stereochemical notation distinguishing the various isomers becomes more complex and the prefixes *cis* and *trans cannot be used to formally name the molecule*. However, the relationship of any two substituents can be informally described using *cis* or *trans*. For example, in the tri-substituted cyclohexane below, the methyl group is *cis* to the ethyl group, and also *trans* to the chlorine. However, the entire molecule cannot be designated as either a *cis* or trans *isomer*. Later sections will describe how to name these more complex molecules (5.5: Sequence Rules for Specifying Configuration)



EXAMPLE 4.2.1

Name the following cycloalkanes:



Solution

These two example represent the two main ways of showing spatial orientation in cycloalkanes.

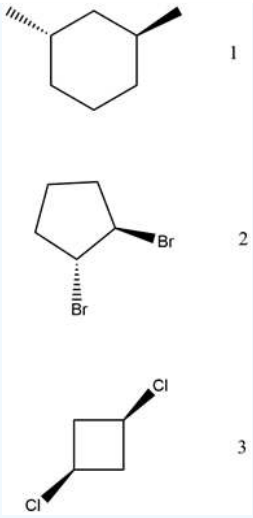
a. In example "a" the cycloalkane is shown as being flat and in the plane of the page. The positioning of the substituents is shown by using dash-wedge bonds. Cis/trans positioning can be determined by looking at the type of bonds attached to the substituents. If the substituents are both on the same side of the ring (Cis) they would both have either dash bonds or wedge bonds. If the the substituents are on opposite side of the ring (Trans) one substituent would have a dash bond and the other a wedge bond. Because both bromo substituents have a wedge bond they are one the same side of the ring and are cis. The name of this molecule is cis-1,4-Dibromocyclohexane.
b. Example "b" shows the cycloalkane ring roughly perpendicular to the plane of the page. When this is done, the upper and lower face of the ring is defined and each carbon in the ring will have a bond one the upper face and a bond on the lower face. Cis substituents will either both be on the upper face or the lower face. Trans substituents will have one on the upper face and one one the lower face. In example "b", one of the methyl substituents is on the upper face of the ring and one is on the lower face which makes them trans to each other. The name of this molecule is *trans*-1,2-Dimethylcyclopropane.

EXERCISE 4.2.2

Draw the following molecules:

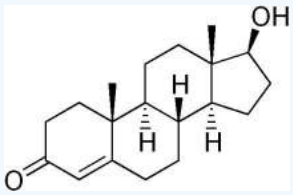
1. *trans*-1,3-dimethylcyclohexane
2. *trans*-1,2-dibromocyclopentane
3. *cis*-1,3-dichlorocyclobutane

Answer



EXERCISE 4.2.3

Cis/Trans nomenclature can be used to describe the relative positioning of substituents on molecules with more complex ring structures. The molecule below is tesosterone, the primary male sex hormone. Is the OH and the adjacent methyl group cis or trans to each other? What can you deduce about the relative positions of the indicated hydrogens?

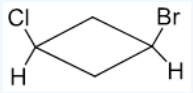


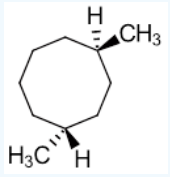
Answer

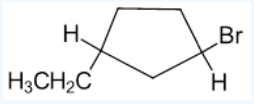
Both the OH and the methyl group have wedge bonds. This implies that they are both on the same side of the testosterone ring making them cis. Two of the hydrogens have wedge bonds while one has a wedge. This means two of the hydrogens are on one side of the testosterone ring while one is on the other side.

EXERCISE 4.2.4

Name the following compounds:







Answer

Cis-1-Bromo-3-Chlorocyclobutane

Trans-1,4-Dimethylcyclooctane

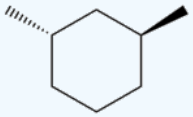
Trans-1-Bromo-3-ethylcyclopentane

EXERCISE 4.2.5

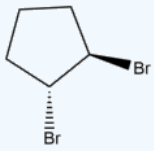
Draw the following molecules:

a. *trans*-1,3-dimethylcyclohexane
b. *trans*-1,2-dibromocyclopentane
c. *cis*-1,3-dichlorocyclobutane

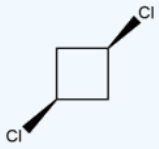
Answer



1



2



3

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4.3: STABILITY OF CYCLOALKANES - RING STRAIN

OBJECTIVES

After completing this section, you should be able to:

- Describe the Baeyer strain theory.
- Describe how the measurement of heats of combustion provides information about the amount of strain present in a cycloalkane ring.
- Determine the relative stability of cyclic compounds, by assessing such factors as angle strain, torsional strain and steric strain.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- angle strain
- steric strain
- torsional strain
- ring strain
- heat of combustion

HEAT OF COMBUSTION AS A MEASURE OF BOND STRENGTH

The combustion of carbon compounds, especially hydrocarbons, has been the most important source of heat energy for human civilizations throughout recorded history. The practical importance of this reaction cannot be denied, but the massive and uncontrolled chemical changes that take place in combustion make it difficult to deduce mechanistic paths. Using the combustion of propane as an example, we see from the following equation that every covalent bond in the reactants has been broken and an entirely new set of covalent bonds have formed in the products. No other common reaction involves such a profound and pervasive change, and the mechanism of combustion is so complex that chemists are just beginning to explore and understand some of its elementary features.

$$\mathrm{CH_3CH_2CH_3 + 5\,O_2 \longrightarrow 3\,CO_2 + 4\,H_2O + heat}$$

Since all the covalent bonds in the reactant molecules are broken, the quantity of heat evolved in this reaction, and any other combustion reaction, is related to the strength of these bonds (and, of course, the strength of the bonds formed in the products). Precise heat of combustion measurements can provide useful information about the structure of molecules and their relative stability.

For example, heat of combustion is useful in determining the relative stability of isomers. Pentane has a heat of combustion of -782 kcal/mol, while that of its isomer, 2,2-dimethylpropane (neopentane), is –777 kcal/mol. These values indicate that 2,3-dimethylpentane is 5 kcal/mol more stable than pentane, since it has a lower heat of combustion.

RING STRAIN

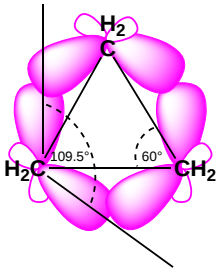
Table **4.3.1** lists the heat of combustion data for some simple cycloalkanes. These cycloalkanes do not have the same molecular formula, so the heat of combustion per each CH_2 unit present in each molecule is calculated (the fourth column) to provide a useful comparison. From the data, cyclopropane and cyclobutane have significantly higher heats of combustion per CH_2, while cyclohexane has the lowest heat of combustion. This indicates that cyclohexane is more stable than cyclopropane and cyclobutane, and in fact, that cyclohexane has a same relative stability as long chain alkanes that are not cyclic. This difference in stability is seen in nature where six membered rings are by far the most common. What causes the difference in stability or the strain in small cycloalkanes?

Table **4.3.1**: Heats of combustion of select hydrocarbons

Cycloalkane $(CH_2)_n$	CH_2 Units n	ΔH^{25° kcal/mol	ΔH^{25° per CH_2 Unit	Ring Strain kcal/mol
Cyclopropane	n = 3	468.7	156.2	27.6
Cyclobutane	n = 4	614.3	153.6	26.4
Cyclopentane	n = 5	741.5	148.3	6.5
Cyclohexane	n = 6	882.1	147.0	0.0
Cycloheptane	n = 7	1035.4	147.9	6.3
Cyclooctane	n = 8	1186.0	148.2	9.6
Cyclononane	n = 9	1335.0	148.3	11.7
Cyclodecane	n = 10	1481	148.1	11.0
$CH_3(CH_2)_mCH_3$	m = large	—	147.0	0.0

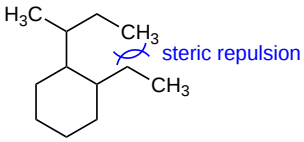
THE BAEYER THEORY ON THE STRAIN IN CYCLOALKANE RINGS

In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane are less stable than cyclohexane, because the the smaller rings are more "strained". There are many different types of strain that contribute to the overall ring strain in cycloalkanes, including angle strain, torsional strain, and steric strain. **Torsional strain** and **steric strain** were previously defined in the discussion of conformations of butane. **Angle Strain** occurs when the sp^3 hybridized carbons in cycloalkanes do not have the expected ideal bond angle of 109.5°, causing an increase in the potential energy. An example of angle strain can be seen in the diagram of cyclopropane below in which the bond angle is 60° between the carbons. The compressed bond angles causes poor overlap of the hybrid orbitals forming the carbon-carbon sigma bonds which in turn creates destabilization.



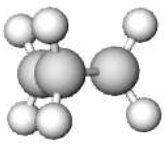
The C-C-C bond angles in cyclopropane (diagram above) (60°) and cyclobutane (90°) are much different than the ideal bond angle of 109.5°. This bond angle causes cyclopropane and cyclobutane to be less stable than molecules such as cyclohexane and cyclopentane, which have a much lower ring strain because the bond angle between the carbons is much closer to 109.5°. Changes in chemical reactivity as a consequence of angle strain are dramatic in the case of cyclopropane, and are also evident for cyclobutane.

In addition to angle strain, there is also steric (transannular) strain and torsional strain in many cycloalkanes. Transannular strain exists when there is steric repulsion between atoms.



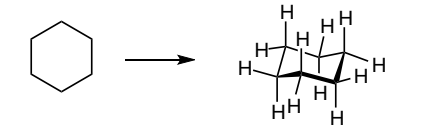
transannular strain

Because cycloalkane lack the ability to freely rotate, torsional (eclipsing) strain exists when a cycloalkane is unable to adopt a staggered conformation around a C-C bond. Torsional strain is especially prevalent in small cycloalkanes, such as cyclopropane, whose structures are nearly planar.



The Eclipsed C-H Bonds in Cyclopropane

Larger rings like cyclohexane, deal with torsional strain by forming conformers in which the rings are not planar. A conformer is a stereoisomer in which molecules of the same connectivity and formula exist as different isomers, in this case, to reduce ring strain. The ring strain is reduced in conformers due to the rotations around the sigma bonds, which decreases the angle and torsional strain in the ring. The non-planar structures of cyclohexane are very stable compared to cyclopropane and cyclobutane, and will be discussed in more detail in the next section.



cyclohexane cyclohexane chair conformer (more stable)

THE TYPES OF STRAIN WHICH CONTRIBUTE TO RING STRAIN IN CYCLOALKANES

- Angle Strain - The strain caused by the increase or reduction of bond angles
- Torsional Strain - The strain caused by eclipsing bonds on adjacent atoms
- Steric Strain - The strain caused by the repulsive interactions of atoms trying to occupy the same space

EXERCISE 4.3.1

trans-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.

Answer

The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however have hydrogen-methyl eclipsing interactions which are not as high in energy as methyl-methyl interactions.

EXERCISE 4.3.2

Cyclobutane has more torsional stain than cyclopropane. Explain this observation.

Answer

Cyclobutane has 4 CH_2 groups while cyclopropane only has 3. More CH2 groups means cyclobutane has more eclipsing H-H interactions and therefore has more torsional strain.

EXERCISES

1. *Trans*-1,2-Dimethylcyclobutane is more stable than *cis*-1,2-dimethylcyclobutane. Explain this observation.
2. The trans form does not have eclipsing methyl groups, therefore lowering the energy within the molecule. It does however have hydrogen-methyl interactions, but are not as high in energy than methyl-methyl interactions.

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4.4: CONFORMATIONS OF CYCLOALKANES

OBJECTIVES

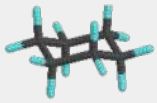
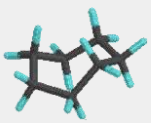
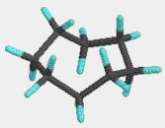
After completing this section, you should be able to

1. describe, and sketch the conformation of cyclopropane, cyclobutane, and cyclopentane.
2. describe the bonding in cyclopropane, and use this to account for the high reactivity of this compound.
3. analyze the stability of cyclobutane, cyclopentane and their substituted derivatives in terms of angular strain, torsional strain and steric interactions.

STUDY NOTES

Notice that in both cyclobutane and cyclopentane, torsional strain is reduced at the cost of increasing angular (angle) strain.

Although the customary line drawings of simple cycloalkanes are geometrical polygons, the actual shape of these compounds in most cases is very different.

cyclopropane	cyclobutane	cyclopentane	cyclohexane	cycloheptane	cyclooctane
					
					

Cyclopropane is necessarily planar (flat), with the carbon atoms at the corners of an equilateral triangle. The 60º bond angles are much smaller than the optimum 109.5º angles of a normal tetrahedral carbon atom, and the resulting angle strain dramatically influences the chemical behavior of this cycloalkane. Cyclopropane also suffers substantial eclipsing strain, since all the carbon-carbon bonds are fully eclipsed. Cyclobutane reduces some bond-eclipsing strain by folding (the out-of-plane dihedral angle is about 25º), but the total eclipsing and angle strain remains high. Cyclopentane has very little angle strain (the angles of a pentagon are 108º), but its eclipsing strain would be large (about 40 kJ/mol) if it remained planar. Consequently, the five-membered ring adopts non-planar puckered conformations whenever possible.

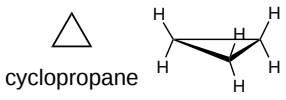
Rings larger than cyclopentane would have angle strain if they were planar. However, this strain, together with the eclipsing strain inherent in a planar structure, can be relieved by puckering the ring. Cyclohexane is a good example of a carbocyclic system that virtually eliminates eclipsing and angle strain by adopting non-planar conformations. Cycloheptane and cyclooctane have greater strain than cyclohexane, in large part due to transannular crowding (steric hindrance by groups on opposite sides of the ring).

Cyclic systems are a little different from open-chain systems. In an open chain, any bond can be rotated 360º, going through many different conformations. That complete rotation isn't possible in a cyclic system, because the parts that would be trying to twist away from each other would still be connected together. Thus cyclic systems have fewer "degrees of freedom" than aliphatic systems; they have "restricted rotation".

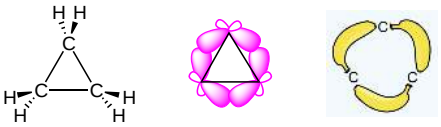
Because of the restricted rotation of cyclic systems, most of them have much more well-defined shapes than their aliphatic counterparts. Let's take a look at the basic shapes of some common rings. Many biologically important compounds are built around structures containing rings, so it's important that we become familiar with them. In nature, three- to six-membered rings are frequently encountered, so we'll focus on those.

CYCLOPROPANE

A three membered ring has no rotational freedom whatsoever. A plane is defined by three points, so the three carbon atoms in cyclopropane are all constrained to lie in the same plane. This lack of flexibility does not allow cyclopropane to form more stable conformers which are non-planar.



The main source of ring strain in cyclopropane is angle strain. All of the carbon atoms in cyclopropane are tetrahedral and would prefer to have a bond angle of 109.5° The angles in an equilateral triangle are actually 60°, about half as large as the optimum angle. The large deviation from the optimal bond angle means that the C-C sigma bonds forming the cyclopropane ring are bent. Maximum bonding occurs when the overlapping orbitals are pointing directly toward each other. The severely strained bond angles in cyclopropane means that the orbitals forming the C-C bonds overlap at a slight angle making them weaker. This strain is partially overcome by using so-called “banana bonds”, where the overlap between orbitals is no longer directly in a line between the two nuclei, as shown here in three representations of the bonding in cyclopropane:



The constrained nature of cyclopropane causes neighboring C-H bonds to all be held in eclipsed conformations. Cyclopropane is always at maximum torsional strain. This strain can be illustrated in a Newman projections of cyclopropane as shown from the side.



Newman Projection of cyclopropane

Cyclopropane isn't large enough to introduce any steric strain. Steric strain does not become a factor until we reach six membered rings. Before that point, rings are not flexible enough to allow for two ring substituents to interact with each other.

The combination of torsional and angle strain creates a large amount of ring strain in cyclopropane which weakens the C-C ring bonds (255 kJ/mol) when compared to C-C bonds in open-chain propane (370 kJ/mol).

CYCLOBUTANE

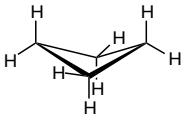
Cyclobutane is a four membered ring. The larger number of ring hydrogens would cause a substantial amount of torsional strain if cyclobutane were planar.



cyclobutane

In three dimensions, cyclobutane is flexible enough to buckle into a "puckered" shape which causes the C-H ring hydrogens to slightly deviate away from being completely eclipsed. This conformation relives some of the torsional strain but increases the angle strain because the ring bond angles decreases to 88°.

In a line drawing, this butterfly shape is usually shown from the side, with the near edges drawn using darker lines.



The deviation of cyclobutane's ring C-H bonds away from being fully eclipsed can clearly be seen when viewing a Newman projections signed down one of the C-C bond.



Newman projection of cyclobutane

- With bond angles of 88° rather than 109.5° degrees, cyclobutane has significant amounts of angle strain, but less than in cyclopropane.
- Although torsional strain is still present, the neighboring C-H bonds are not exactly eclipsed in the cyclobutane's puckered conformation.
- Steric strain is very low. Cyclobutane is still not large enough that substituents can reach around to cause crowding.
- Overall the ring strain in cyclobutane (110 kJ/mol) is slightly less than cyclopropane (115 kJ/mol).

CYCLOPENTANE

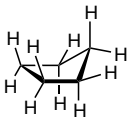
Cyclopentanes are even more stable than cyclobutanes, and they are the second-most common cycloalkane ring in nature, after cyclohexanes. Planar cyclopentane has virtually no angle strain but an immense amount of torsional strain. To reduce torsional strain,

cyclopentane addops a non-planar conformation even though it slightly increases angle strain.



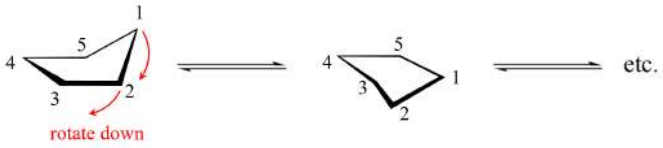
cyclopentane

The lowest energy conformation of cyclopentane is known as the ‘envelope’, with four of the ring atoms in the same plane and one out of plane (notice that this shape resembles an envelope with the flap open). The out-of-plane carbon is said to be in the ***endo*** position (‘*endo*’ means ‘inside’). The envelope removes torsional strain along the sides and flap of the envelope. However, the neighboring carbons are eclipsed along the "bottom" of the envelope, away from the flap.

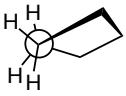


3D structure of cyclopentane (notice that the far top right carbon is the endo position).

At room temperature, cyclopentane undergoes a rapid bond **rotation** process in which each of the five carbons takes turns being in the *endo* position.



Cyclopentane distorts only very slightly into an "envelope" shape in which one corner of the pentagon is lifted up above the plane of the other four. The envelope removes torsional strain along the sides and flap of the envelope by allowing the bonds to be in an almost completely staggered position. However, the neighboring bonds are eclipsed along the "bottom" of the envelope, away from the flap. Viewing a Newman projections of cyclopentane signed down one of the C-C bond show the staggered C-H bonds.

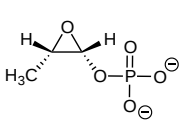


Newman projection of cyclopentane

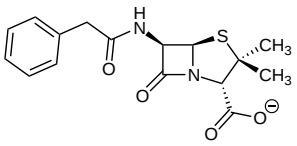
- The angle strain in the envelope conformation of cyclopentane is low. The ideal angle in a regular pentagon is about 107°, very close to the preferred 109.5^{o} tetrahedral bond angle.
- There is some torsional strain in cyclopentane. The envelope conformation reduces torsional strain by placing some bonds in nearly staggered positions. However, other bonds are still almost fully eclipsed.
- Cyclopentane is not large enough to allow for steric strain to be created.
- Overall, cyclopentane has very little ring strain (26 kJ/mol) when compared to cyclopropane and cyclobutane.

C_3-C_5 CYCLOALKANES IN NATURE

If one of the carbon-carbon bonds is broken in cyclopropane or cyclobutane, the ring will ‘spring’ open, releasing energy as the bonds reassume their preferred tetrahedral geometry. The effectiveness of two antibiotic drugs, fosfomycin and penicillin, is due in large part to the high reactivity of the three- and four-membered rings in their structures.

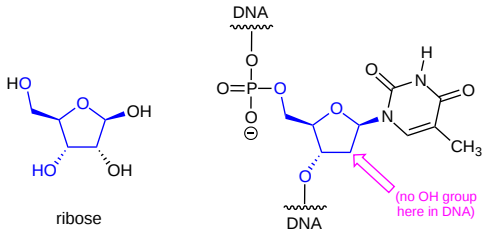


fosfomycin

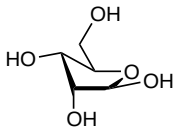


penicillin G

One of the most important five-membered rings in nature is a sugar called ribose – DNA and RNA are both constructed upon ‘backbones’ derived from ribose. Pictured below is one thymidine (T) deoxy-nucleotide from a stretch of DNA. Since the ribose has lost one of the OH groups (at carbon 2 of the ribose ring), this is part of a deoxyribonucleic acid (DNA). If the OH at carbon 2 of the ribose ring was present, this would be part of a ribonucleic acid (RNA).



The lowest-energy conformations for ribose are envelope forms in which either C_3 or C_2 are *endo*, on the same side as the C_5 substituent.



EXERCISE 4.4.1

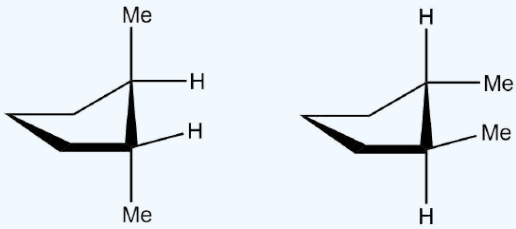
If cyclobutane were to be planar, how many H-H eclipsing interactions would there be? Assuming 4 kJ/mol per H-H eclipsing interaction what would the strain be on this "planar" molecule?

Answer

There are eight eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

EXERCISE 4.4.1

In the two conformations of *trans*-1,2-Dimethylcyclopentane one is more stable than the other. Explain why this is.



Answer

The first conformation is more stable. Even though the methyl groups are *trans* in both models, they are anti to one another in the first structure (which is lower energy) while they are gauche in the second structure increasing strain within the molecule.

EXERCISE 4.4.3

In methylcyclopentane, which carbon would most likely be in the *endo* position?

Answer

The ring carbon attached to the methyl group would most likely be the endo carbon. The large methyl group would create the most torsional strain if eclipsed. Being in the *endo* position would place the bonds is a more staggered position which would reduce strain.

EXERCISE 4.4.4

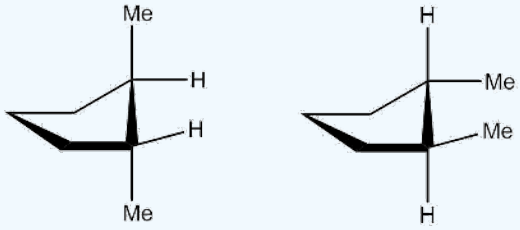
If cyclobutane were to be planar how many H-H eclipsing interactions would there be, and assuming 4 kJ/mol per H-H eclipsing interaction what is the strain on this "planar" molecule?

Answer

There are eight eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

EXERCISE 4.4.5

In the two conformations of *trans*-cyclopentane one is more stable than the other. Explain why this is.



Answer

The first conformation is more stable. Even though the methyl groups are *trans* in both models, in the second structure they are eclipsing one another, therefore increasing the strain within the molecule compared to the first structure where the larger methyl groups are anti to one another.

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4.5: CONFORMATIONS OF CYCLOHEXANE

OBJECTIVES

After completing this section, you should be able to

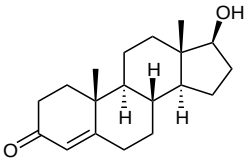
1. explain why cyclohexane rings are free of angular strain.
2. draw the structure of a cyclohexane ring in the chair conformation.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

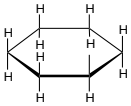
- chair conformation
- twist-boat conformation

We will find that cyclohexanes tend to have the least angle strain and consequently are the most common cycloalkanes found in nature. A wide variety of compounds including, hormones, pharmaceuticals, and flavoring agents have substituted cyclohexane rings.

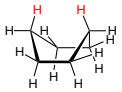


testosterone, which contains three cyclohexane rings and one cyclopentane ring

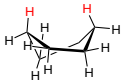
Rings larger than cyclopentane would have angle strain if they were planar. However, this strain, together with the eclipsing strain inherent in a planar structure, can be relieved by puckering the ring. Cyclohexane is a good example of a carbocyclic system that virtually eliminates eclipsing and angle strain by adopting non-planar conformations. Cycloheptane and cyclooctane have greater strain than cyclohexane, in large part due to transannular crowding (steric hindrance by groups on opposite sides of the ring). Cyclohexane has the possibility of forming multiple conformations each of which have structural differences which lead to different amounts of ring strain.



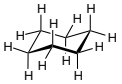
planar structure
severe angle strain (120°)
severe eclipsing strain (all bonds)
small steric strain



boat conformation
slight angle strain
eclipsing strain at two bonds
steric crowding of two hydrogens



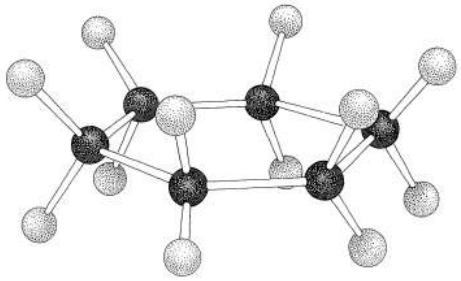
twist boat conformation
slight angle strain
small eclipsing strain
small steric strain



chair conformation
no angle strain
no eclipsing strain
small steric strain

CONFORMATIONS OF CYCLOHEXANE

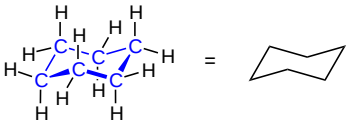
A planar structure for cyclohexane is clearly improbable. The bond angles would necessarily be 120º, 10.5º larger than the ideal tetrahedral angle. Also, every carbon-hydrogen bond in such a structure would be eclipsed. The resulting angle and eclipsing strains would severely destabilize this structure. The ring strain of planar cyclohexane is in excess of 84 kJ/mol so it rarely discussed other than in theory.



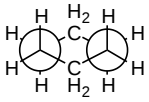
Cyclohexane in the strained planar configuration showing how the hydrogens become eclipsed.

CHAIR CONFORMATION OF CYCLOHEXANE

The flexibility of cyclohexane allows for a conformation which is almost free of ring strain. If two carbon atoms on opposite sides of the six-membered ring are bent out of the plane of the ring, a shape is formed that resembles a reclining beach chair. This **chair conformation** is the lowest energy conformation for cyclohexane with an overall ring strain of 0 kJ/mol. In this conformation, the carbon-carbon ring bonds are able to assume bonding angles of ~111º which is very near the optimal tetrahedral 109.5º so angle strain has been eliminated.

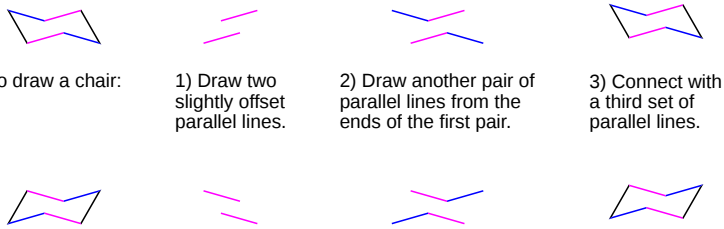


Also, the C-H ring bonds are staggered so torsional strain has also been eliminated. This is clearly seen when looking at a Newman projection of chair cyclohexane sighted down the two central C-C bonds.



Newman projection of cyclohexane

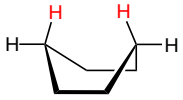
HOW TO DRAW THE CHAIR CONFORMATION



To draw its ring-flip conformer, just start the first pair of lines at the opposite angle.

BOAT CONFORMATION OF CYCLOHEXANE

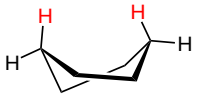
The **Boat Conformation** of cyclohexane is created when two carbon atoms on opposite sides of the six-membered ring are both lifted up out of the plane of the ring creating a shape which slightly resembles a boat. The boat conformation is less stable than the chair form for two major reasons. The boat conformation has unfavorable steric interactions between a pair of 1,4 hydrogens (the so-called "flagpole" hydrogens) that are forced to be very close together (1.83Å). This steric hindrance creates a repulsion energy of about 12 kJ/mol. An additional cause of the higher energy of the boat conformation is that adjacent hydrogen atoms on the 'bottom of the boat' are forced into eclipsed positions. For these reasons, the boat conformation about 30 kJ/mol less stable than the chair conformation.



A boat structure of cyclohexane (the interfering "flagpole" hydrogens are shown in red)

TWIST-BOAT CONFORMATION OF CYCLOHEXANE

The boat form is quite flexible and by twisting it at the bottom created the **twist-boat conformer**. This conformation reduces the strain which characterized the boat conformer. The flagpole hydrogens move farther apart (the carbons they are attached to are shifted in opposite directions, one forward and one back) and the eight hydrogens along the sides become largely but not completely staggered. Though more stable than the boat conformation, the twist-boat (sometimes skew-boat) conformation is roughly 23 kJ/mol less stable than the chair conformation.



A twist-boat structure of cyclohexane

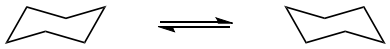
HALF CHAIR CONFORMATION OF CYCLOHEXANE

Cyclohexane can obtain a partially plane conformation called "half chair" but with only with excessive amounts of ring strain. The half chair conformation is formed by taking planar cyclohexane and lifting one carbon out of the plane of the ring. The half chair conformation

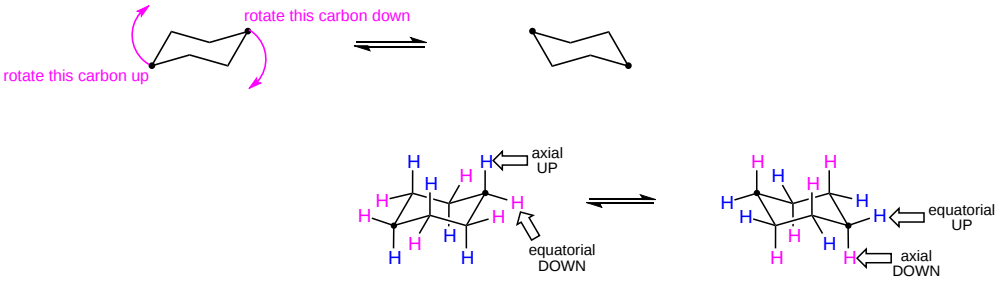
has much of the same strain effects predicted by the fully planar cyclohexane. In the planar portion of half chair cyclohexane the C-C bond angles are forced to 120° which creates significant amounts of angle strain. Also, the corresponding C-H bonds are fully eclipsed which create torsional strain. The out-of-plane carbon allows for some of the ring's bond angles to reach 109.5^o and for some of C-H bonds to not be fully eclipsed. Overall, the half chair conformation is roughly 45 kJ/mol less stable than the chair conformation.

CONFORMATION CHANGES IN CYCLOHEXANE - "RING FLIPS"

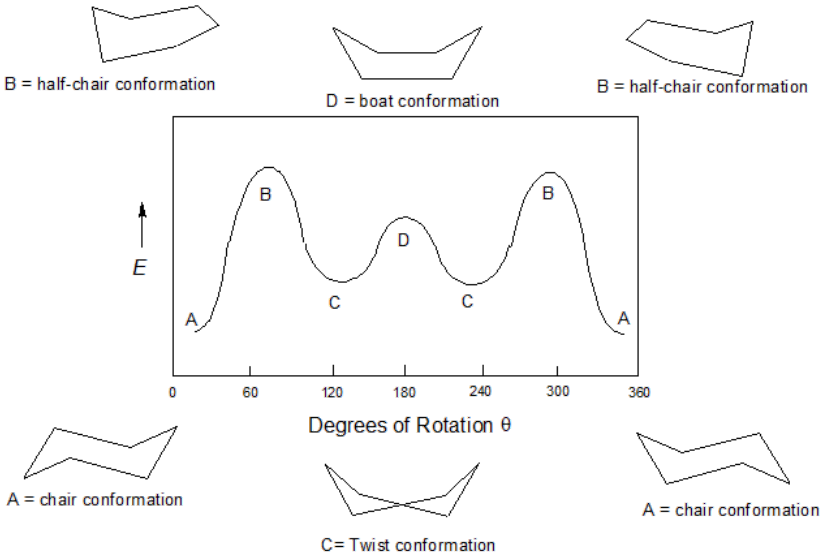
Cyclohexane is rapidly rotating between the two most stable conformations known as the chair conformations in what is called the "ring flip" shown below. The importance of the ring flip will be discussed in the next section.



"Ring flip" describes the rapid equilibrium of cyclohexane rings between the two chair conformations



It is important to note that one chair does not immediately become the other chair, rather the ring must travel through the higher energy conformations as transitions. At room temperature the energy barrier created by the half chair conformation is easily overcome allowing for equilibration between the two chair conformation on the order of 80,000 times per second. Although cyclohexane is continually converting between these different conformations, the stability of the chair conformation causes it to comprises more than 99.9% of the equilibrium mixture at room temperature.



1" id="MathJax-Element-12-Frame" role="presentation" style="position:relative;" tabindex="0">Image of energy diagram of cyclohexane conformations

1" role="presentation" style="position:relative;" tabindex="0">

EXERCISES

1) Consider the conformations of cyclohexane: half chair, chair, boat, twist boat. Order them in increasing ring strain in the molecule.

SOLUTIONS

1) Chair < Twist Boat < Boat < half chair (most ring strain)

QUESTIONS

Q4.5.1

Consider the conformations of cyclohexane, chair, boat, twist boat. Order them in increasing strain in the molecule.

SOLUTIONS

S4.5.1

Chair < Twist Boat < Boat (most strain)

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4.6: AXIAL AND EQUATORIAL BONDS IN CYCLOHEXANE

OBJECTIVES

After completing this section, you should be able to

1. Draw the chair conformation of cyclohexane, with axial and equatorial hydrogen atoms clearly shown and identified.
2. identify the axial and equatorial hydrogens in a given sketch of the cyclohexane molecule.
3. explain how chair conformations of cyclohexane and its derivatives can interconvert through the process of ring flip.

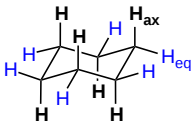
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- axial position
- equatorial position
- ring flip

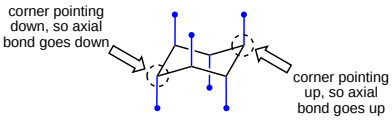
AXIAL AND EQUATORIAL POSITIONS IN CYCLOHEXANE

Careful examination of the chair conformation of cyclohexane, shows that the twelve hydrogens are not structurally equivalent. Six of them are located about the periphery of the carbon ring, and are termed **equatorial**. The other six are oriented above and below the approximate plane of the ring (three in each location), and are termed **axial** because they are aligned parallel to the symmetry axis of the ring.

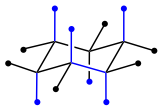


In the figure above, the equatorial hydrogens are colored blue, and the axial hydrogens are black. Since there are two equivalent chair conformations of cyclohexane in rapid equilibrium, all twelve hydrogens have 50% equatorial and 50% axial character.

HOW TO DRAW AXIAL AND EQUATORIAL BONDS

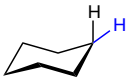


Draw axial bonds **straight up** or **straight down.**



Draw equatorial bonds **up and out** or **down and out.**

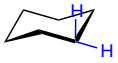
How **not** to draw the chair:



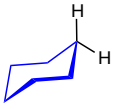
Incorrect. Equatorial bond should be **down** and **out**.



Incorrect. Axial bond should be **straight up**.



Incorrect. Axial bond should be **straight down,** equatorial bond should be **up** and **out**.



Incorrect. Ring should be tilted slightly.

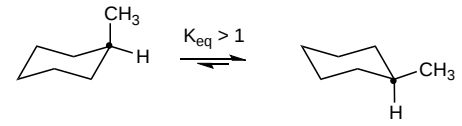
Aside from drawing the basic chair, the key points are:

- Axial bonds alternate up and down, and are shown "vertical".
- Equatorial groups are approximately horizontal, but actually somewhat distorted from that (slightly up or slightly down), so that the angle from the axial group is a bit more than a right angle -- reflecting the common 109.5º bond angle.
- Each carbon has an axial and an equatorial bond.
- Each face of the cyclohexane ring has three axial and three equatorial bonds.
- Each face alternates between axial and equatorial bonds. Then looking at the "up" bond on each carbon in the cyclohexane ring they will alternate axial-equatorial-axial ect.
- When looking down at a cyclohexane ring:
  - the equatorial bonds will form an "equator" around the ring

- the equatorial bonds will form an "equator" around the ring.
  - The axial bonds will either face towards you or away. These will alternate with each axial bond. The first axial bond will be coming towards with the next going away. There will be three of each type.
- Note! The terms cis and trans in regards to the stereochemistry of a ring are not directly linked to the terms axial and equatorial. It is very common to confuse the two. It typically best not to try and directly inter convert the two naming systems.

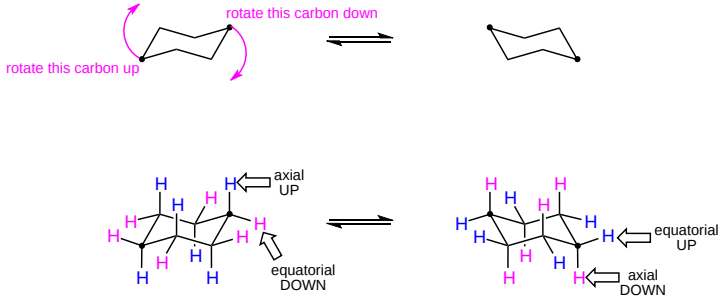
AXIAL VS. EQUATORIAL SUBSTITUENTS

When a substituent is added to cyclohexane, the ring flip allows for two distinctly different conformations. One will have the substituent in the axial position while the other will have the substituent in the equatorial position. In the next section will discuss the energy differences between these two possible conformations. Below are the two possible chair conformations of methylcyclohexane created by a ring-flip. Although the conformation which places the methyl group in the equatorial position is more stable by 7 kJ/mol, the energy provided by ambient temperature allows the two conformations to rapidly interconvert.



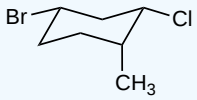
methyl group axial — methyl group equatorial (more stable by **7 kJ/mol**)

The figure below illustrates how to convert a molecular model of cyclohexane between two different chair conformations - this is something that you should practice with models. Notice that a 'ring flip' causes equatorial groups to become axial, and vice-versa.



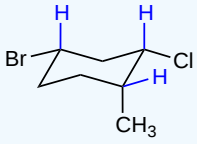
EXAMPLE 4.6.1

For the following please indicate if the substituents are in the axial or equatorial positions.



Solution

Due to the large number of bonds in cyclohexane it is common to only draw in the relevant ones (leaving off the hydrogens unless they are involved in a reaction or are important for analysis). It is still possible to determine axial and equatorial positioning with some thought. With problems such as this it is important to remember that each carbon in a cyclohexane ring has one axial and one equatorial bond. Also, remember that axial bonds are perpendicular with the ring and appear to be going either straight up or straight down. Equatorial bonds will be roughly in the plane of the cyclohexane ring (only slightly up or down). Sometimes it is valuable to draw in the additional bonds on the carbons of interest.



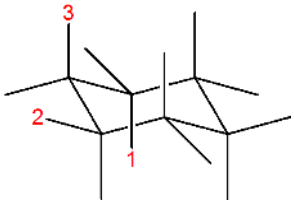
With this it can be concluded that the bromine and chlorine substituents are attached in equatorial positions and the CH_3 substituent is attached in an axial position.

EXERCISES

1) Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

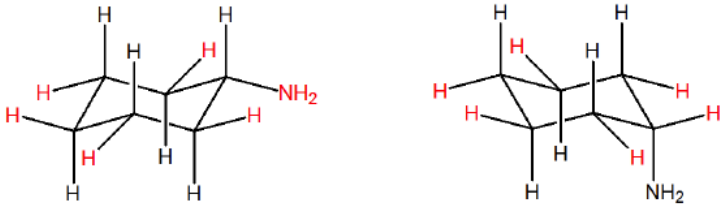
2) Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

3) In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).



SOLUTIONS

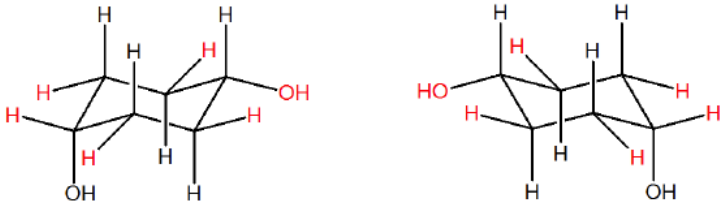
1)



Axial

Equatorial

2)

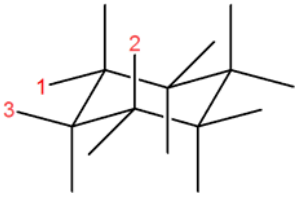


Axial

Equatorial

3) Original conformation: 1 = axial, 2 = equatorial, 3 = axial

Flipped chair now looks like this.



QUESTIONS

Q4.6.1

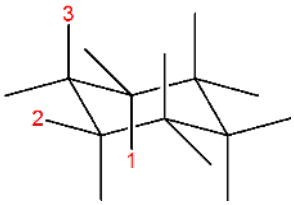
Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

Q4.6.2

Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

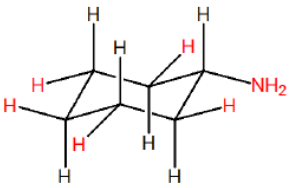
Q4.6.3

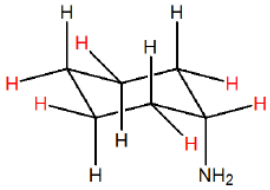
In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).



SOLUTIONS

S4.6.1

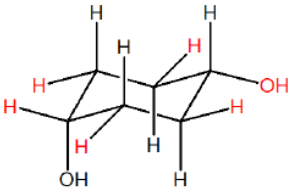


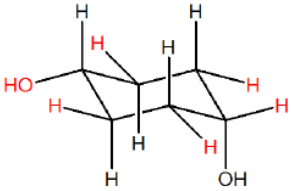


Axial

Equatorial

S4.6.2





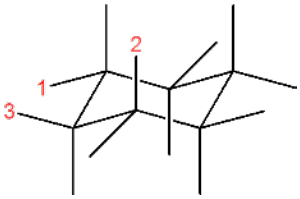
Axial

Equatorial

S4.6.3

Original conformation: 1 = axial, 2 = equatorial, 3 = axial

Flipped chair now looks like this.



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4.7: CONFORMATIONS OF MONOSUBSTITUTED CYCLOHEXANES

OBJECTIVES

After completing this section, you should be able to

1. account for the greater stability of the equatorial conformers of monosubstituted cyclohexanes compared to their axial counterparts, using the concept of 1,3-diaxial interaction.
2. compare the gauche interactions in butane with the 1,3-diaxial interactions in the axial conformer of methylcyclohexane.
3. arrange a given list of substituents in increasing or decreasing order of 1,3-diaxial interactions.

KEY TERMS

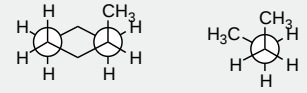
Make certain that you can define, and use in context, the key term below.

- 1,3-diaxial interaction

STUDY NOTES

1,3-Diaxial interactions are steric interactions between an axial substituent located on carbon atom 1 of a cyclohexane ring and the hydrogen atoms (or other substituents) located on carbon atoms 3 and 5.

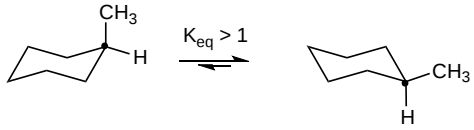
Be prepared to draw Newman-type projections for cyclohexane derivatives as the one shown for methylcyclohexane. Note that this is similar to the Newman projections from chapter 3 such as *n*-butane.



methylcyclohexane *n*-butane

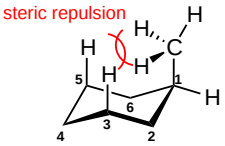
Newman projections of methylcyclohexane and *n*-butane

When a substituent is added to a cyclohexane ring, the two possible chair conformations created during a ring flip are not equally stable. In the example of methylcyclohexane the conformation where the methyl group is in the equatorial position is more stable than the axial conformation by 7.6 kJ/mol at 25° C. The percentages of the two different conformations at equilibrium can be determined by solving the following equation for K (the equilibrium constant): $\Delta E = -RT\ln K$. In this equation ΔE is the energy difference between the two conformations, R is the gas constant (8.314 J/mol•K), T is the temperature in Kelvin, and K is the equilibrium constant for the ring flip conversion. Using this equation, we can calculate a K value of 21 which means about 95% methylcyclohexane molecules have the methyl group in the equatorial position at 25° C.

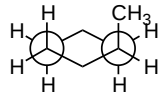


methyl group axial methyl group equatorial
(more stable by **7 kJ/mol**)

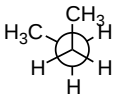
The energy difference between the two conformations comes from strain, called 1,3-diaxial interactions, created when the axial methyl group experiences steric crowding with the two axial hydrogens located on the same side of the cyclohexane ring. Because axial bonds are parallel to each other, substituents larger than hydrogen experience greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents are in the equatorial orientation***. When the methyl group is in the equatorial position this strain is not present which makes the equatorial conformer more stable and favored in the ring flip equilibrium.



Actually, 1,3-diaxial steric strain is directly related to the steric strain created in the gauche conformer of butane discussed in Section: 3-7. When butane is in the gauche conformation 3.8 kJ/mol of strain was created due the steric crowding of two methyl group with a 60° dihedral angle. When looking at the a Newman projection of axial methylcyclohexane the methyl group is at a 60° dihedral angle with the ring carbon in the rear. This creates roughly the same amount of steric strain as the gauche conformer of butante. Given that there is actually two such interactions in axial methylcyclohexane, it makes sense that there is 2(3.8 kJ/mol) = 7.6 kJ/mol of steric strain in this conformation. The Newman projection of equatorial methylcyclohexane shows no such interactions and is therefore more stable.



methylcyclohexane



n-butane

Newman projections of methyl cyclohexane and butane showing similarity of 1,3-diaxial and gauche interactions.

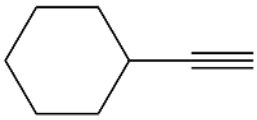
Strain values for other cyclohexane substituents can also be considered. The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane determined the amount of strain generated. The strain generated can be used to evaluate the relative tendency of substituents to exist in an equatorial or axial location. Looking at the energy values in this table, it is clear that as the size of the substituent increases, the 1,3-diaxial energy tends to increase, also. Note that it is the size and not the molecular weight of the group that is important. Table 4.7.1 summarizes some of these strain values values.

Table 4.7.1: A Selection of ΔG° *Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes*

Substituent	-ΔG° (kcal/mol)	Substituent	-ΔG° (kcal/mol)
CH_3–	1.7	O_2N–	1.1
CH_2H_5–	1.8	N≡C–	0.2
$(CH_3)_2CH$–	2.2	CH_3O–	0.5
$(CH_3)_3C$–	≥ 5.0	HO_2C–	0.7
F–	0.3	H_2C=CH–	1.3
Cl–	0.5	C_6H_5–	3.0
Br–	0.5		
I–	0.5		

EXERCISES

1) In the molecule, cyclohexyl ethyne there is little steric strain, why?



2) Calculate the energy difference between the axial and equatorial conformations of bromocyclohexane?

3) Using your answer from Question 2) estimate the percentages of axial and equatorial conformations of bromocyclohexane at 25° C.



Bromo group axial

Bromo group equitorial

4) There very little in 1,3-diaxial strain when going from a methyl substituent (3.8 kJ/mol) to an ethyl substituent (4.0 kJ/mol), why? It may help to use molecular model to answer this question.

SOLUTIONS

1) The ethyne group is linear and therefore does not affect the hydrogens in the 1,3 positions to say to the extent as a bulkier or a bent group (e.g. ethene group) would. This leads to less of a strain on the molecule.

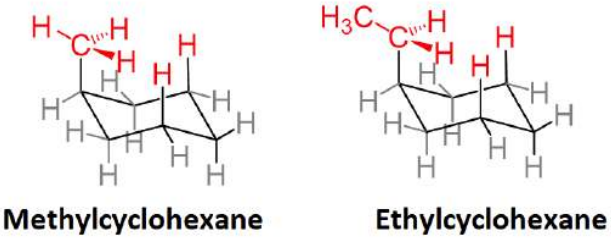


2) The equatorial conformation of bromocyclohexane will have two 1,3 diaxial interactions. The table above states that each interaction accounts for 1.2 kJ/mol of strain. The total strain in equatorial bromocyclohexane will be 2(1.2 kJ/mol) = 2.4 kJ/mol.

3) Remembering that the axial conformation is higher in energy, the energy difference between the two conformations is ΔE = (E equatorial - E axial) = (0 - 2.4 kJ/mol) = -2.4 kJ/mol. After converting ^{o}C to Kelvin and kJ/mol to J/mol we can use the equation $\Delta E = -RT \ln K$ to find that $-\Delta E/RT = \ln K$ or (2.4 x 10^3 J/mol) / (8.313 kJ/mol K • 298 K) = lnK. From this we calculate that K = 2.6. Because the ring flip reaction is an equilibrium we can say that K = [Equatorial] / [Axial]. If assumption is made that [Equatorial] = X then [Axial] must be 1-X. Plugging these values into the equilibrium expression produces K = [X] / [1-X]. After plugging in the calculated value for K, X can be solved algebraically. 2.6 = [X] / [1-X] → 2.6 - 2.6X = X → 2.6 = 3.6X → 2.6/3.6 = X = 0.72. This means that bromocyclohexane is in the equatorial position 72% of the time and in the axial position 28% of the time.



4) The fact that C-C sigma bonds can freely rotate allows the ethyl subsistent to obtain a conformation which places the bulky CH_3 group away from the cyclohexane ring. This forces the ethyl substituent to have only have 1,3- diaxial interactions between hydrogens, which only provides a slight difference to a methyl group.



EXERCISES

QUESTIONS

Q4.7.1

In the molecule, cyclohexyl ethyne there is little steric strain, why?

SOLUTIONS

S4.7.1

The ethyne group is linear and therefore does not affect the hydrogens in the 1,3 positions to say to the extent as a bulkier or a bent group (e.g. ethene group) would. This leads to less of a strain on the molecule.



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4.8: CONFORMATIONS OF DISUBSTITUTED CYCLOHEXANES

OBJECTIVE

After completing this section, you should be able to use conformational analysis to determine the most stable conformation of a given disubstituted cyclohexane.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- conformational analysis

STUDY NOTES

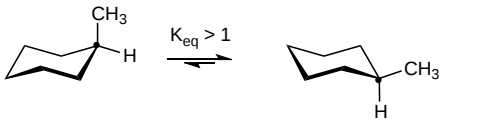
When faced with the problem of trying to decide which of two conformers of a given disubstituted cyclohexane is the more stable, you may find the following generalizations helpful.

1. A conformation in which both substituents are equatorial will always be more stable than a conformation with both groups axial.
2. When one substituent is axial and the other is equatorial, the most stable conformation will be the one with the bulkiest substituent in the equatorial position. Steric bulk decreases in the order

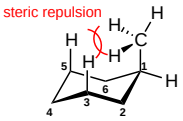
   tert-butyl > isopropyl > ethyl > methyl > hydroxyl > halogens

MONOSUBSTITUTED CYCLOHEXANES

In the previous section, it was stated that the chair conformation in which the methyl group is equatorial is more stable because it minimizes steric repulsion, and thus the equilibrium favors the more stable conformer. This is true for all monosubstituted cyclohexanes. The chair conformation which places the substituent in the equatorial position will be the most stable and be favored in the ring flip equilibrium.



methyl group axial — methyl group equatorial (more stable by **7 kJ/mol**)



DISUBSTITUTED CYCLOHEXANES

Determining the more stable chair conformation becomes more complex when there are two or more substituents attached to the cyclohexane ring. To determine the stable chair conformation, the steric effects of each substituent, along with any additional steric interactions, must be taken into account for both chair conformations.

In this section, the effect of conformations on the relative stability of disubstituted cyclohexanes is examined using the two principles:

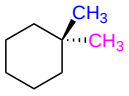
i. Substituents prefer equatorial rather than axial positions in order to minimize the steric strain created of 1,3-diaxial interactions.
ii. The more stable conformation will place the larger substituent in the equatorial position.

1,1-DISUBSTITUTED CYCLOHEXANES

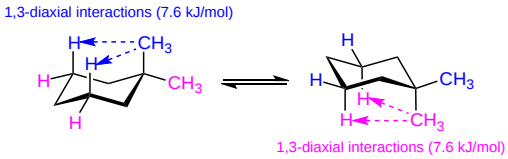
The more stable chair conformation can often be determined empirically or by using the energy values of steric interactions previously discussed in this chapter. Note, in some cases there is no discernable energy difference between the two chair conformations which means they are equally stable.

1,1-dimethylcyclohexane does not have *cis* or *trans* isomers, because both methyl groups are on the same ring carbon. Both chair conformers have one methyl group in an axial position and one methyl group in an equatorial position giving both the same relative stability. The steric strain created by the 1,3-diaxial interactions of a methyl group in an axial position (versus equatorial) is 7.6 kJ/mol (from Table 4.7.1), so both conformers will have equal amounts of steric strain. Thus, the equilibrium between the two conformers does not

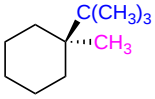
favor one or the other. Note, that both methyl groups cannot be equatorial at the same time without breaking bonds and creating a different molecule.



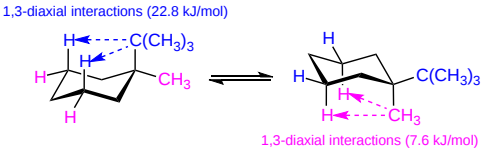
1,1-dimethylcyclohexane



However, if the two groups are different, as in 1-*tert*-butyl-1-methylcyclohexane, then the equilibrium favors the conformer in which the larger group (*tert*-butyl in this case) is in the more stable equatorial position. The energy cost of having one tert-butyl group axial (versus equatorial) can be calculated from the values in table 4.7.1 and is approximately 22.8 kJ/mol. The conformer with the *tert*-butyl group axial is approximately 15.2 kJ/mol (22.8 kJ/mol - 7.6 kJ/mol) less stable then the conformer with the *tert*-butyl group equatorial. Solving for the equilibrium constant K shows that the equatorial is preferred about 460:1 over axial. This means that 1-*tert*-butyl-1-methylcyclohexane will spend the majority of its time in the more stable conformation, with the *tert*-butyl group in the equatorial position.

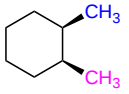


1-(*tert*-butyl)-1-methylcyclohexane

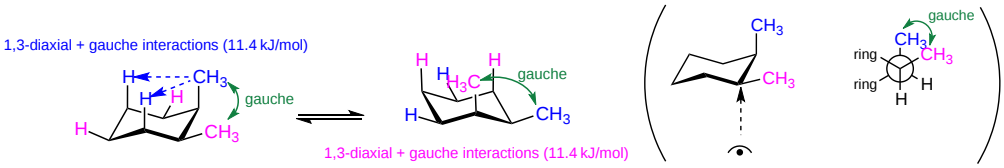


CIS AND *TRANS* STEREOISOMERS OF 1,2-DIMETHYLCYCLOHEXANE

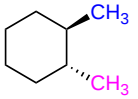
In *cis*-1,2-dimethylcyclohexane, both chair conformations have one methyl group equatorial and one methyl group axial. As previously discussed, the axial methyl group creates 7.6 kJ/mol of steric strain due to 1,3-diaxial interactions. It is important to note, that both chair conformations also have an additional 3.8 kJ/mol of steric strain created by a gauche interaction between the two methyl groups. Overall, both chair conformations have 11.4 kJ/mol of steric strain and are of equal stability.



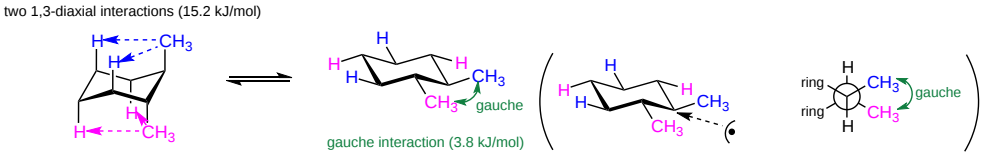
cis-1,2-dimethylcyclohexane



In *trans*-1,2-dimethylcyclohexane, one chair conformer has both methyl groups axial and the other conformer has both methyl groups equatorial. The conformer with both methyl groups equatorial has no 1,3-diaxial interactions however there is till 3.8 kJ/mol of strain created by a gauche interaction. The conformer with both methyl groups axial has four 1,3-Diaxial interactions which creates 2 x 7.6 kJ/mol (15.2 kJ/mol) of steric strain. This conformer is (15.2 kJ/mol -3.8 kJ/mol) 11.4 kJ/mol less stable than the other conformer. The equilibrium will therefore favor the conformer with both methyl groups in the equatorial position.

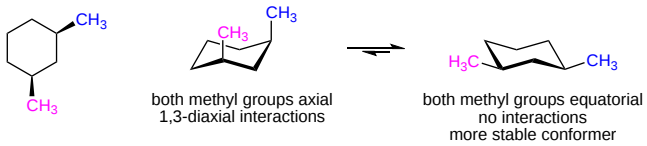


trans-1,2-dimethylcyclohexane

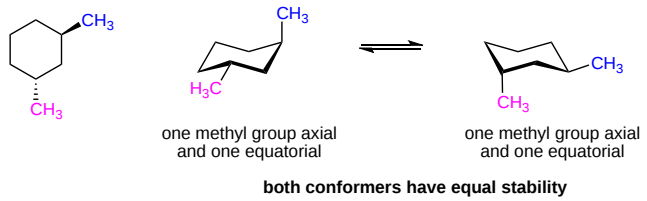


CIS AND *TRANS* STEREOISOMERS OF 1,3-DIMETHYLCYCLOHEXANE

A similar conformational analysis can be made for the *cis* and *trans* stereoisomers of 1,3-dimethylcyclohexane. For *cis*-1,3-dimethylcyclohexane one chair conformation has both methyl groups in axial positions creating 1,3-diaxial interactions. The other conformer has both methyl groups in equatorial positions thus creating no 1,3-diaxial interaction. Because the methyl groups are not on adjacent carbons in the cyclohexane rings gauche interactions are not possible. Even without energy calculations it is simple to determine that the conformer with both methyl groups in the equatorial position will be the more stable conformer.



For *trans*-1,3-dimethylcyclohexane both conformations have one methyl axial and one methyl group equatorial. Each conformer has one methyl group creating a 1,3-diaxial interaction so both are of equal stability.



SUMMARY OF DISUBSTITUED CYCLOHEXANE CHAIR CONFORMATIONS

When considering the conformational analyses discussed above a pattern begins to form. There are only two possible relationships which can occur between ring-flip chair conformations:

1) AA/EE: One chair conformation places both substituents in axial positions creating 1,3-diaxial interactions. The other conformer places both substituents in equatorial positions creating no 1,3-diaxial interactions. This diequatorial conformer is the more stable regardless of the substituents.

2) AE/EA: Each chair conformation places one substituent in the axial position and one substituent in the equatorial position. If the substituents are the same, there will be equal 1,3-diaxial interactions in both conformers making them equal in stability. However, if the substituents are different then different 1,3-diaxial interactions will occur. The chair conformation which places the larger substituent in the equatorial position will be favored.

Substitution type	Chair Conformation Relationship
cs-1,2-disubstituted cyclohexanes	AE/EA
trans-1,2-disubstituted cyclohexanes	AA/EE
cis-1,3-disubstituted cyclohexanes	AA/EE
trans-1,3-disubstituted cyclohexanes	AE/EA
cis-1,4-disubstituted cyclohexanes	AE/EA
trans-1,4-disubstituted cyclohexanes	AA/EE

✔ EXAMPLE 4.8.1

For *cis*-1-chloro-4-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *cis*-1,4-disubstitued cyclohexanes should have two chair conformations each with one substituent axial and one equatorial. Based on this, we can surmise that the energy difference of the two chair conformations will be based on the difference

in the 1,3-diaxial interactions created by the methyl and chloro substituents.



As predicted, each chair conformer places one of the substituents in the axial position. Because the methyl group is larger and has a greater 1,3-diaxial interaction than the chloro, the most stable conformer will place it the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol - 2.0 kJ/mol) 5.6 kJ/mol more stable than the other.

EXAMPLE 4.8.2

For *trans*-1-chloro-2-methylcyclohexane, draw the most stable chair conformation and determine the energy difference between the two chair conformers.

Solution

Based on the table above, *trans*-1,2-disubstitued cyclohexanes should have one chair conformation with both substituents axial and one conformation with both substituents equatorial. Based on this, we can predict that the conformer which places both substituents equatorial will be the more stable conformer. The energy difference of the two chair conformations will be based on the 1,3-diaxial interactions created by both the methyl and chloro substituents.

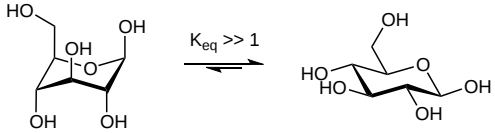


As predicted, one chair conformer places both substituents in the axial position and other places both substituents equatorial. The more stable conformer will place both substituents in the equatorial position, as shown in the structure on the right. Using the 1,3-diaxial energy values given in the previous sections we can calculate that the conformer on the right is (7.6 kJ/mol + 2.0 kJ/mol) 9.6 kJ/mol more stable than the other.

CONFORMATIONAL ANALYSIS OF COMPLEX SIX MEMBERED RING STRUCTURES

Cyclohexane can have more than two substituents. Also, there are multiple six membered rings which contain atoms other than carbon. All of these systems usually form chair conformations and follow the same steric constraints discussed in this section. Because the most commonly found rings in nature are six membered, conformational analysis can often help in understanding the usual shapes of some biologically important molecules. In complex six membered ring structures a direct calculation of 1,3-diaxial energy values may be difficult. In these cases a determination of the more stable chair conformer can be made by empirically applying the principles of steric interactions.

A later chapter will discuss how many sugars can exist in cyclic forms which are often six remembered rings. When in an aqueous solution the six carbon sugar, glucose, is usually a six membered ring adopting a chair conformation. When looking at the two possible ring-clip chair conformations, one has all of the substituents axial and the other has all the substutents equatorial. Even without a calculation, it is clear that the conformation with all equatorial substituents is the most stable and glucose will most commonly be found in this conformation.

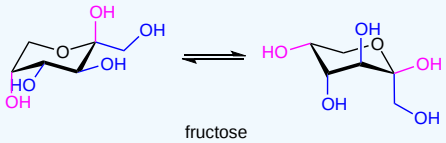


glucose
(β-glucopyranose form)

https://chem.libretexts.org/@go/page/31415

EXAMPLE 4.8.3

The six carbon sugar, fructose, in aqueous solution is also a six-membered ring in a chair conformation. Which of the two possible chair conformations would be expected to be the most stable?



fructose
(β-fructopyranose form)

Solution

The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position (pictured on the right). The left structure has 3 equatorial substituents while the structure on the right only has two equatorial substituents.

EXERCISES

1. Draw the two chair conformations for *cis*-1-ethyl-2-methylcyclohexane using bond-line structures and indicate the more energetically favored conformation.

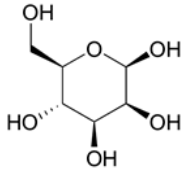
2. Draw the most stable conformation for *trans*-1-ethyl-3-methylcyclohexane using bond-line structures.

3. Draw the most stable conformation for trans-1-*t*-butyl-4-methylcyclohexane using bond-line structures.

4. Draw the most stable conformation fo *trans*-1-isopropyl-3-methylcyclohexane.

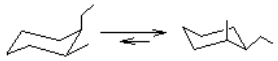
5. Can a 'ring flip' change a *cis*-disubstituted cyclohexane to *trans*? Explain.

6. Draw the two chair conformations of the six-carbon sugar mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

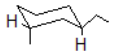


mannose

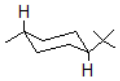
SOLUTIONS

1. 

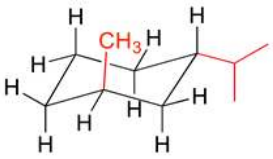
larger ethyl group in equatorial position is favored

2. 

larger ethyl group in equatorial position is favored

3. 

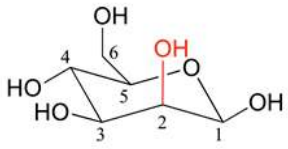
both alkyl groups in equatorial position

4. 

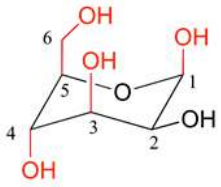
The bulkier isopropyl groups is in the equatorial position.

5. No. In order to change the relationship of two substituents on a ring from *cis* to *trans*, you would need to break and reform two covalent bonds. Ring flips involve only *rotation* of single bonds.

6.



major chair form of mannose
(only one substituent axial)



minor chair form of mannose
(four substituents axial)

EXERCISES

QUESTIONS

Q4.8.1

For the following molecules draw the most stable chair conformation and explain why you chose this as an answer

1 = *trans*-1,2-dimethylcyclohexane

2 = *cis*-1,3-dimethylcyclohexane

SOLUTIONS

S4.8.1

1 – The most stable conformation would be to have the methyl groups equatorial reducing steric interaction

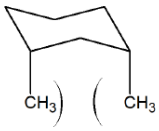
2 – The most stable conformation would be to have the groups equatorial this would reduce the strain if they were axial



1



2



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4.9: CONFORMATIONS OF POLYCYCLIC MOLECULES

OBJECTIVE

After completing this section, you should be able to draw the structures and construct molecular models of simple polycyclic molecules.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bridgehead carbon atom
- polycyclic molecule

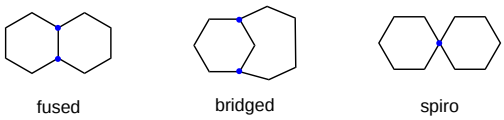
STUDY NOTES

A *bridgehead carbon atom* is a carbon atom which is shared by at least two rings. The hydrogen atom which is attached to a bridgehead carbon may be referred to as a bridgehead hydrogen.

Note that bicyclo[2.2.1]heptane is the systematic name of norborane. You need not be concerned over the IUPAC name of norbornane. The nomenclature of compounds of this type is beyond the scope of this course.

NOMENCLATURE OF BICYCLIC RING SYSTEMS

There are many hydrocarbons and hydrocarbon derivatives with two rings having common carbon atoms. There are three main ways that the two rings can be connected. The first is called a **fused bicyclic** ring structure where the two rings share a covalent bond and a have two **bridgehead** carbons (marked in red on the structures below). A bridgehead is defined as a carbon that is part of two or more rings. Hydrogens attached to bridge head carbons are often referred to as bridge head hydrogens. The two rings can also be connected by a bridge containing one or more carbons to form a **bridged bicyclic** molecule. Lastly, the two rings can be joined with a singe bridge head carbon to form **spiro bicyclic** molecules.



Bicyclic Isomers of $C_{10}H_{18}$

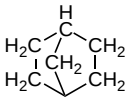
NAMING FUSED AND BRIDGED COMPOUNDS

Fused and bridged bicyclic compounds are follow similar naming conventions:

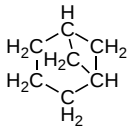
1. Count the total number of carbons in both rings. This is the parent name. (eg. ten carbons in the system would be decane)
2. Count the number of carbons between the bridgeheads, then place the numbers in square brackets in descending order separated by periods. Fused and bridged bycyclic compounds should have three numbers such as [2.2.0]. For fused compounds one of the numbers should be zero.
3. Place the word **bicyclo** at the beginning of the name.



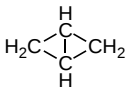
Examples with carbons and hydrogens explicitly shown:



bicyclo[2.2.1]heptane



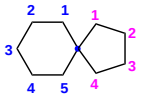
bicyclo[3.1.1]heptane



bicyclo[1.1.0]butane

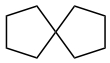
NAMING SPIRO COMPOUNDS

Spiro bicyclics are named using the same basic rules. Because there is only one bridgehead carbon only two numbers will be required in the brackets. Also, the word **spiro** is placed at the beginning.



spiro[5.4]decane

EXAMPLES



spiro[4.4]nonane



spiro[3.2]hexane

CONFORMATIONS IN BICYCLIC RING SYSTEMS

As expected, the connection of two rings has defined effects on the possible conformations. However, the ideas previously discussed in this chapter can be used for conformational analysis. Fused rings have the possibility of two isomers where the bridgehead hydrogens are either *cis* or *trans* along the shared bond. These two isomers have significant differences in flexibility and stability as seen in bicyclo[4,4,0]decane more commonly known as decalin. If the positioning of the bridgehead hydrogens are shown in a fused ring the prefix cis or trans should be included in the name.

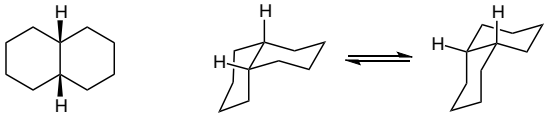
The trans-isomer is the easiest to describe because the fusion of the two rings creates a rigid, roughly planar, structure made up of two chair conformations. Unlike cyclohexane, the two rings cannot flip from one chair form to another. Accordingly, the orientation of the any substituents is fixed in either an axial or equatorial position in *trans*-decalin. This means that the C-C bonds coming away from the fused edge are held in equatorial positions relative to each ring thus preventing the possibility of any 1,3-diaxial interactions occurring between ring atoms.



***trans* -decalin**
(rigid)

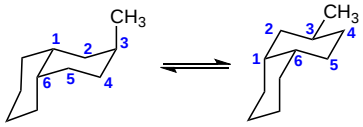
2kcal mol−1" id="MathJax-Element-1-Frame" role="presentation" style="position:relative;" tabindex="0">

The two rings in *cis*-decalin are also both held in a chair conformations. In comparison, the chair-chair forms of *cis*-decalin are relatively flexible, and inversion of both rings at once occurs fairly easily.



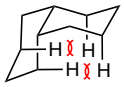
***cis* -decalin**
(more flexible)

The flexibility of *cis*-decalin allows for a substituent to interconvert between axial and equatorial conformations. In much the same fashion as cyclohexane, equatorial substituents tend to create less steric strain and create a more stable conformer.



(Note: atoms are mapped in blue for clarity.)

A major difference in *cis*-decalin is the fact that one of C-C bonds coming away from the fused edge is held an an axial position. This is true in both ring-flip conformations. This axial C-C bond causes 1,3-diaxial interactions to occur in *cis*-decalin making it roughly 8.4 kJ/mol less stable than *trans*-decalin. This amount of 1,3-diaxial steric strain is roughly equivalent to that of an ethyl substituent attached to a cyclohexane ring (8.0 kJ/mol)



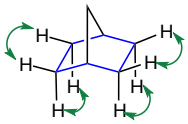
✕ = steric strain

Bicyclic compounds with a bridge typically have very little flexibility and are often held in a ridged conformation. The molecule norbornane represent a cyclohexane ring connected by a single carbon bridge.



norbornane, or
bicyclo[2.2.1]heptane

Norbornane is estimated to have 72 kJ/mol of ring strain which can be understood when viewing the contained rings. The carbon bridge in norbornane holds the cyclohexane ring at the bottom in a boat conformation creating torsional strain from eclipsing bonds along the edge.



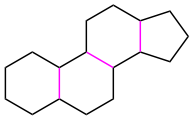
(green arrows used to illustrate
eclipsing hydrogens)

Also, the carbon bridge forms a cyclopentane ring (shown in red below making up the right side of the structure) with increased angle strain throughout the whole molecule.

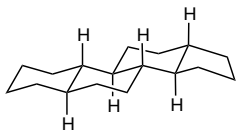


POLYCYCLIC SYSTEMS IN NATURE

Fused ring systems like decalin are very common in natural products. In fact, similar ring systems are found in steroids, which are an important class of lipids. Steroids generally have structures that include three six-membered rings and a five-membered ring connected by three fused bonds. Most natural steroids have a *trans* configuration at all three fusion points. This tends to give steroids a rigid and semi-flat structure.

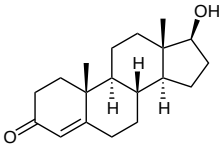


basic steroid ring confguration
(fused bonds highlighted in purple)

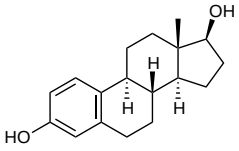


trans-trans-trans

Sex hormones are an example of steroids. The primary male hormone, testosterone, is responsible for the development of secondary sex characteristics. Two female sex hormones, progesterone and estrogen (or estradiol) control the ovulation cycle. Notice that the male and female hormones have only slight differences in structures, but yet have very different physiological effects. Testosterone promotes the normal development of male genital organs and is synthesized from cholesterol in the testes. It also promotes secondary male sexual characteristics such as deep voice, facial and body hair.

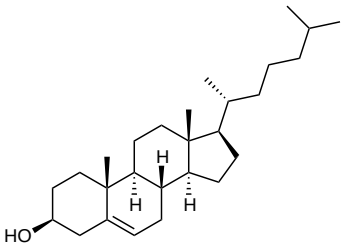


testosterone



estradiol

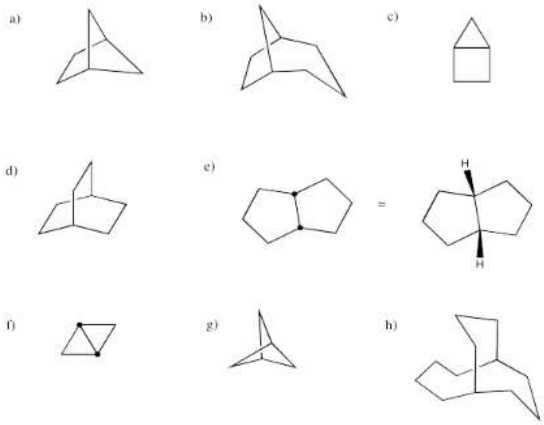
The best known and most abundant steroid in the body is cholesterol. Cholesterol is formed in brain tissue, nerve tissue, and the blood stream. It is the major compound found in gallstones and bile salts. Cholesterol also contributes to the formation of deposits on the inner walls of blood vessels. These deposits harden and obstruct the flow of blood. This condition, known as atherosclerosis, results in various heart diseases, strokes, and high blood pressure.



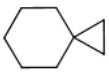
cholesterol

EXERCISES

1)



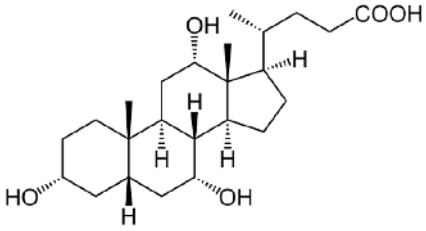
i)



j)



3) The following molecule is cholic acid. Determine if the three fused bonds have a *cis* or *trans* configuration.



SOLUTIONS

1)

a) Bicyclo[2.1.1]hexane

b) Bicyclo[3.2.1]octane

c) Bicyclo[2.1.0]pentane (more commonly called "housane")

d) Bicyclo[2.2.2]octane

e) cis-Bicyclo[3.3.0]octane

f) cis-Bicyclo[1.1.0]butane

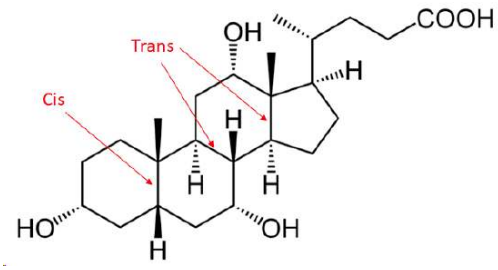
g) Bicyclo[1.1.1]pentane

h) Bicyclo[4.3.3]dodecane

i) Spiro[5.2]octane

j) Spiro[3.3]heptane

2)



QUESTIONS

Q4.9.1

Someone stated that *trans*-decalin is more stable than *cis*-decalin. Explain why this is incorrect.

SOLUTIONS

S4.9.1

Cis-decalin has fewer steric interactions than *trans*-decalin.

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4.S: ORGANIC COMPOUNDS- CYCLOALKANES AND THEIR STEREOCHEMISTRY (SUMMARY)

CONCEPTS & VOCABULARY

4.1: Naming Cycloalkanes

- Cycloalkanes are saturated hydrocarbons that have the generic formula $\mathbf{C_nH_{2n}}$, where **n** is the number of carbons in the ring.
- The IUPAC rules for naming cycloalkanes is very similar to the rules used for naming alkanes.

4.2: Cis-Trans Isomerism in Cycloalkanes

- **Stereoisomers** are molecules that have the same molecular formula, the same atom connectivity, but they differ in the relative spatial orientation of the atoms.
- Di-substituted cycloalkanes exhibit ***cis***- / ***trans***- stereoisomerism. The ***cis***- isomer has both substituents on the same face of the ring, while the **trans**- isomer has groups on opposite faces of the ring.

4.3: Stability of Cycloalkanes - Ring Strain

- **Ring strain** is the total strain in a ring due to **torsional strain**, **steric strain** and **angle strain**.
- Angle strain is when the C-C-C bond angles in rings are different than 109.5º, the optimal bond angle for sp^3 hybridized carbons.
- Ring strain causes small cycloalkanes, like cyclopropane and cyclobutane, to be much less stable than other cycloalkanes.

4.4: Conformations of Cycloalkanes

- Cyclopentane has less ring strain than cyclopropane and cyclobutane, because its ring carbons have more flexibility to rotate away from planarity, resulting in lower angle and torsional strains.

4.5: Conformations of Cyclohexane

- Cyclohexane has significantly lower ring strain than smaller cycloalkanes, because cyclohexane can adopt non-planar structures, which minimize angle strain and torsional strain.
- The common non-planar structures of cyclohexane are the boat, twist-boat, and chair conformations. The most stable, and hence, the most common, is the chair conformation.

4.6: Axial and Equatorial Bonds in Cyclohexane

- The two chair conformations of cyclohexane interconvert rapidly at room temperature in a process called **chair flip** or **ring flip**.
- In the chair conformation of cyclohexane, of the two groups attached to each ring carbon, one of the groups occupies the **axial** position, while the other group occupies the **equatorial** position.
- A group that was axial will switch to the equatorial position during a ring flip, and vice versa.

4.7: Conformations of Monosubstituted Cyclohexanes

- To minimize the steric effects of **1,3-diaxial interactions**, the single group on a monosubstituted cyclohexane ring will prefer to be in the equatorial position over the axial position. The larger the group, the greater is the preference shifts.

4.8: Conformations of Disubstituted Cyclohexanes

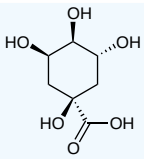
- The preference for large groups to be in the equatorial position effects the relative stability of the *cis* and *trans* isomers of disubstituted cyclohexanes. **Conformational analysis** is the process used to determine which isomer, *cis* or *trans*, is most stable.

4.9: Conformations of Polycyclic Molecules

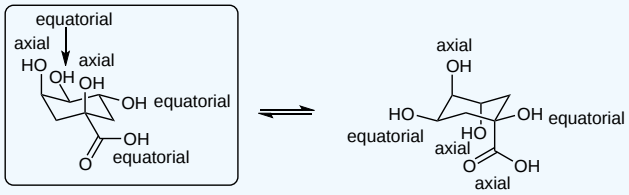
SUMMARY PROBLEMS

? EXERCISE 4.*S*.1

The following molecule, quinic acid, is a natural product that can be obtained from a variety of sources including the coffee bean. Draw both chair conformations for this molecule, identify each substituent in both structures as axial or equatorial, and clearly indicate which chair conformation is the most stable.



Answer

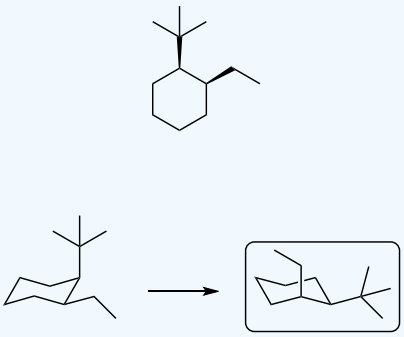


The circled conformation is more stable because it has more equatorial substituents (3 versus 2) and the largest group (the carboxylic acid) is equatorial.

EXERCISE 4.S.2

Convert the following name to a skeletal structure: *cis*-1-*t*-butyl-2-ethylcyclohexane. Then, draw this molecule in a chair conformation and perform a ring flip. Circle the most stable of the two conformations.

Answer

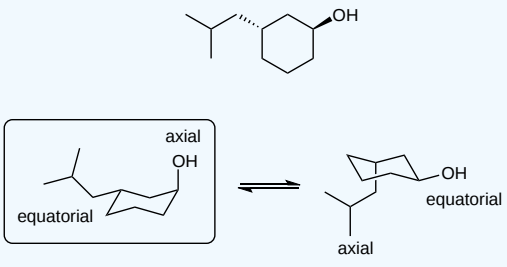


Remember that, due to its large size, the *t*-butyl substituent locks the cyclohexane ring into one conformation with the *t*-butyl in the equatorial position. Thus, this isn't an equilibrium. It exists only as the circled conformation.

EXERCISE 4.S.3

Convert the following name to a skeletal structure: *trans*-3-isobutylcyclohexanol. Then, draw the two chair conformations, label substituents as axial or equatorial, and circle the more stable conformation.

Answer



The circled molecule is most stable because the larger substituent is equatorial.

SKILLS TO MASTER

- Skill 4.1 Be able to name and draw cycloalkanes
- Skill 4.2 Identify and draw the *cis*- and *trans*- stereoisomers of disubstituted cycloalkanes.
- Skill 4.3 Determine the effects of torsional strain, steric strain, and angle strain on the overall ring strain of a cycloalkane.
- Skill 4.4 Draw the chair conformers of cyclohexane.
- Skill 4.5 Draw and identify the axial and equatorial positions in a chair conformer of cyclohexane and its ring-flip conformer.
- Skill 4.6 Use conformational analysis to determine the most stable stereoisomer in disubstituted and polysubstituted cyclohexanes.

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CHAPTER OVERVIEW

5: STEREOCHEMISTRY AT TETRAHEDRAL CENTERS

LEARNING OBJECTIVES

After you have completed Chapter 5, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use molecular models in solving problems on stereochemistry.
- solve road-map problems that include stereochemical information.
- define, and use in context, the new key terms.

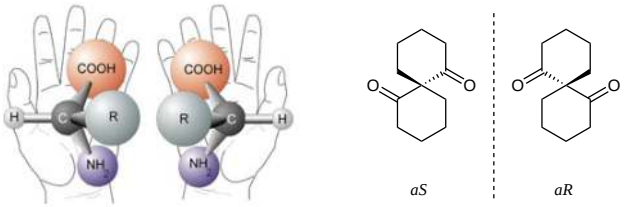
This chapter introduces the concept of chirality, and discusses the structure of compounds containing one or two chiral centers. A convenient method of representing the three-dimensional arrangement of the atoms in chiral compounds is explained; furthermore, throughout the chapter , considerable emphasis is placed on the use of molecular models to assist in the understanding of the phenomenon of chirality. The chapter continues with an examination of stereochemistry—the three-dimensional nature of molecules. The subject is introduced using the experimental observation that certain substances have the ability to rotate plane-polarized light. Finally, certain reactions of alkenes are re-examined in the light of the new material encountered in this chapter.

5.0: Chapter Objectives and Introduction
5.1: Enantiomers and the Tetrahedral Carbon
5.2: The Reason for Handedness in Molecules - Chirality
5.3: Optical Activity
5.4: Pasteur's Discovery of Enantiomers
5.5: Sequence Rules for Specifying Configuration
5.6: Diastereomers
5.7: Meso Compounds
5.8: Racemic Mixtures and the Resolution of Enantiomers
5.9: A Review of Isomerism
5.10: Chirality at Nitrogen, Phosphorus, and Sulfur
5.11: Prochirality
5.12: Chirality in Nature and Chiral Environments
5.S: Stereochemistry at Tetrahedral Centers (Summary)
5.xx: Enantiomers and Diastereomers

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5.0: CHAPTER OBJECTIVES AND INTRODUCTION

The opposite of chiral is **achiral**. Achiral objects are superimposable with their mirror images. If the molecules are superimposable, they are identical to each other. For example, two pieces of paper are achiral. In contrast, **chiral** objects, like our hands, are non-superimposable mirror images of each other. Try to line up your left hand perfectly with your right hand, so that the palms are both facing in the same directions. Spend about a minute doing this. Do you see that they cannot line up exactly?



The same thing applies to some molecules. A chiral molecule has a mirror image that cannot line up with it perfectly - the mirror images are non-superimposable. This pair of non-superimposable mirror image molecules are called **enantiomers**. But why are chiral molecules so interesting? Just like your left hand will not fit properly in your right glove, one of the enantiomers of a molecule may not work the same way in your body, as the other. It turns out that many of the biological molecules such as our DNA, amino acids and sugars, are chiral molecules.

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5.1: ENANTIOMERS AND THE TETRAHEDRAL CARBON

OBJECTIVES

After completing this section, you should be able to

1. use molecular models to show that only a tetrahedral carbon atom satisfactorily accounts for the lack of isomerism in molecules of the type CH_2XY, and for the existence of optical isomerism in molecules of the type CHXYZ.
2. determine whether two differently oriented wedge-and-broken-line structures are identical or represent a pair of enantiomers.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

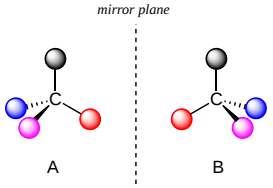
- enantiomer

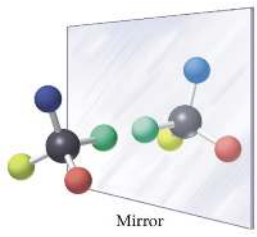
STUDY NOTES

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of the most interesting types of isomer is the mirror-image stereoisomer, a non-superimposable set of two molecules that are mirror images of one another. The existence of these molecules are determined by a a concept known as **chirality**. The word “chiral” was derived from the Greek word for hand, because our hands are a good example of chirality since they are non-superimposable mirror images of each other.

CHIRAL MOLECULES

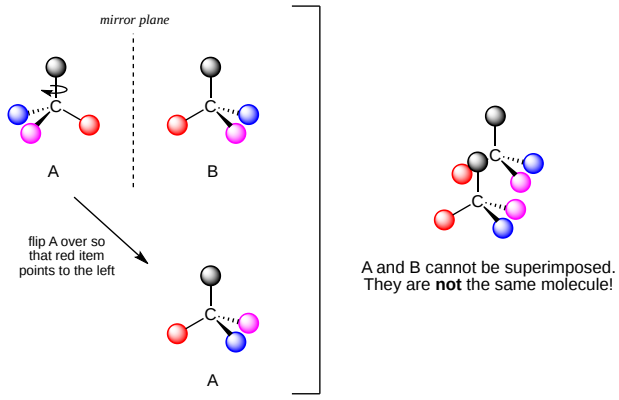
The term **chiral**, from the Greek work for 'hand', refers to anything which cannot be superimposed on its own mirror image. Certain organic molecules are chiral meaning that they are not superimposable on their mirror image. Chiral molecules contain one or more **chiral centers**, which are almost always tetrahedral (sp^3-hybridized) carbons with four different substituents. Consider the molecule A below: a tetrahedral carbon, with four different substituents denoted by balls of four different colors.





The mirror image of A, which we will call B, is drawn on the right side of the figure, and an imaginary mirror is in the middle. Notice that every point on A lines up through the mirror with the same point on B: in other words, if A looked in the mirror, it would see B looking back.

Now, if we flip compound A over and try to superimpose it point for point on compound B, we find that we cannot do it: if we superimpose any two colored balls, then the other two are misaligned.



A is not superimposable on its mirror image (B), thus by definition A is a chiral molecule. It follows that B also is not superimposable on *its* mirror image (A), and thus it is also a chiral molecule.

A and B are called **stereoisomers or optical isomers**: molecules with the same molecular formula and the same bonding arrangement, but *a different arrangement of atoms in space*. **Enantiomers** are pairs of stereoisomers which are mirror images of each other: thus, A and B are enantiomers. It should be self-evident that a chiral molecule will always have one (and *only* one) enantiomer: enantiomers come in pairs. Enantiomers have identical physical properties (melting point, boiling point, density, and so on). However, enantiomers do differ in how they interact with polarized light (we will learn more about this soon) and they may also interact in very different ways with other chiral molecules - proteins, for example. We will begin to explore this last idea in later in this chapter, and see many examples throughout the remainder of our study of biological organic chemistry.

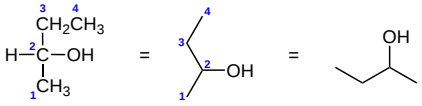
THE MANY SYNONYMS OF THE CHIRAL CARBON

Be aware - all of the following terms can be used to describe a chiral carbon.

chiral carbon = asymmetric carbon = optically active carbon = stereo carbon = stereo center = chiral center

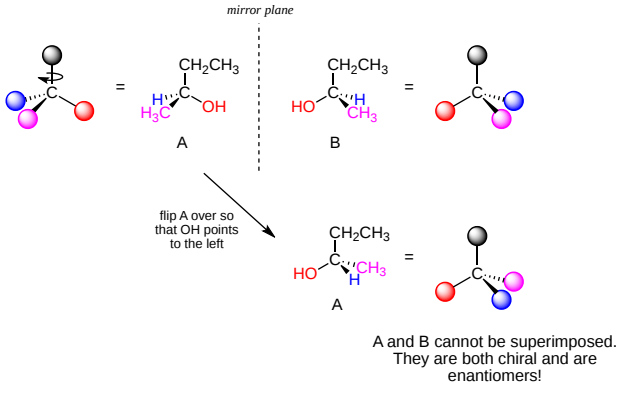
Let's apply our chirality discussion to real molecules.

Consider 2-butanol, drawn in two dimensions below.



2-butanol
(drawn in 2D)

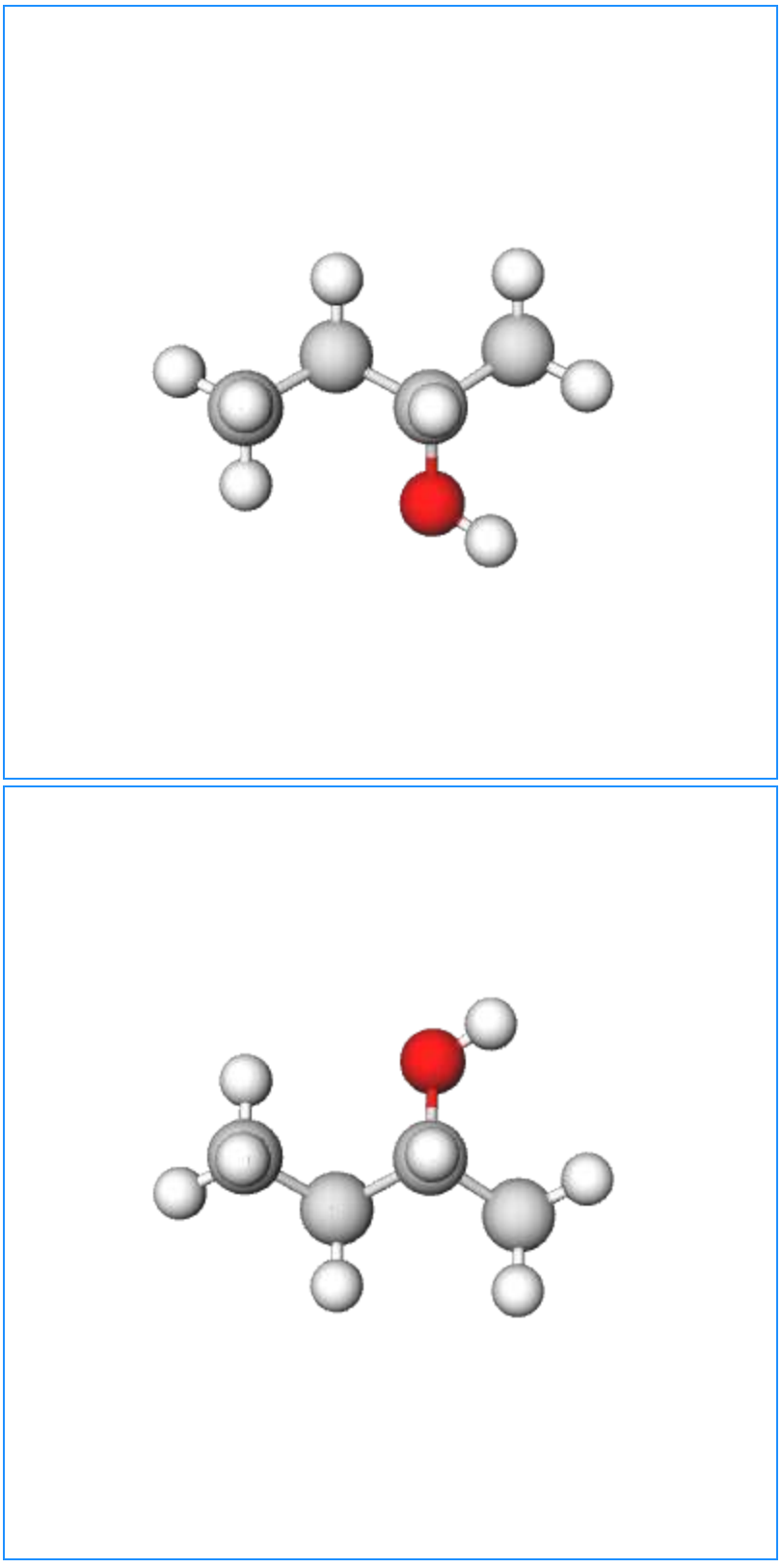
Carbon #2 is a chiral center: it is sp^3-hybridized and tetrahedral (even though it is not drawn that way above), and the four substituents attached to is are different: a hydrogen (H) , a methyl (-CH_3) group, an ethyl (-CH_2CH_3) group, and a hydroxyl (OH) group. If the bonding at C_2 of 2-butanol is drawn in three dimensions and this structure called A. Then the mirror image of A can be drawn to form structure B.



When we try to superimpose A onto B, we find that we cannot do it. Because structure A and B are not superimposable on their mirror image they are both chiral molecules. Because A and B are different due only to the arrangement of atoms in space they are stereoisomers. Because A and B are mirror images of each other they are also enantiomers. When looking at simplified line structures is clear that there are two distinct ways of drawing 2-butanol which only differ in their spatial arrangement around a chiral carbon.



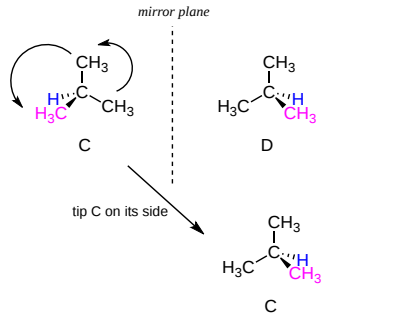
two enantiomers of 2-butanol



The 3D Structures of the Two Enantiomers of 2-Butanol

For comparison, 2-propanol, is an achiral molecule because is lacks a chiral carbon. Carbon #2 is bonded to two identical substituents (methyl groups), and so it is not a chiral carbon. Being achiral means that 2-propanol should be superimposable on its mirror image which is shown in the figure below. A more detailed explaination on why 2-propanol is achiral will be given in the next section.

2-propanol is achiral:



STEREOISOMERS

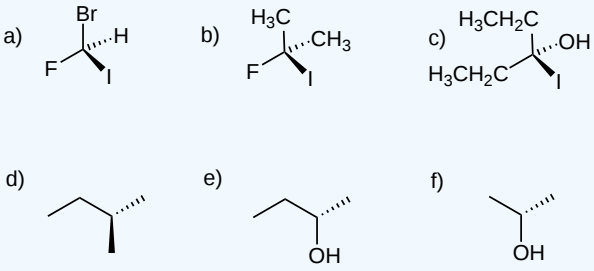
Stereoisomers have been defined as molecules with the same connectivity but different arrangements of the atoms in space. It is important to note that there are two types of stereoisomers: geometric and optical.

Optical isomers are molecules whose structures are mirror images but cannot be superimposed on one another in any orientation. Optical isomers have identical physical properties, although their chemical properties may differ in asymmetric environments. Molecules that are nonsuperimposable mirror images of each other are said to be chiral.

Geometric isomers differ in the relative position(s) of substituents in a rigid molecule. Simple rotation about a C–C σ bond in an alkene, for example, cannot occur because of the presence of the π bond. The substituents are therefore rigidly locked into a particular spatial arrangement. Thus a carbon–carbon multiple bond, or in some cases a ring, prevents one geometric isomer from being readily converted to the other. The members of an isomeric pair are identified as either cis or trans, and interconversion between the two forms requires breaking and reforming one or more bonds. Because their structural difference causes them to have different physical and chemical properties, cis and trans isomers are actually two distinct chemical compounds.mers have the same connectivity, but different arrangements of atoms in space. Geometric isomers will be discussed in more detain in **Sections 7.4 and 7.5**.

? EXERCISE 5.1.1

Identify the following molecules as chiral or achiral.



Answer

a. chiral (4 different groups off C)
b. achiral (2 identical -CH_3 substituents off central C)
c. achiral (2 identical -CH_2CH_3 substituents off central C)
d. achiral (2 identical CH_3 substituents off carbon 2)
e. chiral (4 different groups off carbon 2)
f. achiral (2 identical CH_3 substituents off central C)

EXERCISE 5.1.2

Determine if the following sets of compounds in each group are enantiomers or the same compound.

a) 

b) 

c) 

d) 

Answer

a. enantiomers – non superimposable mirror images
b. same compound – when you rotate the molecule on the right it is identical to the one on the left
c. enantiomers – non superimposable mirror images
d. enantiomers – non superimposable mirror images

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5.2: THE REASON FOR HANDEDNESS IN MOLECULES - CHIRALITY

OBJECTIVES

After completing this section, you should be able to

1. determine whether or not a compound is chiral, given its Kelulé, condensed or shorthand structure, with or without the aid of molecular models.
2. label the chiral centres (carbon atoms) in a given Kelulé, condensed or shorthand structure.

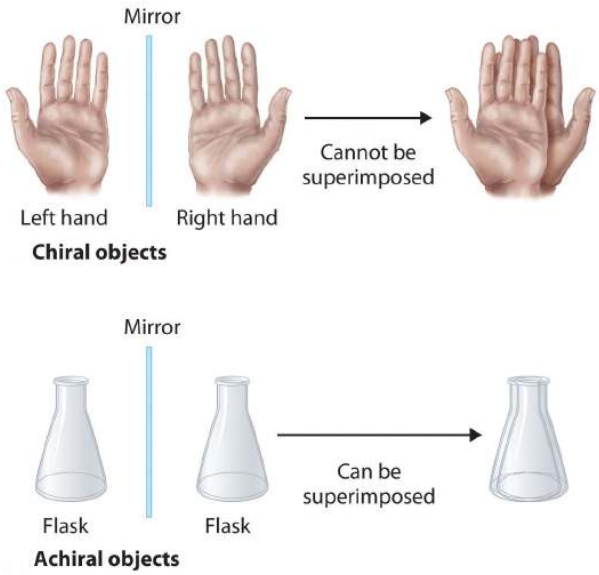
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

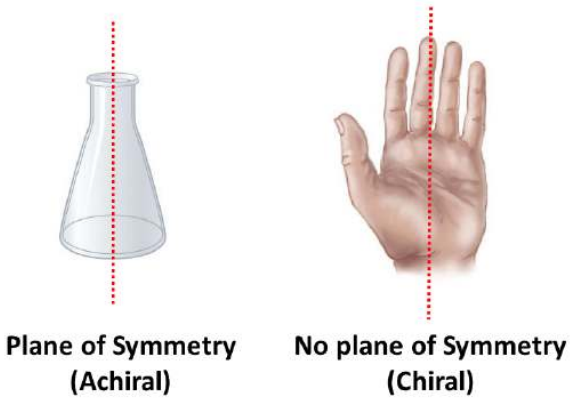
- achiral
- chiral
- chiral (stereogenic) centre
- plane of symmetry

SYMMETRY AND CHIRALITY

Molecules that are nonsuperimposable mirror images of each other are said to be chiral (pronounced “ky-ral,” from the Greek cheir, meaning “hand”). Examples of some familiar chiral objects are your hands. Your left and right hands are nonsuperimposable mirror images. (Try putting your right shoe on your left foot—it just doesn’t work.) An achiral object is one that can be superimposed on its mirror image, as shown by the superimposed flasks 25.7.1b in the figure below. .

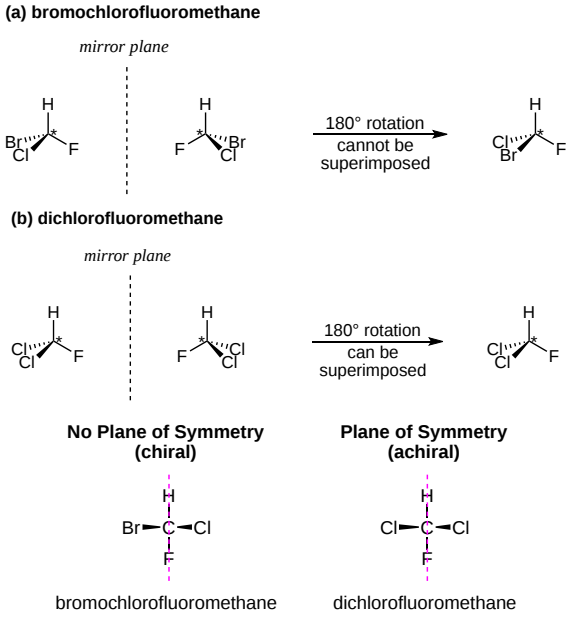


An an important questions is why is one chiral and the other not? The answer is that the flask has a plane of symmetry and your hand does not. A plane of symmetry is a plane or a line through an object which divides the object into two halves that are mirror images of each other. When looking at the flask, a line can be drawn down the middle which separates it into two mirror image halves. However, a similar line down the middle of a hand separates it into two non-mirror image halves. This idea can be used to predict chirality. If an object or molecule has a plane of symmetry it is achiral. If if lacks a plane of symmetry it is chiral.



Symmetry can be used to explain why a carbon bonded to four different substituents is chiral. When a carbon is bonded to fewer than four different substituents it will have a plane of symmetry making it achiral. A carbon atom that is bonded to four different substituents loses all symmetry, and is often referred to as an asymmetric carbon. The lack of a plane of symmetry makes the carbon chiral. The presence of a single chiral carbon atom sufficient to render the molecule chiral, and modern terminology refers to such groupings as chiral centers or stereo centers.

An example is shown in the bromochlorofluoromethane molecule shown in part (a) of the figure below. This carbon, is attached to four different substituents making it chiral. which is often designated by an asterisk in structural drawings. If the bromine atom is replaced by another chlorine to make dichlorofluoromethane, as shown in part (b) below, the molecule and its mirror image can now be superimposed by simple rotation. Thus the carbon is no longer a chiral center. Upon comparison, bromochlorofluoromethane lacks a plane of symmetry while dichlorofluoromethane has a plane of symmetry.

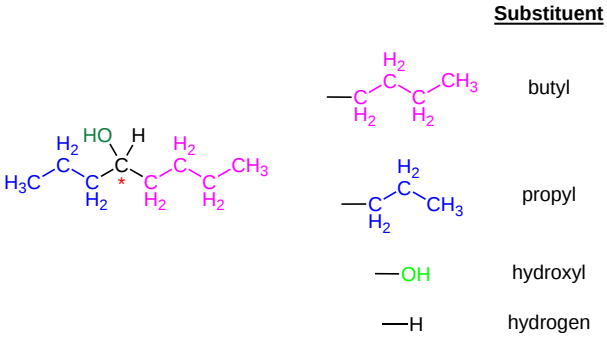


IDENTIFYING CHIRAL CARBONS

Identifying chiral carbons in a molecule is an important skill for organic chemists. The presence of a chiral carbon presents the possibility of a molecule having multiple stereoisomers. Most of the chiral centers we shall discuss in this chapter are asymmetric carbon atoms, but it should be recognized that other tetrahedral or pyramidal atoms may become chiral centers if appropriately substituted. Also, when more than one chiral center is present in a molecular structure, care must be taken to analyze their relationship before concluding that a specific molecular configuration is chiral or achiral. This aspect of stereoisomerism will be treated later. Because an carbon requires four different substituents to become asymmertric, it can be said, with few exceptions, that sp^2 and sp hybridized carbons involved in multiple bonds are achiral. Also, any carbon with more than one hydrogen, such as a $-CH_3$ or $-CH_2-$ group, are also achiral.

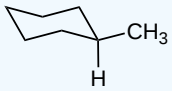
Looking for planes of symmetry in a molecule is useful, but often difficult in practice. It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions, the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral.

Determining if a carbon is bonded to four distinctly different substituents can often be difficult to ascertain. Remember even the slightest difference makes a substituent unique. Often these difference can be distant from the chiral carbon itself. Careful consideration and often the building of molecular models may be required. A good example is shown below. It may appear that the molecule is achiral, however, when looking at the groups directly attached to the possible chiral carbon, it is clear that they all different. The two alkyl groups are differ by a single -CH_2- group which is enough to consider them different.



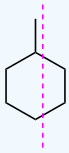
EXAMPLE 5.2.1

Predict if the following molecule would be chiral or achiral:



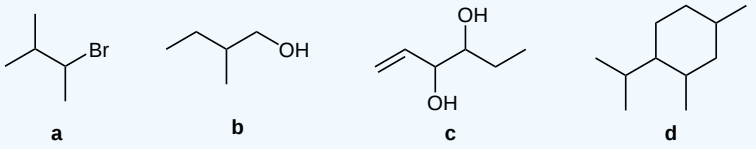
Answer

Achiral. When determining the chirality of a molecule, it best to start by locating any chiral carbons. An obvious candidate is the ring carbon attached to the methyl substituent. The question then becomes: does the ring as two different substituents making the substituted ring carbon chiral? With an uncertainty such as this, it is then helpful try to identify any planes of symmetry in the molecule. This molecule does have a plane of symmetry making the molecule achiral. The plane of symmetry would be easier see if the molecule were view from above. Typically, monosubstituted cycloalkanes have a similar plane of symmetry making them all achiral.

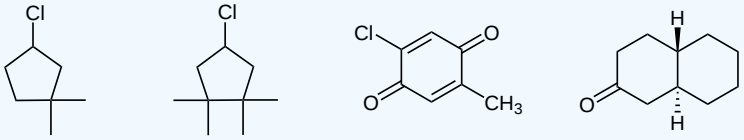


EXERCISE 5.2.1

Determine if each of the following molecules are chiral or achiral. For chiral molecules indicate any chiral carbons.

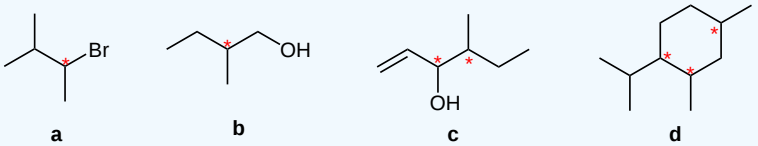


a b c d

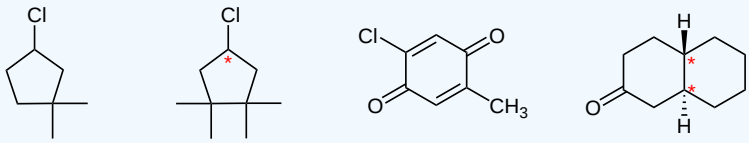


e f g h

Answer



a b c d



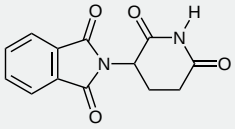
e f g h

Explanation

Structures F and G are achiral. The former has a plane of symmetry passing through the chlorine atom and bisecting the opposite carbon-carbon bond. The similar structure of compound E does not have such a symmetry plane, and the carbon bonded to the chlorine is a chiral center (the two ring segments connecting this carbon are not identical). Structure G is essentially flat. All the carbons except that of the methyl group are sp^2 hybridized, and therefore trigonal-planar in configuration. Compounds C, D & H have more than one chiral center, and are also chiral.

NOTE

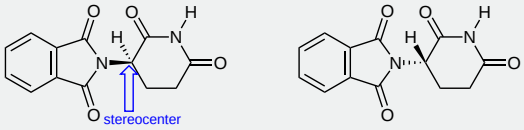
In the 1960's, a drug called thalidomide was widely prescribed in the Western Europe to alleviate morning sickness in pregnant women.



thalidomide

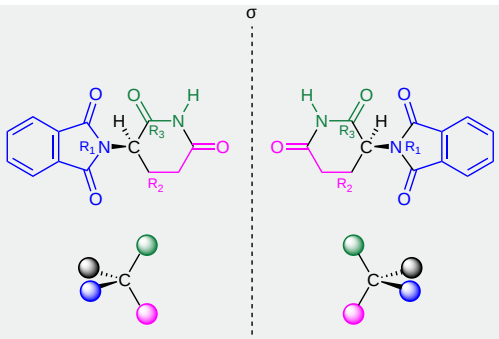
Thalidomide had previously been used in other countries as an antidepressant, and was believed to be safe and effective for both purposes. The drug was not approved for use in the U.S.A. It was not long, however, before doctors realized that something had gone horribly wrong: many babies born to women who had taken thalidomide during pregnancy suffered from severe birth defects.

Researchers later realized the problem lay in the fact that thalidomide was being provided as a mixture of two different isomeric forms.



effective isomer mutagenic isomer

One of the isomers is an effective medication, the other caused the side effects. Both isomeric forms have the same molecular formula and the same atom-to-atom connectivity, so they are not constitutional isomers. Where they differ is in the arrangement in three-dimensional space about one tetrahedral, sp^3-hybridized carbon. These two forms of thalidomide are **stereoisomers**. If you make models of the two stereoisomers of thalidomide, you will see that they too are mirror images, and cannot be superimposed.

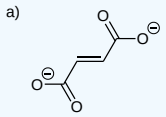


As a historical note, thalidomide was never approved for use in the United States. This was thanks in large part to the efforts of Dr. Frances Kelsey, a Food and Drug officer who, at peril to her career, blocked its approval due to her concerns about the lack of adequate safety studies, particularly with regard to the drug's ability to enter the bloodstream of a developing fetus. Unfortunately, though, at that time clinical trials for new drugs involved widespread and unregulated distribution to doctors and their patients across the country, so families in the U.S. were not spared from the damage caused.

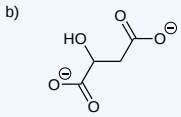
Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

EXAMPLE 5.2.2

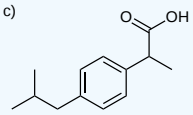
Label the molecules below as chiral or achiral, and locate all stereocenters.



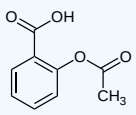
fumarate
(a citric acid cycle intermediate)



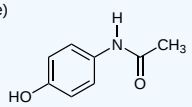
malate
(a citric acid cycle intermediate)



ibuprofen

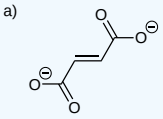


acetylsalicylic acid
(aspirin)

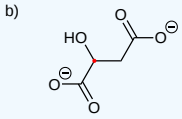


acetaminophen
(active ingredient in Tylenol)

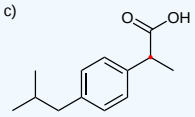
Answer



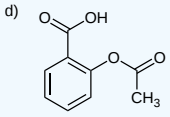
fumarate
(achiral)



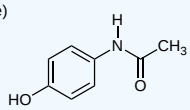
malate
(chiral)



ibuprofen
(chiral)



acetylsalicylic acid
(achiral)

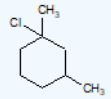


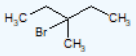
acetaminophen
(achiral)

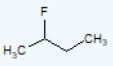
EXERCISE 5.2.2

1) For the following compounds, star (*) each chiral center, if any.

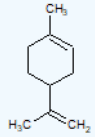
(a) (b) (c)



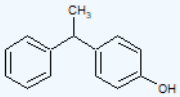




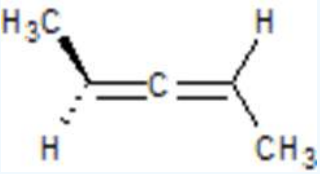
(d) (e) (f)







2) Explain why the following compound is chiral.



3) Determine which of the following objects is chiral.

a) A Glove.

b) A nail.

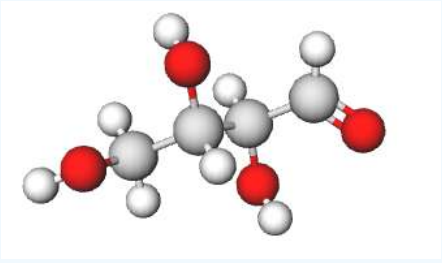
c) A pair of sunglasses.

d) The written word "Chiral".

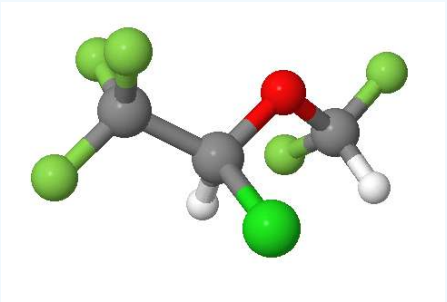
4) Place an "*" by all of the chrial carbons in the following molecules.

a)

Erythrose, a four carbon sugar.

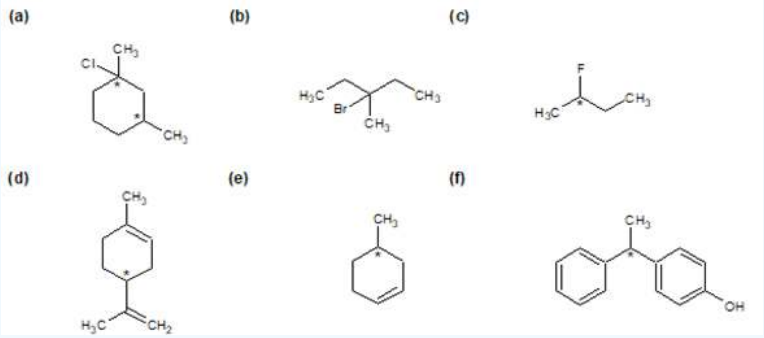


b) Isoflurane, an anestetic. Bright green = Chlorine, Pale green = Fluorine.



Answer

1)



2) Though the molecule does not contain a chiral carbon, it is chiral as it is non-superimposable on its mirror image due to its twisted nature (the twist comes from the structure of the double bonds needing to be at 90° angles to each other, preventing the molecule from being planar).

3)

a) Just as hands are chiral a glove must also be chiral.

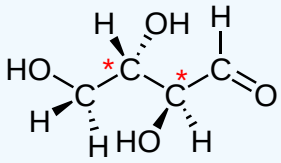
b) A nail has a plane of symmetry which goes down the middle making it a achiral.

c) A pair of sunglasses has a plane of symmetry which goes through the nose making it achiral.

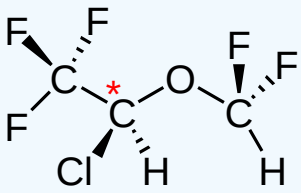
d) Most written words are chiral. Look one in a mirror to confirm this.

4

a)

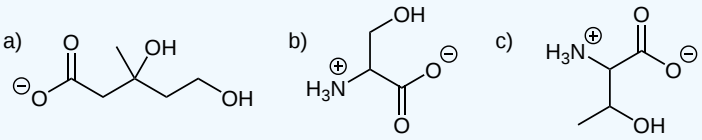


b)



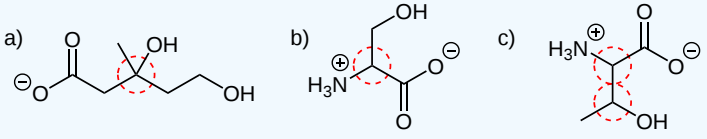
EXERCISE 5.2.3

Circle all of the carbon stereocenters in the molecules below.



mevalonate serine threonine

Answer

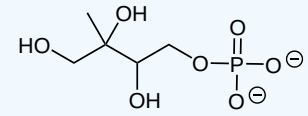


mevalonate serine threonine

EXERCISE 5.2.4

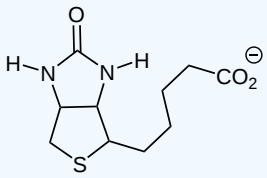
Circle all of the carbon stereocenters in the molecules below.

a)



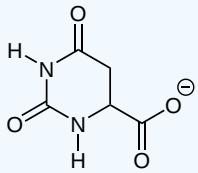
2-methylerythritol-4-phopshate

b)



biotin

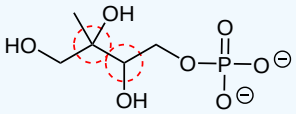
c)



dihydroorotate

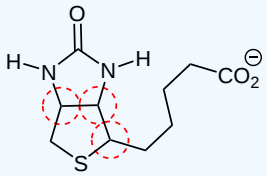
Answer

a)



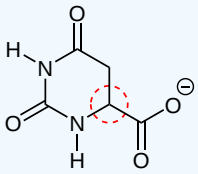
2-methylerythritol-4-phopshate

b)



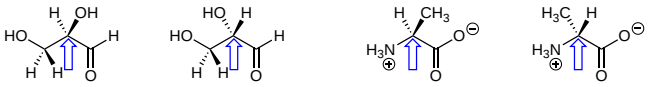
biotin

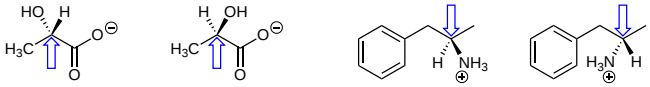
c)



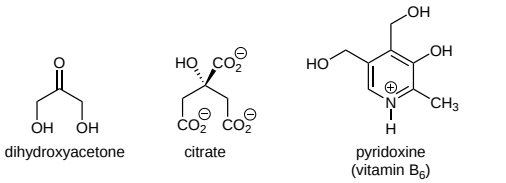
dihydroorotate

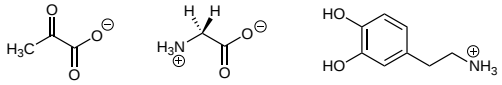
Here are some more examples of chiral molecules that exist as pairs of enantiomers. In each of these examples, there is a single stereocenter, indicated with an arrow. (Many molecules have more than one stereocenter, but we will get to that that a little later!)





Here are some examples of molecules that are **achiral** (*not* chiral). Notice that none of these molecules has a stereocenter.



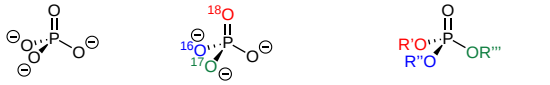


It is difficult to illustrate on the two dimensional page, but you will see if you build models of these achiral molecules that, in each case, there is at least one **plane of symmetry**, where one side of the plane is the mirror image of the other. Chirality is tied conceptually to the idea of asymmetry, and *any molecule that has a plane of symmetry cannot be chiral*. When looking for a plane of symmetry, however, we must consider all possible conformations that a molecule could adopt. Even a very simple molecule like ethane, for example, is asymmetric in many of its countless potential conformations – but it has obvious symmetry in both the eclipsed and staggered conformations, and for this reason it is achiral.

Looking for planes of symmetry in a molecule is useful, but often difficult in practice. In most cases, the easiest way to decide whether a molecule is chiral or achiral is to look for one or more stereocenters - with a few rare exceptions (see section 3.7B), the general rule is that molecules with at least one stereocenter are chiral, and molecules with no stereocenters are achiral. Carbon stereocenters are also referred to quite frequently as **chiral carbons**.

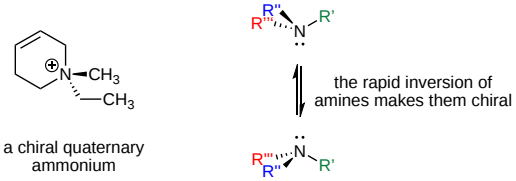
When evaluating a molecule for chirality, it is important to recognize that the question of whether or not the dashed/solid wedge drawing convention is used is irrelevant. Chiral molecules are sometimes drawn without using wedges (although obviously this means that stereochemical information is being omitted). Conversely, wedges may be used on carbons that are not stereocenters – look, for example, at the drawings of glycine and citrate in the figure above. Just because you see dashed and solid wedges in a structure, do not automatically assume that you are looking at a stereocenter.

Other elements in addition to carbon can be stereocenters. The phosphorus center of phosphate ion and organic phosphate esters, for example, is tetrahedral, and thus is potentially a stereocenter.



We will see in chapter 10 how researchers, in order to investigate the stereochemistry of reactions at the phosphate center, incorporated sulfur and/or ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) to create chiral phosphate groups. Phosphate triesters are chiral if the three substituent groups are different.

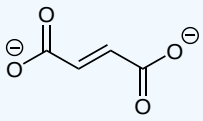
Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



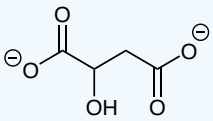
EXERCISE 5.2.5

Label the molecules below as chiral or achiral, and circle all stereocenters.

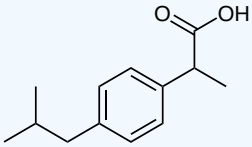
a) fumarate (a citric acid cycle intermediate)



b) malate (a citric acid cycle intermediate)

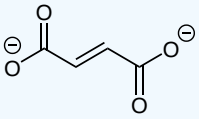


b) malate (a citric acid cycle intermediate)

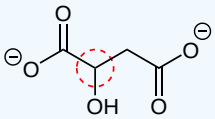


Answer

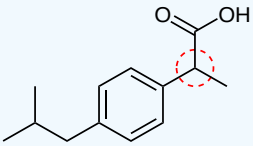
a) achiral (no stereocenters)



b) chiral



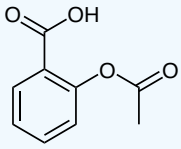
c) chiral



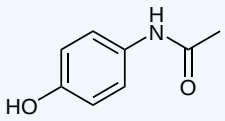
EXERCISE 5.2.6

Label the molecules below as chiral or achiral, and circle all stereocenters.

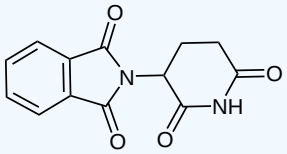
a) acetylsalicylic acid (aspirin)



b) acetaminophen (active ingredient in Tylenol)

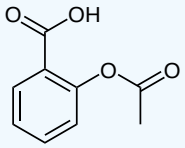


c) thalidomide (drug that caused birth defects in pregnant mothers in the 1960's)

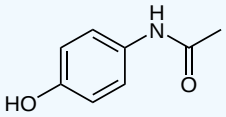


Answer

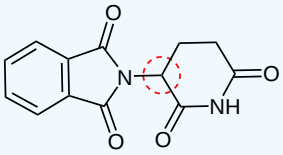
a) achiral (no stereocenters)



b) achiral (no stereocenters)



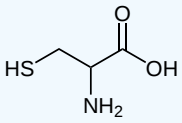
c) chiral



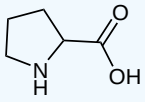
EXERCISE 5.2.7

Draw both enantiomers of the following chiral amino acids.

a) Cysteine

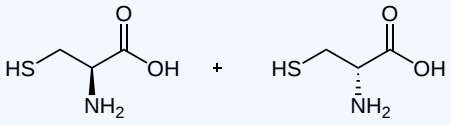


b) Proline

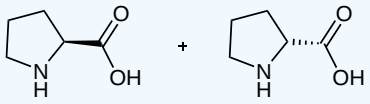


Answer

a)



b)



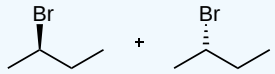
EXERCISE 5.2.8

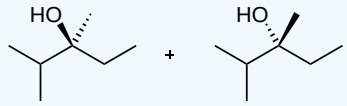
Draw both enantiomers of the following compounds from the given names.

a) 2-bromobutane

b) 2,3-dimethyl-3-pentanol

Answer

a) 

b) 

EXERCISE 5.2.9

Which of the following body parts are chiral?

a) Hands b) Eyes c) Feet d) Ears

Answer

a) Hands- chiral since the mirror images cannot be superimposed (think of the example in the beginning of the section)

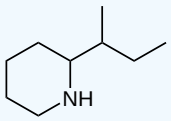
b) Eyes- achiral since mirror images that are superimposable

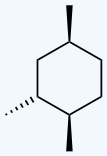
c) Feet- chiral since the mirror images cannot be superimposed (Does your right foot fit in your left shoe?)

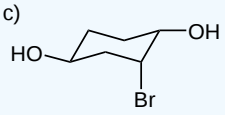
d) Ears- chiral since the mirror images cannot be superimposed

EXERCISE 5.2.10

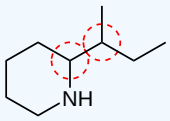
Circle the chiral centers in the following compounds.

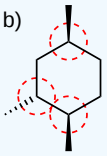
a) 

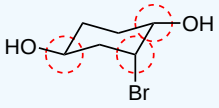
b) 

c) 

Answer

a) 

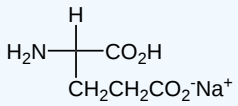
b) 

c) 

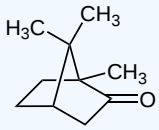
EXERCISE 5.2.11

Identify the chiral centers in the following compounds.

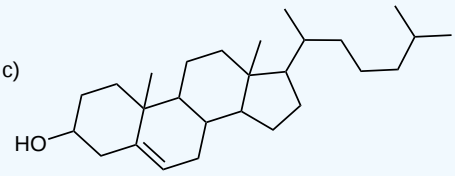
a)



b)

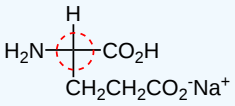


c)

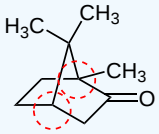


Answer

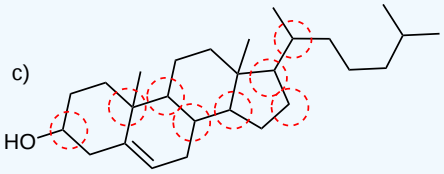
a)



b)



c)



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5.3: OPTICAL ACTIVITY

OBJECTIVES

After completing this section, you should be able to

1. describe the nature of plane-polarized light.
2. describe the features and operation of a simple polarimeter.
3. calculate the specific rotation of a compound, given the relevant experimental data.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- analyzer
- dextrorotatory
- levorotatory
- optically active
- plane-polarized light
- polarimeter
- polarizer
- specific rotation, $[\alpha]_D^{20}$

STUDY NOTES

A *polarizer* is a device through which only light waves oscillating in a single plane may pass. A *polarimeter* is an instrument used to determine the angle through which plane-polarized light has been rotated by a given sample. You will have the opportunity to use a polarimeter in the laboratory component of the course. An *analyzer* is the component of a polarimeter that allows the angle of rotation of plane-polarized light to be determined.

Specific rotations are normally measured at 20°C, and this property may be indicated by the symbol $[\alpha]_D^{20}$. Sometimes the solvent is specified in parentheses behind the specific rotation value, for example,

$$[\alpha]_D^{20} = +12^o\,(\text{chloroform})$$

For liquids, the specific rotation may be obtained using the neat liquid rather than a solution; in such cases the formula is

$$[\alpha]_D^{\text{temp}}\,(\text{neat}) = \alpha \times l \times d$$

where α is the observed rotation, l is the path length of the cell (measured in decimetres, dm), and d is the density of the liquid.

Identifying and distinguishing enantiomers is inherently difficult, since their physical and chemical properties are largely identical. Fortunately, a nearly two hundred year old discovery by the French physicist Jean-Baptiste Biot has made this task much easier. This discovery disclosed that the right- and left-handed enantiomers of a chiral compound perturb plane-polarized light in opposite ways. This perturbation is unique to chiral molecules, and has been termed **optical activity**.

POLARIMETRY

Plane-polarized light is created by passing ordinary light through a polarizing device, which may be as simple as a lens taken from polarizing sun-glasses. Such devices transmit selectively only that component of a light beam having electrical and magnetic field vectors oscillating in a single plane. The plane of polarization can be determined by an instrument called a **polarimeter** (Figure **5.3.1**).

Monochromatic (single wavelength) light, is polarized by a fixed polarizer next to the light source. A sample cell holder is located in line with the light beam, followed by a movable polarizer (the analyzer) and an eyepiece through which the light intensity can be observed. In modern instruments an electronic light detector takes the place of the human eye. In the absence of a sample, the light intensity at the detector is at a maximum when the second (movable) polarizer is set parallel to the first polarizer ($\alpha = 0^o$). If the analyzer is turned 90º to the plane of initial polarization, all the light will be blocked from reaching the detector.

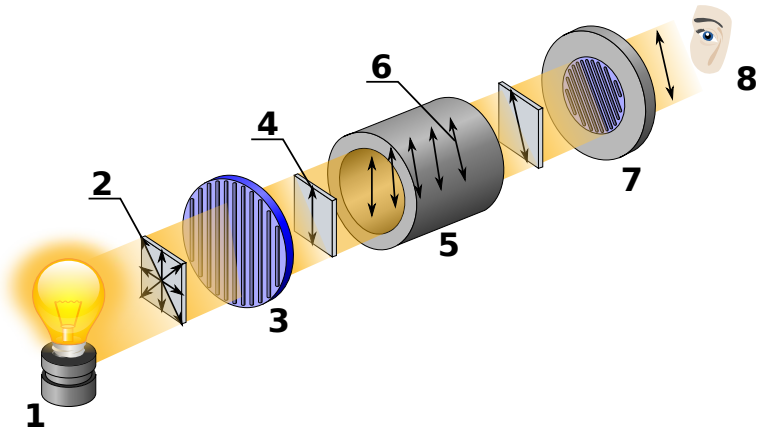


Figure **5.3.1**: Operating principle of an optical polarimeter. 1. Light source 2. Unpolarized light 3. Linear polarizer 4. Linearly polarized light 5. Sample tube containing molecules under study 6. Optical rotation due to molecules 7. Rotatable linear analyzer 8. Detector. (CC BY-SA 3.0 Unported; Kaidor via Wikipedia)

Chemists use polarimeters to investigate the influence of compounds (in the sample cell) on plane polarized light. Samples composed only of achiral molecules (e.g. water or hexane), have no effect on the polarized light beam. However, if a single enantiomer is examined (all sample molecules being right-handed, or all being left-handed), the plane of polarization is rotated in either a clockwise (positive) or counter-clockwise (negative) direction, and the analyzer must be turned an appropriate matching angle, **α**, if full light intensity is to reach the detector. In the above illustration, the sample has rotated the polarization plane clockwise by +90º, and the analyzer has been turned this amount to permit maximum light transmission.

The observed rotations (α) of enantiomers are opposite in direction. One enantiomer will rotate polarized light in a clockwise direction, termed **dextrorotatory** or (+), and its mirror-image partner in a counter-clockwise manner, termed **levorotatory** or (–). The prefixes dextro and levo come from the Latin *dexter*, meaning right, and *laevus*, for left, and are abbreviated *d* and *l* respectively. If equal quantities of each enantiomer are examined , using the same sample cell, then the magnitude of the rotations will be the same, with one being positive and the other negative. To be absolutely certain whether an observed rotation is positive or negative it is often necessary to make a second measurement using a different amount or concentration of the sample. In the above illustration, for example, α might be –90º or +270º rather than +90º. If the sample concentration is reduced by 10%, then the positive rotation would change to +81º (or +243º) while the negative rotation would change to –81º, and the correct α would be identified unambiguously.

Since it is not always possible to obtain or use samples of exactly the same size, the observed rotation is usually corrected to compensate for variations in sample quantity and cell length. Thus it is common practice to convert the observed rotation, α, to a **specific rotation**, by the following formula:

$$[\alpha]_D = \frac{\alpha}{lc} \tag{5.3.1}$$

where

- $[\alpha]_D$ is the specific rotation
- l is the cell length in dm
- c is the concentration in g/ml
- D designates that the light used is the 589 line from a sodium lamp

Compounds that rotate the plane of polarized light are termed **optically active**. Each enantiomer of a stereoisomeric pair is optically active and has an equal but opposite-in-sign specific rotation. Specific rotations are useful in that they are experimentally determined constants that characterize and identify pure enantiomers. For example, the lactic acid enantiomers have the following specific rotations:

- Carvone from caraway: $[\alpha]_D^{20} = +62.5^o$ (this isomer may be referred to as (+)-carvone or d-carvone)
- Carvone from spearmint: $[\alpha]_D^{20} = -62.5^o$ (this isomer may be referred to as (–)-carvone or l-carvone)

and carvone enantiomers have the following specific rotations:

- Lactic acid from muscle tissue: $[\alpha]_D^{20} = +2.5^o$ (this isomer may be referred to as (+)-lactic acid or d-lactic acid)
- Lactic acid from sour milk: $[\alpha]_D^{20} = -2.5^o$ (this isomer may be referred to as (–)-lactic acid or l-lactic acid)

A 50:50 mixture of enantiomers has no observable optical activity. Such mixtures are called **racemates** or racemic modifications, and are designated (±). When chiral compounds are created from achiral compounds, the products are racemic unless a single enantiomer of a chiral

co-reactant or catalyst is involved in the reaction. The addition of **HBr** to either cis- or trans-2-butene is an example of racemic product formation (the chiral center is colored red).

$$CH_3CH{=}CHCH_3 + HBr \longrightarrow (\pm)\ CH_3CH_2\color{red}{C}HBrCH_3$$

Chiral organic compounds isolated from living organisms are usually optically active, indicating that one of the enantiomers predominates (often it is the only isomer present). This is a result of the action of chiral catalysts we call enzymes, and reflects the inherently chiral nature of life itself. Chiral synthetic compounds, on the other hand, are commonly racemates, unless they have been prepared from enantiomerically pure starting materials.

There are two ways in which the condition of a chiral substance may be changed:

1. A racemate may be separated into its component enantiomers. This process is called **resolution**.
2. A pure enantiomer may be transformed into its racemate. This process is called **racemization**.

ENANTIOMERIC EXCESS

The "optical purity" is a comparison of the optical rotation of a pure sample of unknown stereochemistry versus the optical rotation of a sample of pure enantiomer. It is expressed as a percentage. If the sample only rotates plane-polarized light half as much as expected, the optical purity is 50%.

$$\%\ \text{optical purity} = \frac{\text{specific rotation of mixture}}{\text{specific rotation of pure enantiomer}} \times 100\%$$

Because *R* and *S* enantiomers have equal but opposite optical activity, it naturally follows that a 50:50 racemic mixture of two enantiomers will have no observable optical activity. If we know the specific rotation for a chiral molecule, however, we can easily calculate the ratio of enantiomers present in a mixture of two enantiomers, based on its measured optical activity. When a mixture contains more of one enantiomer than the other, chemists often use the concept of **enantiomeric excess (ee)** to quantify the difference. Enantiomeric excess can be expressed as:

$$ee = \frac{(\%\ \text{more abundant enantiomer} - 50) \times 100\%}{50}$$

For example, a mixture containing 60% *R* enantiomer (and 40% *S* enantiomer) has a 20% enantiomeric excess of R: ((60-50) x 100) / 50 = 20 %.

? EXERCISE 5.3.1

The specific rotation of (*S*)-carvone is (+)61°, measured 'neat' (pure liquid sample, no solvent). The optical rotation of a neat sample of a mixture of *R* and *S* carvone is measured at (-)23°. Which enantiomer is in excess, and what is its ee? What are the percentages of (*R*)- and (*S*)-carvone in the sample?

Answer

The observed rotation of the mixture is levorotary (negative, counter-clockwise), and the specific rotation of the pure *S* enantiomer is given as dextrorotary (positive, clockwise), meaning that the pure *R* enantiomer must be levorotary, and the mixture must contain more of the *R* enantiomer than of the *S* enantiomer.

Rotation (*R*/*S* Mix) = [Fraction(*S*) × Rotation (*S*)] + [Fraction(*R*) × Rotation (*R*)]

Let Fraction (*S*) = x, therefore Fraction (*R*) = 1 – x.

Rotation (*R*/*S* Mix) = x[Rotation (*S*)] + (1 – x)[Rotation (*R*)].

–23 = x(+61) + (1 – x)(–61)

Solve for x: x = 0.3114 and (1 – x) = 0.6885

Therefore the percentages of (*R*)- and (*S*)-carvone in the sample are 68.9% and 31.1%, respectively.

ee = [(% more abundant enantiomer – 50) × 100]/50. = [68.9 – 50) × 100]/50 = 37.8%.

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration

Chiral molecules are often labeled according to the sign of their specific rotation, as in (S)-(+)-carvone and (R)-(-)-carvone, or (±)-carvone for the racemic mixture. However, there is no relationship whatsoever between a molecule's R/S designation and the sign of its specific rotation. Without performing a polarimetry experiment or looking in the literature, we would have no idea that (-)-carvone has the R configuration and (+)-carvone has the S configuration.

SEPARATION OF CHIRAL COMPOUNDS

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used of this technique is known as chiral resolution.

? EXERCISE 5.3.2

A 3.20 g sample of morphine ($[\alpha]_D$ = -132) was dissolved in 10.0 mL of acetic acid ($[\alpha]_D$ = 0). If it is put into a sample tube with a path length of 2.00 cm, what would be its observed rotation (α)?

Answer

The specific rotation, $[\alpha]_D$ = (observed rotation, α (degrees))/ [(pathlength, *l* (dm)) x (concentration, c (g/cm^3))] = α/(*l* x c)

Solving for α, α = $[\alpha]_D$ x *l* x c

($[\alpha]_D$ = -132) x (*l* = 2.00 cm = 0.200 dm) x (c = 3.20 g / 10.0 cm^3 = 0.320 g/cm^3)

α = -132 x 0.200 dm x 0.320 g/cm^3 = -8.45 º

? EXERCISE 5.3.3

Is the morphine in the previous excercise dextrorotatory or levorotatory?

Answer

Since morphine has a (-) rotation, it indicates that it rotates light to the left (counterclockwise) and morphine is levorotatory.

? EXERCISE 5.3.4

Label the following compounds as dextrorotatory or levorotatory.

a. sucrose ($[\alpha]_D$ = + 66.7)
b. cholesterol ($[\alpha]_D$ = - 31.5)
c. cocaine ($[\alpha]_D$ = - 16)
d. chloroform ($[\alpha]_D$ = 0)

Answer

a. sucrose ($[\alpha]_D$ = + 66.7) dextrorotatory
b. cholesterol ($[\alpha]_D$ = - 31.5) levorotatory
c. cocaine ($[\alpha]_D$ = - 16) levorotatory
d. chloroform ($[\alpha]_D$ = 0) neither, not optically active

? EXERCISE 5.3.5*a*

The specific rotation of (*S*)-carvone is (+) 61º when measured neat (pure liquid sample with no solvent). The optical rotation of a neat sample of a mixture of R and S carvone is measured at (-) 23 º.

a) Which enantiomer is in excess?

Answer

Since the pure *S* enantiomer ((+) 61°) is dextrorotatory (positive, clockwise), the *R* enantiomer must be levorotatory. The observed rotation of the mixture is levorotatory since its negative (counterclockwise). This means the mixture must contain more of the *R* enantiomer than the *S* enantiomer.

EXERCISE 5.3.5b

b) What are the percentages of (*S*)- and (*R*)- carvone in the sample mixture?

Answer

Optical rotation (α) of the (*R*/*S* mixture) = [fraction (*S*) x $[\alpha]_D$ (*S*)] + [fraction (*R*) x $[\alpha]_D$ (*R*)]

To determine the fraction of S and R, we make y = fraction (*S*) and 1 – y = fraction (*R*)

-23° = y x (61°) + (1 – y) x (-61°) solving for y: y = 0.3114 and (1-y) = 0.6885

Therefore the percentage of (*S*)-carvone is 31.1 % and (*R*)-carvone is 68.9 %

EXERCISE 5.3.5c

c) What is the ee (enantiomeric excess)?

Answer

ee = [(% more abundant isomer – 50) x 100]/50 = [(68.9 – 50) x100]/50 = 37.8 % ee

EXERCISE 5.3.6a

Determine the ee's of the following from the percentages

- 95 % (*R*)- tartaric acid and 5.0 % (*S*)- tartaric acid

Answer

[(95 – 50) x 100] / 50 = 90 % ee (*R*)-tartaric acid

EXERCISE 5.3.6b

Determine the ee's of the following from the percentages

- 75 % (*S*)- limonene and 25 % (*R*)- limonene

Answer

[(75 – 50) x 100] / 50 = 50 % ee (*S*)- limonene

EXERCISE 5.3.6c

Determine the ee's of the following from the percentages

- 85 % (*R*) cysteine

Answer

(85 – 50) x 100] / 50 = 70 % ee (*R*)-cysteine

EXERCISE 5.3.6d

Determine the ee's of the following from the percentages

- 50 % (*S*) alanine

Answer

(50 – 50) x 100] / 50 = 0 % ee, racemic mixture

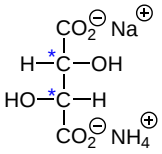
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5.4: PASTEUR'S DISCOVERY OF ENANTIOMERS

OBJECTIVE

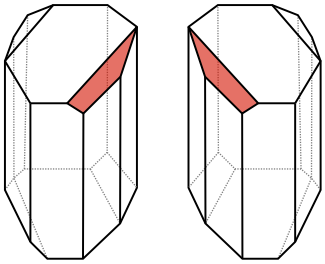
After completing this section, you should be able to discuss how the results of work carried out by Biot and Pasteur contributed to the development of the concept of the tetrahedral carbon atom.

Because enantiomers have identical physical and chemical properties in achiral environments, separation of the stereoisomeric components of a racemic mixture or racemate is normally not possible by the conventional techniques of distillation and crystallization. In some cases, however, the crystal habits of solid enantiomers and racemates permit the chemist (acting as a chiral resolving agent) to discriminate enantiomeric components of a mixture. As background for the following example, it is recommended that the section on crystal properties be reviewed. Tartaric acid, its potassium salt known in antiquity as "tartar", has served as the locus of several landmark events in the history of stereochemistry. In 1832 the French chemist Jean Baptiste Biot observed that tartaric acid obtained from tartar was optically active, rotating the plane of polarized light clockwise (**dextrorotatory**). An optically inactive, higher melting, form of tartaric acid, called racemic acid was also known.



sodium ammonium tartrate

A little more than a decade later, young Louis Pasteur conducted a careful study of the crystalline forms assumed by various salts of these acids. He noticed that under certain conditions, the sodium ammonium mixed salt of the racemic acid formed a mixture of enantiomorphic hemihedral crystals; a drawing of such a pair is shown below. Pasteur reasoned that the dissymmetry of the crystals might reflect the optical activity and dissymmetry of its component molecules. After picking the different crystals apart with a tweezer, he found that one group yielded the known dextrorotatory tartaric acid measured by Biot; the second led to a previously unknown levorotatory tartaric acid, having the same melting point as the dextrorotatory acid. Today we recognize that Pasteur had achieved the first resolution of a racemic mixture, and laid the foundation of what we now call stereochemistry.



Optical activity was first observed by the French physicist Jean-Baptiste Biot. He concluded that the change in direction of plane-polarized light when it passed through certain substances was actually a rotation of light, and that it had a molecular basis. His work was supported by the experimentation of Louis Pasteur. Pasteur observed the existence of two crystals that were mirror images in tartaric acid, an acid found in wine. Through meticulous experimentation, he found that one set of molecules rotated polarized light clockwise while the other rotated light counterclockwise to the same extent. He also observed that a mixture of both, a *racemic mixture* (or *racemic modification*), did not rotate light because the optical activity of one molecule canceled the effects of the other molecule. Pasteur was the first to show the existence of chiral molecules.

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5.5: SEQUENCE RULES FOR SPECIFYING CONFIGURATION

OBJECTIVES

After completing this section, you should be able to

1. assign Cahn-Ingold-Prelog priorities to a given set of substituents.
2. determine whether a given wedge-and-broken-line structure corresponds to an *R* or an *S* configuration, with or without the aid of molecular models.
3. draw the wedge-and-broken-line structure for a compound, given its IUPAC name, complete with *R* or *S* designation.
4. construct a stereochemically accurate model of a given enantiomer from either a wedge-and-broken-line structure or the IUPAC name of the compound, complete with *R* or *S* designation.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- absolute configuration
- *R* configuration
- *S* configuration

STUDY NOTES

When designating a structure as *R* or *S*, you must ensure that the atom or group with the lowest priority is pointing away from you, the observer. The easiest way to show this is to use the wedge-and-broken-line representation. You can then immediately determine whether you are observing an *R* configuration or an *S* configuration.

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The method for this is formally known as *R*/*S* nomenclature.

INTRODUCTION

The method of unambiguously assigning the handedness of molecules was originated by three chemists: R.S. Cahn, C. Ingold, and V. Prelog and, as such, is also often called the Cahn-Ingold-Prelog rules. In addition to the Cahn-Ingold system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

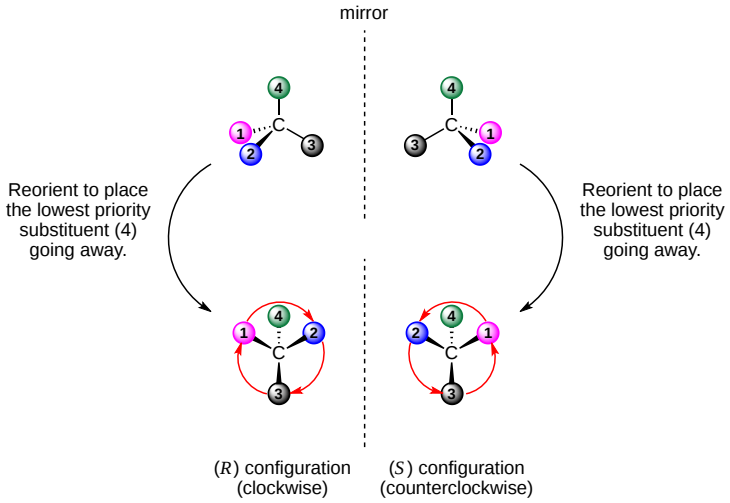
1. X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
2. Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

However, for non-laboratory purposes, it is beneficial to focus on the (*R*)/(*S*) system. The sign of optical rotation, although different for the two enantiomers of a chiral molecule,at the same temperature, **cannot** be used to establish the absolute configuration of an enantiomer; this is because the sign of optical rotation for a particular enantiomer may change when the temperature changes.

STEREOCENTERS ARE LABELED (*R*) OR (*S*)

The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as (*R*) or (*S*).

The **Cahn-Ingold-Prelog** rules of assign priorities the groups directly bonded to the chiral carbon. Having ranked the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) is given a dash bond to indicate it points directly away from us. We then look at the three remaining substituents, which now appear to radiate toward us which is shown by using wedge bonds. If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent is clockwise, we say that the chirality center has the (R) configuration (Latin rectus, meaning “right”). If an arrow from is counterclockwise, the chirality center has the (S) configuration (Latin sinister, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a Right (clockwise) turn. Note, the (R) or (S) configurations represent the two enantiomers of a chiral molecule. The (R) or (S) configuration is often added as a prefix, in parenthesis, to a chiral molecule's name to indicate which enantiomer is being discussed (e.g., (R)-2-bromobutane). If more than chiral carbon is present in a chiral molecule, each carbon's number is included before the (R) or (S) configuration. Ex: (2R,4S,6R)-2-bromo-6-chloro-4-methylheptane.



SEQUENCE RULES TO ASSIGN PRIORITIES TO SUBSTITUENTS

Before applying the (*R*) and (*S*) nomenclature to a stereocenter, the substituents must be prioritized according to the following rules:

RULE 1

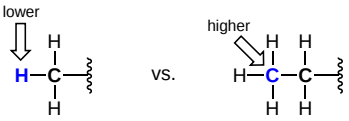
First, examine at the atoms directly attached to the stereocenter of the compound. A atom with a higher atomic number takes precedence over a atom with a lower atomic number. Hydrogen is the lowest possible priority atom, because it has the lowest atomic number.

1. The atom with higher atomic number has higher priority (I > Br > Cl > S > P > F > O > N > C > H).
2. When comparing isotopes, the atom with the higher mass number has higher priority [$^{18}O > {}^{16}O$ or $^{15}N > {}^{14}N$ or $^{13}C > {}^{12}C$ or T (^{3}H) > D (^{2}H) > H].

RULE 2

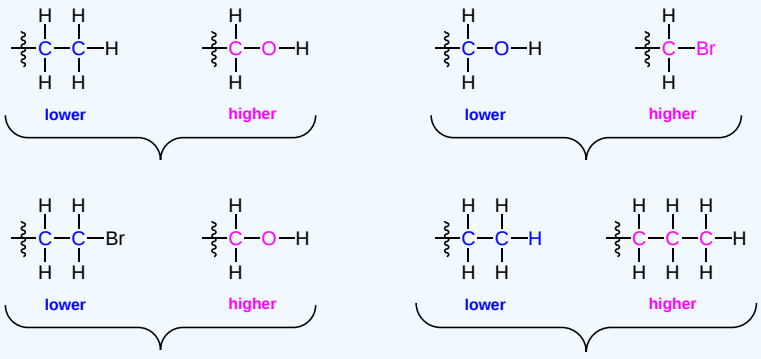
If there are two or more substituents which have the same element directly attached to chiral carbon, proceed along the substituent chains until a point of difference is found. Determine which of the chains has the first connection to an atom with the highest priority (the highest atomic number). That chain has the higher priority.

For example: an ethyl substituent takes priority over a methyl substituent. At the connectivity of the stereocenter, both have a carbon atom, which are equal in rank. Going down the chains, a methyl has only has hydrogen atoms attached to it, whereas the ethyl has two hydrogen atoms and a carbon atom. The carbon atom on the ethyl is the first point of difference and has a higher atomic number than hydrogen; therefore the ethyl takes priority over the methyl.



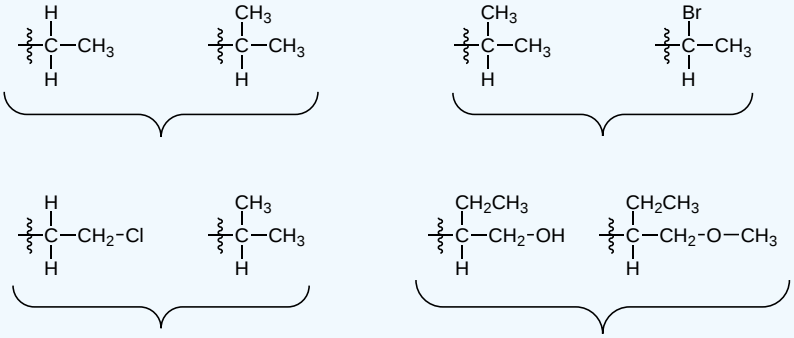
The "-H" (left) ranks lower than the "C-" (right) based on the relative molecular weights at the first point of difference.

✔ EXAMPLE 5.5.1



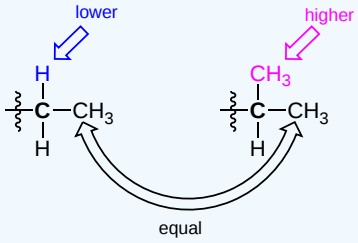
WORKED EXERCISE 5.5.1

For the following pairs of substituents, determine which would have the higher and lower priority based on the **Cahn-Ingold-Prelog** rules. Explain your answer.



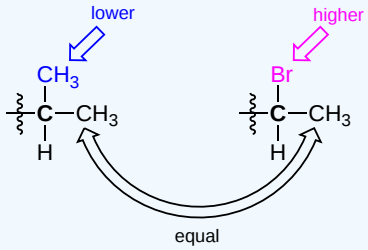
Answer

A 1-methylethyl substituent takes precedence over an ethyl substituent. Connected to the first carbon atom, ethyl only has one other carbon, whereas the 1-methylethyl has two carbon atoms attached to the first; this is the first point of difference. Therefore, 1-methylethyl ranks higher in priority than ethyl, as shown below:



The "C-" (right) ranks higher than the "H-" (left) based on the first point of difference and their relative atomic numbers.

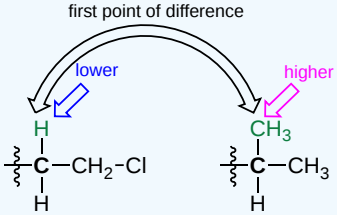
However:



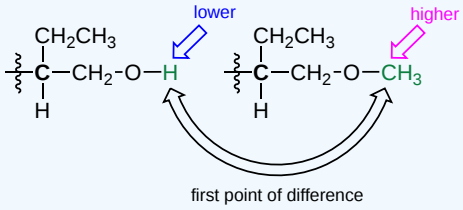
In this case, even though the bold carbon on the right structure has two connections to a non-hydrogen atom (C), it is the lower priority. This is because one of the atoms attached to the bold carbon on the left molecule ranks higher than any of the atoms attached to the bold carbon on the right structure, since Br has a higher atomic number than C.

Caution!!

Keep in mind that priority is determined by the **first** point of difference along the two similar substituent chains. After the first point of difference, the rest of the chain is irrelevant.

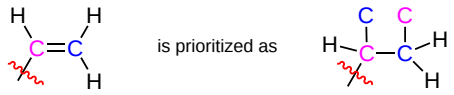


When looking for the first point of difference on similar substituent chains, one may encounter branching. If there is branching, choose the branch that is higher in priority. If the two substituents have similar branches, rank the elements within the branches until a point of difference.

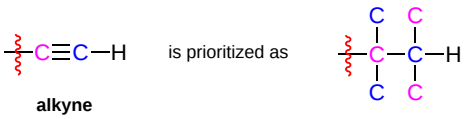


RULE 3

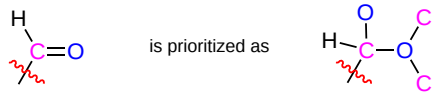
For assigning priority, multiple bonds are treated as if each bond of the multiple bond is bonded to a unique atom. For example, an alkene substituent (CH_2=CH-) has higher priority than an ethyl substituent (CH_3CH_2-). The alkene carbon priority is "two" bonds to carbon atoms and one bond to a hydrogen atom compared with the ethyl carbon that has only one bond to a carbon atom and two bonds to two hydrogen atoms. Similarly, alkyne substituent (HCC-) would have an even higher priority because the alkyne carbon is treated as if it is bonded to three carbons. This method remains the same with compounds containing a carbonyl (C=O) group. The carbon of an aldehyde substituent (O=CH-) is treated as if it is bonded to a hydrogen and two oxygen atoms.



alkene



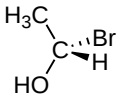
alkyne



aldehyde

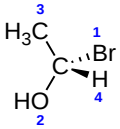
DETERMINING (*R*) OR (*S*) CONFIGURATION USING A MOLECULAR MODEL

In order to demonstrate how to determine the (*R*)/(*S*) configuration of the chiral carbon in the following molecule using molecular models, first construct a model of the bromoethanol structure:

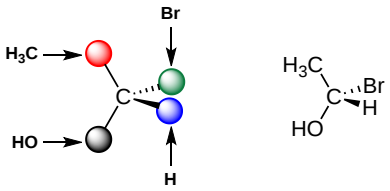


First make a molecular model of a tetrahedral carbon with four different substituents. In many cases, this will appear as a carbon with four bonds with a different colored ball attached to each bond.

For the molecule in question, determine the location of the chiral carbon and assign CIP priorities to the substituents. In this case, Br gets the highest priority because it has the highest atomic number. The O in the OH substituent gets priority 2 and the C in CH_3 gets priority 3. Lastly, H gets the lowest priority, 4, because it has the smallest atomic number.



Now take your molecular model and orientate it to match the molecule in question. Remember in the dash/wedge representation, two regular bonds are in the plane of the page. The wedge bond is coming toward you and the dashed bond is going away from you. If you were to hold a piece of paper directly in front of you, the substituents with the regular bond should both be touching the piece of paper. The dashed bond should be pointing behind the piece of paper and the wedge bond should be pointing in front.



In this structure, the bromine is going away from you, the hydrogen is coming toward you and the hydroxide and methyl groups are in the plane of the page.

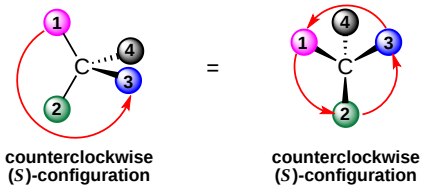
Then based on the position, assign each substituent on the chiral carbon a colored ball on your molecular model. In this case, bromine is going away so it is assigned the green ball. The hydrogen is coming toward you so it is assigned the blue ball. The last two substituents are in the plane of the page, however, the CH_3 is positioned higher so it is assigned the red ball which leaves OH being assigned the black ball.

Lastly, grab onto the ball for the lowest priority substitutent, in this case the blue one, and point the other three substituents towards you. The three bonds should be angled towards you as if they all have wedge bonds. Assign the original substituents and their corresponding CIP priorities to the three colored balls. The green ball was assigned to bromine which was given priority one. The OH was assigned to the black ball and given priority two. The CH_3 was assigned to the red ball and given priority three. In this case the priorities are going counter clockwise so the chiral carbon has an **(*S*)** configuration.

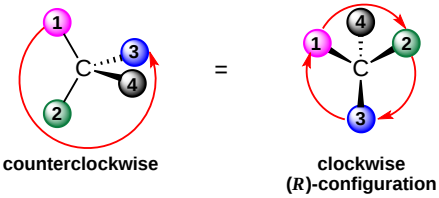
DETERMINING (*R*) OR (*S*) CONFIGURATION WITHOUT A MOLECULAR MODEL

If a molecular model cannot be used there are a couple of simple methods which can be applied if the dash/wedge bond system is being used.

After assigning CIP priorities, if the lowest priority substituent (4) is on the dash bond the configuration of substituents 1-3 can be assigned directly. As shown in the figure below, the configuration of substituents 1-3 does not change when moving to sight down the bond of substituent 4. In both cases, substituents 1-3 are ordered in a counterclockwise fashion which gives the chiral carbon an (*S*) configuration.

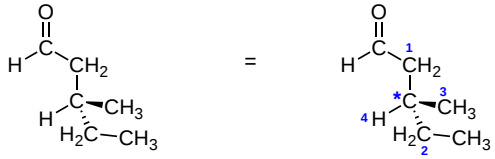


The opposite is true if the lowest priority substituent (4) is on the wedge bond. As shown in the figure below, the configuration of substituents 1-3 is inverted when moving to sight down the bond of substituent 4. When the lowest priority substituent is on the wedge bond, the configuration of substituents 1-3 can be assigned directly only if the direction is inverted. i.e. clockwise = (*S*) and counterclockwise = (*R*).

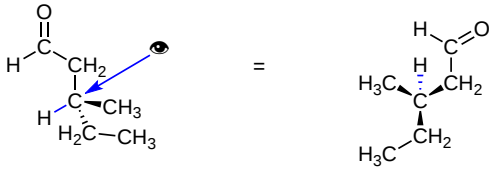


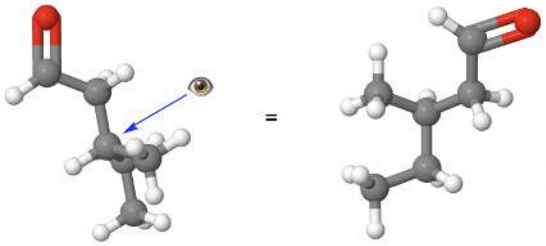
With the lowest priority group in front, drawing an arc from 1 to 2 to 3 gives the reverse of the configuration.

However, if the lowest priority substituent is on one of the regular bonds when the dash/wedge system is being used then configurations are best assigned by changing perspectives. This method can also be used if the three-dimensional configuration of the chiral carbon is represented. First, locate the chiral carbon and assign CIP priorities to its substituents. Then while perceiving the drawn molecule as a three-dimensional image, mentally change your perspective such that you are looking down the bond between the chiral carbon and the lowest CIP ranked substituent (#4). If done correctly, the bonds for substituents 1-3 should be coming towards you as wedge bonds. You can then follow the direction of the CIP priority numbers to determine the (*R*)/(*S*) configuration of the chiral carbon.



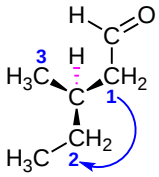
Locate the chiral carbon and assign CIP priorities to its substituents.





Mentally sight down the bond between the chiral carbon and the lowest CIP ranked substituent.

This bond is shown in magenta.



clockwise

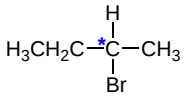
(*R*)-configuration

Follow the direction of the CIP priority numbers to determine the (*R*)/(*S*) configuration.

DRAWING THE STRUCTURE OF A CHIRAL MOLECULE FROM ITS NAME

Draw the structure of (*S*)-2-Bromobutane:

1) Draw the basic structure of the molecule and determine the location of the chiral carbon.



2) Determine the chiral carbon's substituents and assign them a CIP priority.

-H (Priority 4)

-CH_3 (Priority 3)

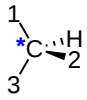
-CH_2CH_3 (Priority 2)

-Br (Priority 1)

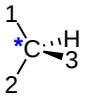
3) Draw the chiral carbon in a dash/wedge form and add the lowest priority substituent to the dash bond. In this case, the lowest priority substituent is -H.



4) Add the remaining substituents in a clockwise fashion for (*R*) and a counterclockwise fashion for (*S*).



clockwise
(*R*)-configuration

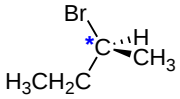


counterclockwise
(*S*)-configuration

The molecule posed in this question has an (*S*) configuration so the remaining substituents are added in a counterclockwise fashion.



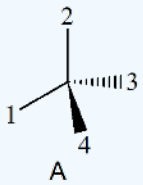
counterclockwise
(*S*)-configuration



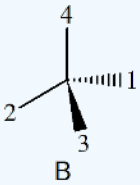
(*S*)-2-bromobutane

EXERCISE 5.5.1

1) Orient the following so that the least priority (4) atom is paced behind, then assign stereochemistry ((*R*) or (*S*)).



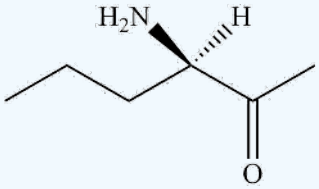
A



B

2) Draw (*R*)-2-bromobutan-2-ol.

3) Assign (*R*)/(*S*) to the following molecule.



4) Which in the following pairs would have a higher CIP priority?

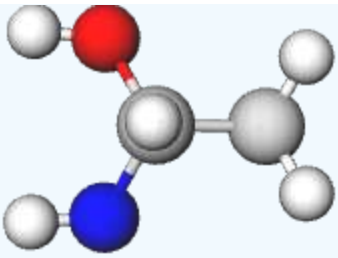
a. -H or -Cl
b. -Br or -I
c. $-CH_2OH$ or $-OCH_3$
d. $-CH_2CH_3$ or $-CH{=}CH_2$
e. $-NH_2$ or -OH

5) Rank the following substituents in order of their CIP priority:

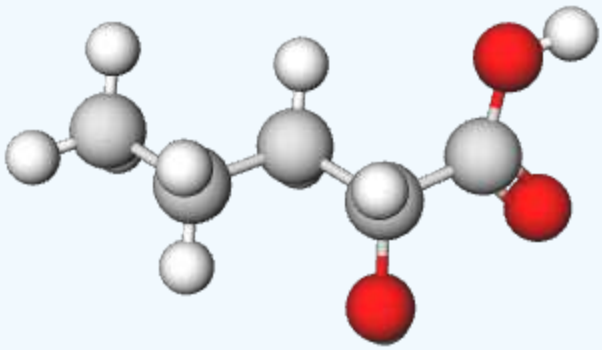
a. -H, $-OCH_3$, $-CH_2OH$, -OH
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. -CN, $-NH_2$, -CH=O, $-NHCH_3$
d. -SH, $-SCH_3$, -OH, $-OOCH_3$

6) Determine if the chiral carbon in the following molecules have an (*R*) or (*S*) configuration. Red = Oxygen & Blue = Nitrogen.

a)

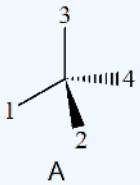


b)

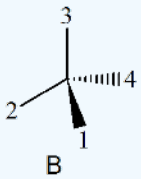


Answer

1) A is (*S*) and B is (*R*).

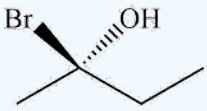


A



B

2)



3) The stereocenter is (*R*).

4)

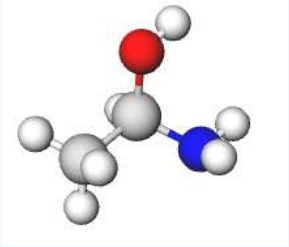
a. -Cl
b. -I
c. $-OCH_3$
d. $-CH=CH_2$
e. -OH

5) Rank the following substituents in order of their CIP priority:

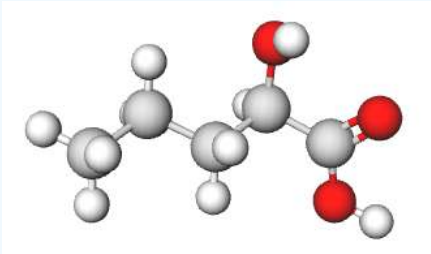
a. $-OCH_3$, -OH, $-CH_2OH$, -H,
b. -OH, $-CO_2H$, -CH=O, $-CH_2OH$
c. $-NHCH_3$, $-NH_2$, -CH=O, -CN
d. $-SCH_3$, -SH, $-OOCH_3$, -OH

6)

a) The chiral carbon is (*R*). The four substituents of the chiral carbon are -OH (1), $-NH_2$ (2), $-CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a clockwise fashion so the chiral carbon is (*R*).



b) The chiral carbon is (*S*). The four substituents of the chiral carbon are $-CO_2H$ (1), -OH (2), $-CH_2CH_2CH_3$ (3), and -H (4). Then looking down the lowest priority bond, you should roughly see what appears in the picture below. The substituents with priorities 1-3 are ordered in a counterclockwise fashion so the chiral carbon is (*S*).



? EXERCISE 5.5.2

Identify which substituent in the following sets has a higher ranking.

a. -H or $-CH_3$
b. $-CH_2CH_2CH_3$ or CH_2CH_3
c. $-CH_2Cl$ or CH_2OH

Answer

a. **$-CH_3$**
b. **$-CH_2CH_2CH_3$**
c. **$-CH_2Cl$**

EXERCISE 5.5.3

Identify which substituent in the following sets has a higher ranking.

a. $-NH_2$ or -N=NH
b. $-CH_2CH_2OH$ or $-CH_2OH$
c. $-CH=CH_2$ or $-CH_2CH_3$

Answer

a) **-N=NH**

b) **$-CH_2OH$**

c) **$-CH=CH_2$**

EXERCISE 5.5.4

Place the following sets of substituents in each group in order of lowest priority (1st) to highest priority (4th)

a. $-NH_2$, -F, -Br, $-CH_3$
b. -SH, $-NH_2$, -F, -H

Answer

a) $-CH_3$ < $-NH_2$ < -F, < -Br

b) -H < $-NH_2$ < -F, < -SH

EXERCISE 5.5.5

Place the following sets of substituents in each group in order of lowest priority (1st) to highest priority (4th)

a. $-CH_2CH_3$, -CN, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$
b. $-CH_2NH_2$, $-CH_2SH$, $-C(CH_3)_3$, -CN

Answer

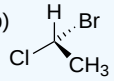
a) $-CH_2CH_3$ < $-CH_2CH_2OH$ < $-CH_2CH_2CH_2OH$, < -CN

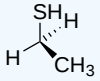
b) $-C(CH_3)_3$ < $-CH_2NH_2$ < -CN < $-CH_2SH$

EXERCISE 5.5.6

Assign the following chiral centers as (*R*) or (*S*).

a) 

b) 

c) 

Answer

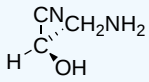
a) **(*S*)**: I > Br > F > H. The lowest priority substituent is going backwards so following the highest priority, it goes left (counterclockwise).

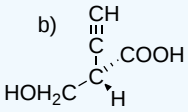
b) **(*R*)**: Br > Cl > CH_3 > H. Using a model kit, you need to rotate the H to the back position where the Br is. This causes the priority to go to the left (clockwise) when looking at it with the H in the back position. Alternatively, if you do not have a model kit, you can imagine the structure 3-dimensionally and since the lowest priority (H) is facing up (as drawn), if you look at it from below, starting with Br (1st priority) and moving towards Cl (2nd priority), you are moving right (clockwise) which represents (*R*) stereochemistry.

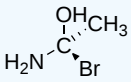
c) **Neither (*R*) or (*S*)**: Since there are two identical substituents (H's) the molecule is achiral and cannot be assigned (*R*) or (*S*).

EXERCISE 5.5.7

Assign the following chiral centers as (*R*) or (*S*).

a) 

b) 

c) 

Answer

a) **(*R*)**: OH > CN (C triple bonded to N) > CH_2NH_2 > H. The H needs to be moved to the back position which causes the priority to go to the right (clockwise) which indicates (*R*).

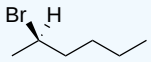
b) **(*S*)**: COOH > CH_2OH > C CH > H. Since the H is coming forward, you can assign the priority and it goes to the right (clockwise which would be (*R*)) but since the lowest priority is forward, you have to switch it to (*S*). Alternatively, you can rotate the molecule to put the lowest priority to the back and you'll see that it rotates left (or counterclockwise) for (*S*).

c) **(*S*)**: Br > OH > NH_2 > CH_3. Since the lowest priority is going back, you can follow the priority and see that it is going left (counterclockwise) and therefore (*S*).

EXERCISE 5.5.8

Draw the structure of (*R*)-2-bromohexane.

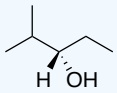
Answer



EXERCISE 5.5.9

Draw the structure of (*S*)-2-methyl-3-pentanol.

Answer



REFERENCES

1. Schore and Vollhardt. *Organic Chemistry Structure and Function.* New York:W.H. Freeman and Company, 2007.
2. McMurry, John and Simanek, Eric. *Fundamentals of Organic Chemistry*. 6th Ed. Brooks Cole, 2006.

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5.6: DIASTEREOMERS

OBJECTIVES

After completing this section, you should be able to

1. calculate the maximum number of stereoisomers possible for a compound containing a specified number of chiral carbon atoms.
2. draw wedge-and-broken-line structures for all possible stereoisomers of a compound containing two chiral carbon atoms, with or without the aid of molecular models.
3. assign (*R*)/(*S*) configurations to wedge-and-broken-line structures containing two chiral carbon atoms, with or without the aid of molecular models.
4. determine, with or without the aid of molecular models, whether two wedge-and-broken-line structures containing two chiral carbon atoms are identical, represent a pair of enantiomers, or represent a pair of diastereomers.
5. draw the wedge-and-broken-line structure of a specific stereoisomer of a compound containing two chiral carbon atoms, given its IUPAC name and (*R*)/(*S*) configuration.

KEY TERMS

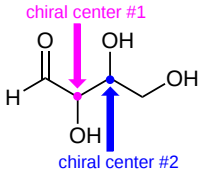
Make certain that you can define, and use in context, the key term below.

- diastereomer

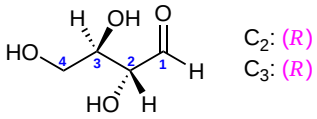
Diastereomers are two molecules which are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers. Unlike enantiomers which **are mirror images** of each other and **non-superimposable**, diastereomers are **not mirror images** of each other and **non-superimposable**. Diastereomers can have different physical properties and reactivity. They have different melting points and boiling points and different densities. In order for diastereomer stereoisomers to occur, a compound must have **two or more** stereocenters.

INTRODUCTION

So far, we have been analyzing compounds with a single chiral center. Next, we turn our attention to those which have multiple chiral centers. We'll start with some stereoisomeric four-carbon sugars with two chiral centers.



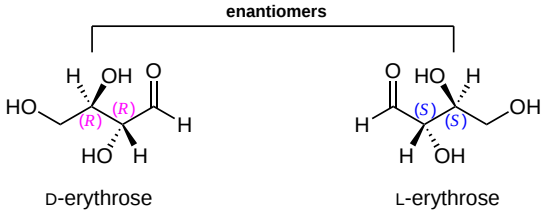
We will start with a common four-carbon sugar called D-erythrose.



D-erythrose

A note on sugar nomenclature: biochemists use a special system to refer to the stereochemistry of sugar molecules, employing names of historical origin in addition to the designators '*D*' and '*L*'. You will learn about this system if you take a biochemistry class. We will use the *D/L* designations here to refer to different sugars, but we won't worry about learning the system.

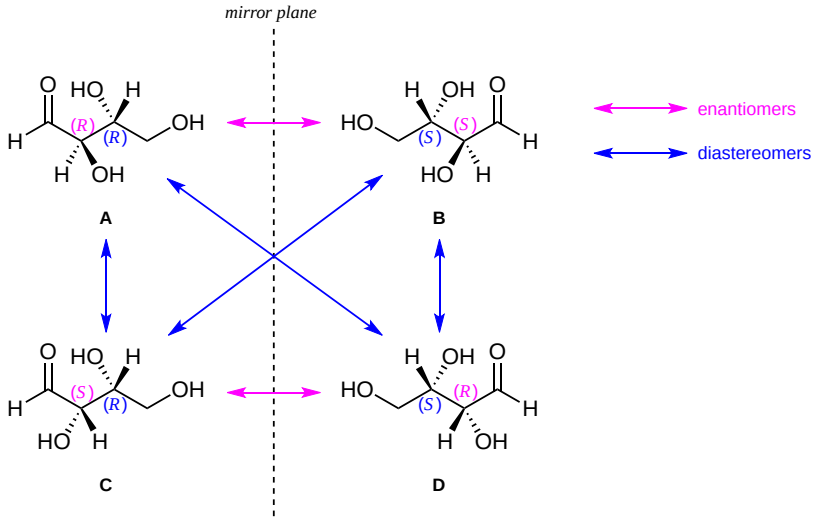
As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the (*R*) configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose have an enantiomer? Of course it does – if it is a chiral molecule, it must. The enantiomer of erythrose is its mirror image, and is named L-erythrose (once again, you should use models to convince yourself that these mirror images of erythrose are not superimposable).



Notice that both chiral centers in L-erythrose both have the (*S*) configuration. To avoid confusion, we will simply refer to the different stereoisomers by capital letters.

Now let's consider all the possible stereoisomers.

Look first at compound A below. Both chiral centers in have the (*R*) configuration (you should confirm this for yourself!). The mirror image of Compound A is compound B, which has the (*S*) configuration at both chiral centers. If we were to pick up compound A, flip it over and put it next to compound B, we would see that they are *not* superimposable (again, confirm this for yourself with your models!). A and B are nonsuperimposable mirror images: in other words, enantiomers.



Now, look at compound C, in which the configuration is (*S*) at chiral center 1 and (*R*) at chiral center 2. Compounds A and C are stereoisomers: they have the same molecular formula and the same bond connectivity, but a different arrangement of atoms in space (recall that this is the definition of the term 'stereoisomer). However, they are *not* mirror images of each other (confirm this with your models!), and so they are *not* enantiomers. By definition, they are **diastereomers** of each other.

Notice that compounds C and B also have a diastereomeric relationship, by the same definition.

So, compounds A and B are a pair of enantiomers, and compound C is a diastereomer of both of them. Does compound C have its own enantiomer? Compound D is the mirror image of compound C, and the two are not superimposable. Therefore, C and D are a pair of enantiomers. Compound D is also a diastereomer of compounds A and B.

This can also seem very confusing at first, but there some simple shortcuts to analyzing stereoisomers:

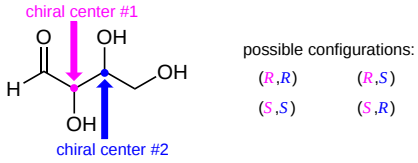
STEREOISOMER SHORTCUTS

If ***all*** of the chiral centers are of opposite (*R*)/(*S*) configuration between two stereoisomers, they are enantiomers.

If ***at least one, but not all*** of the chiral centers are opposite between two stereoisomers, they are diastereomers.

> These shortcuts to not take into account the possibility of additional stereoisomers due to alkene groups: we will come to that later

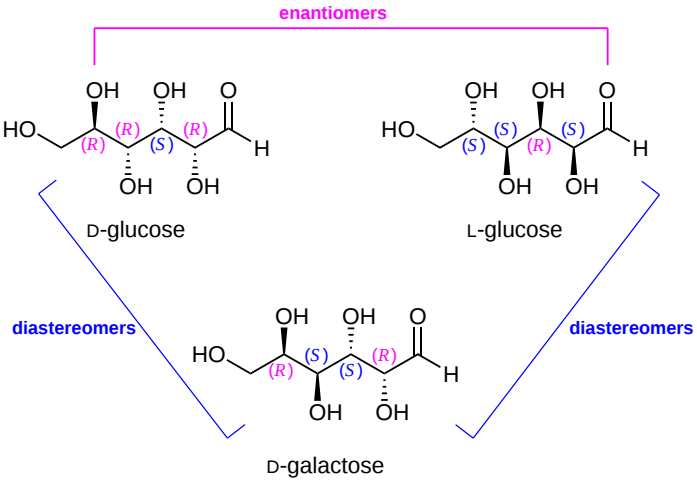
Here's another way of looking at the four stereoisomers, where one chiral center is associated with red and the other blue. Pairs of enantiomers are stacked together.



We know, using the shortcut above, that the enantiomer of (*R*,*R*) must be (*S*,*S*) - both chiral centers are different. We also know that (*R*,*S*) and (*S*,*R*) are diastereomers of (*R*,*R*), because in each case one - but not both - chiral centers are different.

DETERMINING THE MAXIMUM NUMBER OF STEREOISOMERS FOR A COMPOUND

In general, a structure with *n* stereocenters will have a maximum of 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can exist in either an open-chain or a cyclic form). There are two enantiomers of glucose, called D-glucose and L-glucose. The D-enantiomer is the common sugar that our bodies use for energy. It has $n = 4$ stereocenters, so therefore there are $2^n = 2^4 = 16$ possible stereoisomers (including D-glucose itself).

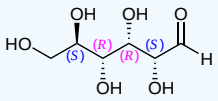


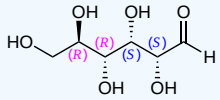
In L-glucose, all of the stereocenters are inverted relative to *D*-glucose. That leaves 14 diastereomers of D-glucose: these are molecules in which at least one, but not all, of the stereocenters are inverted relative to D-glucose. One of these 14 diastereomers, a sugar called *D*-galactose, is shown above: in D-galactose, one of four stereocenters is inverted relative to D-glucose. Diastereomers which differ in only one stereocenter (out of two or more) are called **epimers**. D-glucose and D-galactose can therefore be refered to as epimers as well as diastereomers.

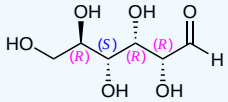
✔ EXAMPLE 5.6.1

- Draw the structure of L-galactose, the enantiomer of D-galactose.
- Draw the structure of two more diastereomers of D-glucose. One should be an epimer.

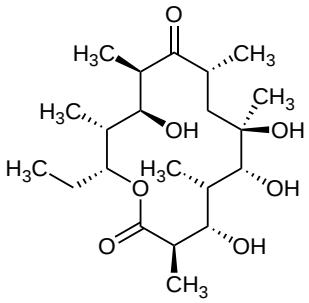
Answer


L-galactose


L-mannose
(epimer of D-glucose)


L-gulose
(diasteromer of D-glucose)

Erythronolide B, a precursor to the 'macrocyclic' antibiotic erythromycin, has 10 stereocenters. It's enantiomer is that molecule in which all 10 stereocenters are inverted.



erythronolide B

In total, there are 2^{10} = 1024 stereoisomers in the erythronolide B family: 1022 of these are diastereomers of the structure above, one is the enantiomer of the structure above, and the last ***is*** the structure above.

We know that enantiomers have identical physical properties and equal but opposite degrees of specific rotation. Diastereomers, in theory at least, have different physical properties – we stipulate 'in theory' because sometimes the physical properties of two or more diastereomers are so similar that it is very difficult to separate them. In addition, the specific rotations of diastereomers are unrelated – they could be the same sign or opposite signs, and similar in magnitude or very dissimilar.

? EXERCISE 5.6.1

Determine the number of stereoisomers a molecule can have with…

a. 3 chiral centers
b. 1 chiral center
c. 6 chiral centers

Answer

Since a molecule with n chiral centers can have 2^n stereoisomers…

a. 2^3 = 8 possible stereoisomers
b. 2^1 = 2 possible stereoisomers
c. 2^6 = 64 possible stereoisomers

? EXERCISE 5.6.2*a*

What is the relationship between enantiomers?

Answer

They are mirror images of each other and when 2 or more chiral centers are present, every stereocenter is the opposite in its enantiomer.

? EXERCISE 5.6.2*b*

How does the stereochemistry in diastereomers differ from each other?

Answer

In diastereomers, one or more of the chiral centers is the opposite but they all can't be the opposite or else they'd be enantiomers.

EXERCISE 5.6.2c

What are epimers?

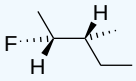
Answer

Epimers are when **only one** chiral center is the opposite (in molecules with 2 or more chiral centers) in its diastereomer.

EXERCISE 5.6.3a

Draw the structure of (2R,3R) 2-fluoro-3-methylhexane.

Answer

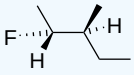


2R,3R

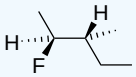
EXERCISE 5.6.3b

Draw both diastereomers of (2R,3R) 2-fluoro-3-methylhexane.

Answer



2R,3S

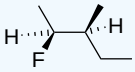


2S,3R

EXERCISE 5.6.3c

Draw the enantiomer of (2R,3R) 2-fluoro-3-methylhexane.

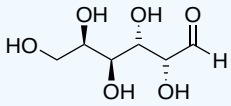
Answer



2S,3S

EXERCISE 5.6.4a

Draw the structure of L-galactose, the enantiomer of D-galactose.

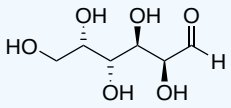


S, R, R, S

D-galactose

Answer

https://chem.libretexts.org/@go/page/31425



S, *R*, *R*, *S*

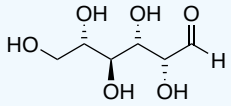
L-galactose

EXERCISE 5.6.4*b*

Draw a diastereomer of D-galactose that is an epimer.

Answer

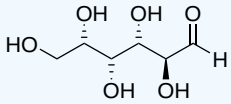
You can draw an epimer by drawing D-galactose with 1 (and only 1) of its chiral centers reversed. Here's an example when you switch only the first chiral center (in red). (There are 3 other epimers that could be drawn as long as you only swap a single chiral center in the diastereomer that you use.)



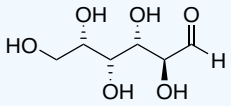
R, *R*, *R*, *S*

EXERCISE 5.6.4*c*

Identify if the following diastereomer of galactose is an epimer of D- galactose or L- galactose.



Answer

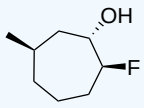


S, *R*, *S*, *S*

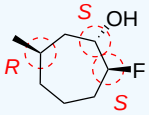
Since the diastereomer above only varies from L-galactose by 1 chiral center, the above is an epimer in relationship to L-galactose. Since it varies from D-galactose by 3 chiral centers, it is not an epimer but a diastereomer. Since not all of the chiral centers are swapped, it is not an enantiomer!

EXERCISE 5.6.5*a*

For the compound shown below, label each chiral center as R or S.



Answer



https://chem.libretexts.org/@go/page/31425

EXERCISE 5.6.5b

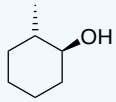
How many stereoisomers are possible for the compound in part a)?

Answer

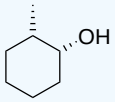
Since there are 3 chiral centers, $2^3 = 8$ possible stereoisomers.

EXERCISE 5.6.6

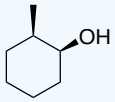
Consider the stereoisomers below.



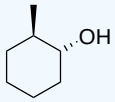
i



ii



iii



iv

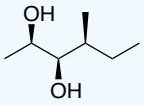
a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of ii?
c. Which is/are an epimer of i?

Answer

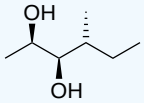
a. iv is an enantiomer of i since both chiral centers are switched and they are non superimposable mirror images.
b. i & iv are diastereomers of ii since they are stereoisomers that are not mirror images.
c. ii and iii are epimers of i since they are diastereomers with only 1 chiral center switched and the other one the same.

EXERCISE 5.6.7

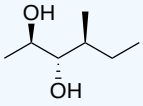
Consider the 8 stereoisomers below.



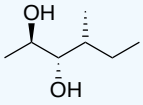
i



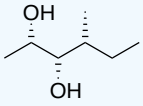
ii



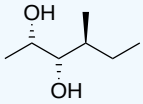
iii



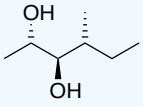
iv



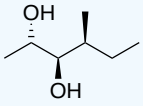
v



vi



vii



viii

a. Which is/are an enantiomer of i?
b. Which is/are a diastereomer of i?
c. Which is/are an epimer of i?

Answer

a. v is an enantiomer since all three chiral centers are switched and they are non superimposable mirror images.
b. ii, iii, iv, vi, vii & viii are diastereomers of i since they are stereoisomers that are not mirror images.
c. ii,iii & viii are epimers of i since they are diastereomers with only 1 chiral center switched and the other chiral centers the same.

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5.7: MESO COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. determine whether or not a compound containing two chiral carbon atoms will have a meso form, given its Kekulé, condensed or shorthand structure, or its IUPAC name.
2. draw wedge-and-broken-line structures for the enantiomers and meso form of a compound such as tartaric acid, given its IUPAC name, or its Kekulé, condensed or shorthand structure.
3. make a general comparison of the physical properties of the enantiomers, meso form and racemic mixture of a compound such as tartaric acid.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- meso compound

STUDY NOTES

You may be confused by the two sets of structures showing “rotations.” Of course in each case the two structures shown are identical, they represent the same molecule looked at from two different perspectives. In the first case, there is a 120° rotation around the single carbon-carbon bond. In the second, the whole molecule is rotated 180° top to bottom.

INTRODUCTION

A meso compound is an achiral compound that has chiral centers. A meso compound contains an internal plane of symmetry which makes it superimposable on its mirror image and is optically **inactive** although it contains two or more stereocenters. Remember, an internal plane of symmetry was shown to make a molecule achiral in **Section 5.2**.

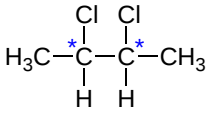
In general, a meso compound should contain two or more identical substituted stereocenters. Also, it has an internal symmetry plane that divides the compound in half. These two halves reflect each other by the internal mirror. The stereochemistry of reflected stereocenters should "cancel out". What it means here is that when we have an internal plane that splits the compound into two symmetrical sides, the stereochemistry of both left and right side should be opposite to each other, and therefore, resulting the molecule being **optically inactive**.

IDENTIFICATION

A meso compound must have:

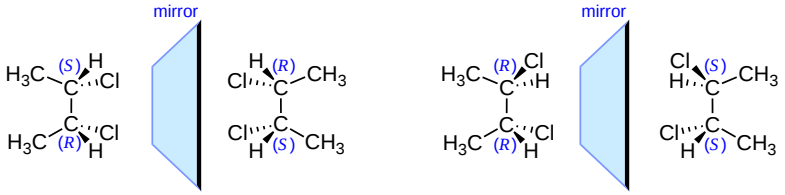
1. Two or more stereocenters.
2. An internal plane of symmetry, or internal mirror, that lies in the compound.
3. Stereochemistry that cancels out. This means reflected stereocenter should have the same substituents and be inverted. For instance, in a meso compound with two stereocenters one should be R and the other S.

The compounds 2,3-dichlorobutane contains two chiral carbons and therefore would be expected to provide $2^2 = 4$ different stereoisomers. These stereoisomers should be made up of two pairs of enantiomers.



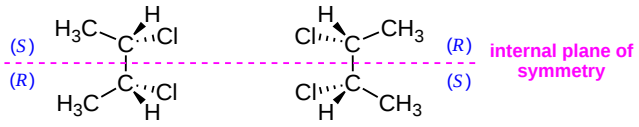
2,3-dichlorobutane

After drawing out all the possible stereoisomers of 2,3-dichlorobutane, the pair on the right in the figure below are mirror images. Also, they are non-superimposable because they have distinctly different conformation (R,R & S,S). This makes the pair enantiomers of each other. However, the pair on the left represent a meso compound, they both are identical despite being mirror images.



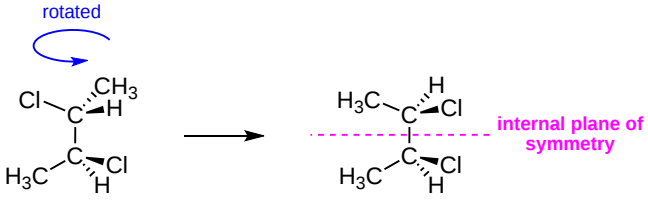
identical (meso) **enantiomers**

Upon further investigation, the meso compound has an internal plane of symmetry which is not present in the pair of enantiomers. The plane of symmetry in the meso compound comes about because there are two chiral carbons present, both chiral carbons are identically substituted (Cl, H, CH_3), and one chiral carbon is R and the other is S. Despite being represented as mirror images, both structures represent the same compound. This is best proven by making molecular models of both representations and then superimposing them. Overall, 2,3-dichlorobutane only has three possible stereosiomers, the pair of enantiomers and the meso compound.



identical (meso)

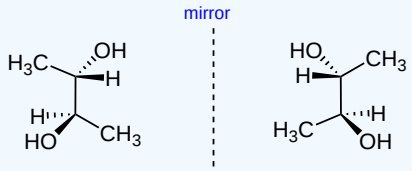
When looking for an internal plane of symmetry, it is important to remember that sigma bonds (single bonds) can rotate. Just because the immediate representation of a molecule does not have a plane of symmetry does not mean that one cannot be obtained through rotation. Often the substituents attached to a stereocenter need to be rotated to recognize the internal plane of symmetry. As the stereocenter is rotated, its configuration does not change. Building a molecular model when considering a possible meso compound is an invaluable tool because it allows for easy rotation of chiral carbons. An example of how rotation of a chiral carbon can reveal an internal plane of symmetry is shown below.



meso compound

EXAMPLE 5.7.1

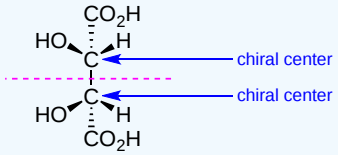
Below are the two mirror images of (meso)-2,3-Butanediol. Because it is a meso compound, the two structures are identical. Show that both mirror images can be obtained by simply rotating the three-dimensional structure provided below.



(meso)-2,3-butanediol

GLmol

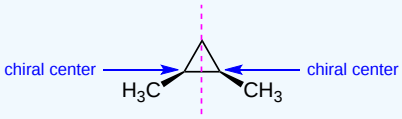
EXAMPLE 5.7.2



1

1 has a plane of symmetry (the horizontal plane going through the red broken line) and, therefore, is achiral; 1 has chiral centers. Thus, 1 is a meso compound.

EXAMPLE 5.7.3

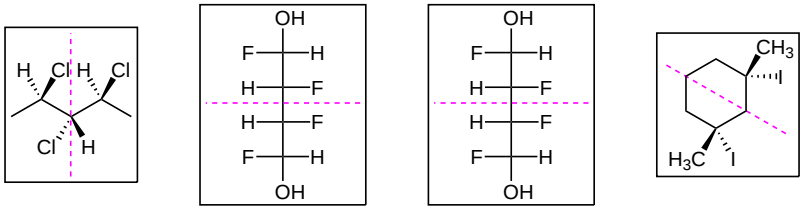


2

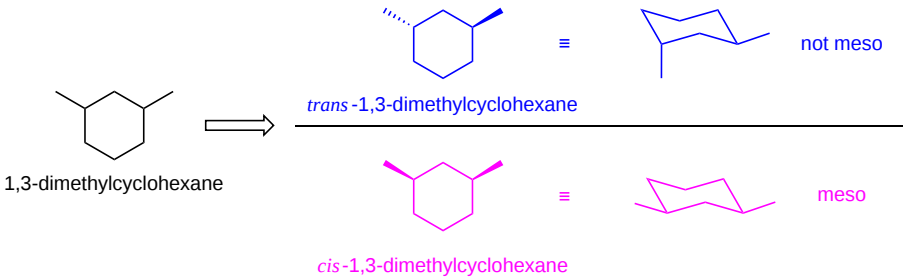
This molecules has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has has two chiral centers. Thus, its is a meso compound.

OTHER EXAMPLES OF MESO COMPOUNDS

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cycloalkanes. Although two chiral carbons must be present, meso compounds can have many more. Notice that in every case a plane of symmetry is present.

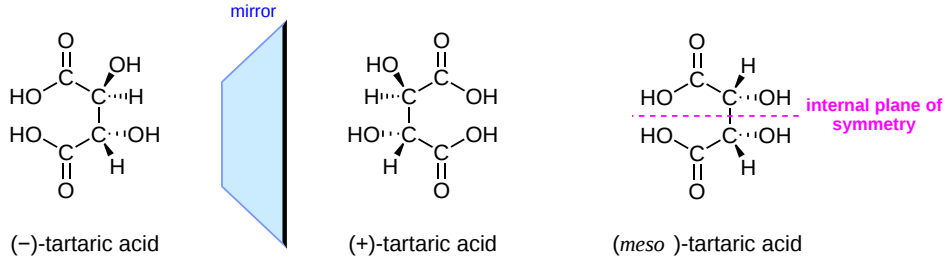


In general, a disubstituted cycloalkane is meso if the two substituents are the same and they are in a *cis* conformation. *Trans* disubstituted cycloalkanes are not meso regardless if the two substituents are the same.



OPTICAL ACTIVITY ANALYSIS OF A MESO COMPOUND

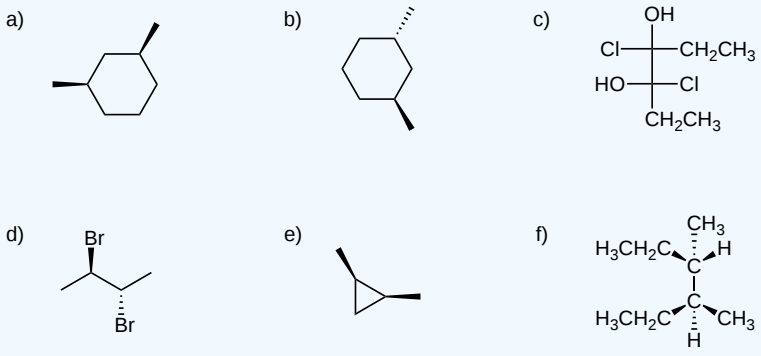
When the optical activity of a meso compound is attempted to be determined with a polarimeter, the indicator will not show (+) or (-). It simply means there is no certain direction of rotation of the polarized light, neither levorotatory (-) and dexorotatory (+) because a meso compound is achiral (optically inactive). Investigations of isomeric tartaric acid (2,3-dihydroxybutanedioic acid), carried out by Louis Pasteur in the mid 19th century, were instrumental in elucidating some of the subtleties of stereochemistry. Tartaric acid, has two chiral but only three stereoisomers. Two of these stereoisomers are enantiomers and the third is an achiral a **meso** compound. Some physical properties of these stereoisomers of tartaric acid are given in the table below. Notice that the enantiomers have the same amount of optical rotation but in different directons. Meso-tartaric acid produces no optical rotation because it is achiral and not optically active. Meso-tartaric acid is actually a diastereomer of both (-) and (+)-tartaric acid, which gives it a distinctly different melting point.



(+)-tartaric acid:	$[\alpha]_D = +13^o$	m.p. 172 ºC
(–)-tartaric acid:	$[\alpha]_D = -13^o$	m.p. 172 ºC
meso-tartaric acid:	$[\alpha]_D = 0^o$	m.p. 140 ºC

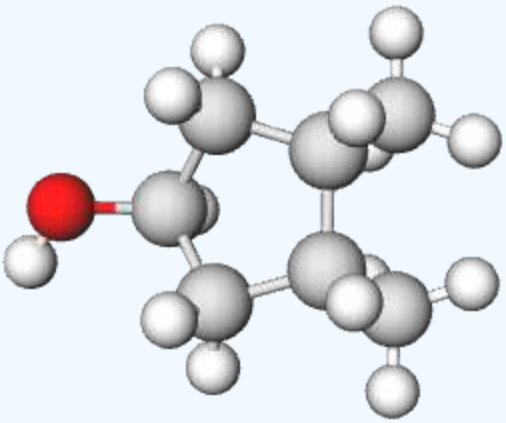
? EXERCISE 5.7.1

1) Determine which of the following molecules are meso.



2) Explain why 2,3-dibromobutane has the possibility of being a meso compound while 2,3-dibromopentane does not.

3) Observe the following compound and determine if it is a meso compound. If so indicate the plane of symmetry. Red = oxygen. Remember sigma bonds are able to rotate.

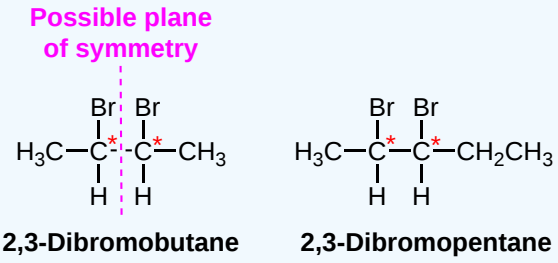


GLmol

Answer

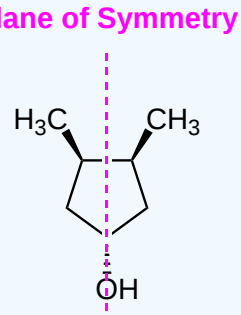
1) A C, D, E are meso compounds.

2) One of the requirements of a meso compound is that the reflected chiral carbons have the same substituents. The compound 2,3-dibromobutane, fulfills this requirement (Br, H, CH_3) and can possibly be a meso compound if the two chiral carbons have the appropriate configuration (R & S). The substituents of the two chiral carbons in 2,3-dibromopentane do not have the same substituents (Br, H, CH_3 vs. Br, H, CH_2CH_3). This 2,3-dibromopentane cannot form a meso compound regardless of the configurations of its chiral carbons.



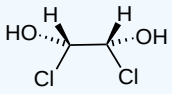
2,3-Dibromobutane **2,3-Dibromopentane**

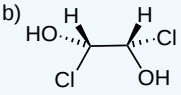
3) The compound is meso.

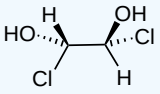


EXERCISE 5.7.1

Which of the following are meso compounds?

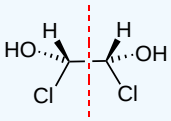
a) 

b) 

c) 

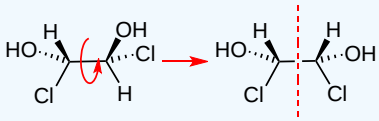
Answer

a) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) between the C's (and it has stereochemistry of *S* & *R*).



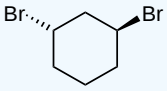
b) This is not a meso compound. No matter how you rotate the C-C bond, you do not see a plane of symmetry (and its stereochemistry is *S* & *S*)

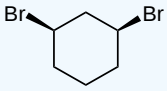
c) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) that can be seen when you rotate the C-C bond (and it has stereochemistry of *S* & *R*).

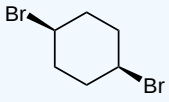


EXERCISE 5.7.2

Which of the following are meso compounds?

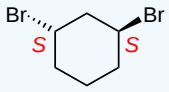
a) 

b) 

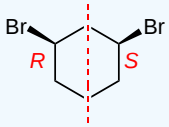
c) 

Answer

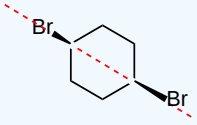
a) This is not a meso compound. There is no plane of symmetry and has stereochemistry of *S* & *S*.



b) This is a meso compound. There is an internal plane of symmetry (dashed line shown in red) and it has stereochemistry of *R* & *S*.



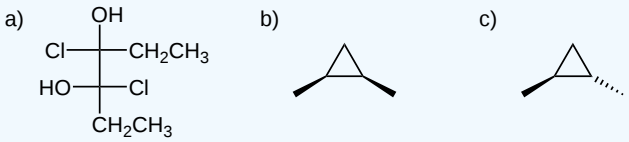
c) This is not a meso compound (even though it has planes of symmetry). The plane of symmetry shown in red makes it so that both chiral centers have symmetrical groups (the ring) and thus the compound is not chiral (so it can't be a meso compound).



EXERCISE 5.7.3

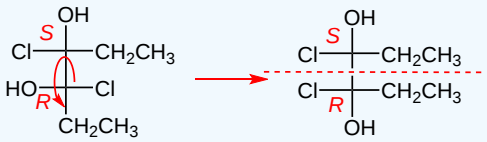
Which of the following are meso compounds?

https://chem.libretexts.org/@go/page/31426

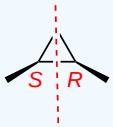


Answer

a) This is a meso compound. If you rotate between the C-C bond, you can see that it has a mirror plane between the C's (shown in red on the structure to the right). Notice how rotating a C-C bond doesn't change the stereochemistry of the molecule (*S* & *R*).



b) This is a meso compound. You can see the plane of symmetry in red and the compound has stereochemistry of *S* & *R*.



c) This is not a meso compound. There is no plane of symmetry and it has stereochemistry of *S* & *S*.

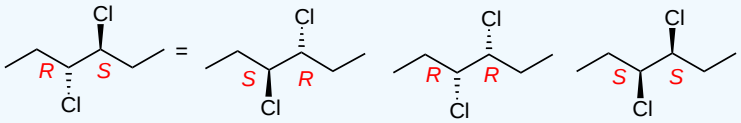


? EXERCISE 5.7.4

Determine (and draw) if any of the forms of 3,4-dichlorohexane are a meso compound.

Answer

Looking at the 4 different possibilities below, i & ii are equivalent structures (with R & S stereochemistry) so it is a meso compound. iii & iv are not meso compounds but are enantiomers to each other.



i ii iii iv

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5.8: RACEMIC MIXTURES AND THE RESOLUTION OF ENANTIOMERS

OBJECTIVES

After completing this section, you should be able to

1. describe a common process for separating a mixture of enantiomers.
2. explain why racemic mixtures do not rotate plane-polarized light.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- racemic mixture (or racemate)
- resolve

STUDY NOTES

A *racemic mixture* is a 50:50 mixture of two enantiomers. Because they are mirror images, each enantiomer rotates plane-polarized light in an equal but opposite direction and is optically inactive. If the enantiomers are separated, the mixture is said to have been *resolved*. A common experiment in the laboratory component of introductory organic chemistry involves the resolution of a racemic mixture.

The dramatic biochemical consequences of chirality are illustrated by the use, in the 1950s, of the drug Thalidomide, a sedative given to pregnant women to relieve morning sickness. It was later realized that while the (+)-form of the molecule, was a safe and effective sedative, the (−)-form was an active teratogen. The drug caused numerous birth abnormalities when taken in the early stages of pregnancy because it contained a mixture of the two forms.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called resolution. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. For example, if a racemic mixture of a chiral alcohol is reacted with a enantiomerically pure carboxylic acid, the result is a mixture of diastereomers: in this case, because the pure (R) entantiomer of the acid was used, the product is a mixture of (R-R) and (R-S) diastereomeric esters, which can, in theory, be separated by their different physical properties. Subsequent hydrolysis of each separated ester will yield the 'resolved' (enantiomerically pure) alcohols. The used in this technique are known as 'Moscher's esters', after Harry Stone Moscher, a chemist who pioneered the method at Stanford University.

As noted earlier, chiral compounds synthesized from achiral starting materials and reagents are generally racemic (i.e. a 50:50 mixture of enantiomers). Separation of racemates into their component enantiomers is a process called **resolution**. Since enantiomers have identical physical properties, such as solubility and melting point, resolution is extremely difficult. Diastereomers, on the other hand, have different physical properties, and this fact is used to achieve resolution of racemates. Reaction of a racemate with an enantiomerically pure chiral reagent gives a mixture of diastereomers, which can be separated. Reversing the first reaction then leads to the separated enantiomers plus the recovered reagent.

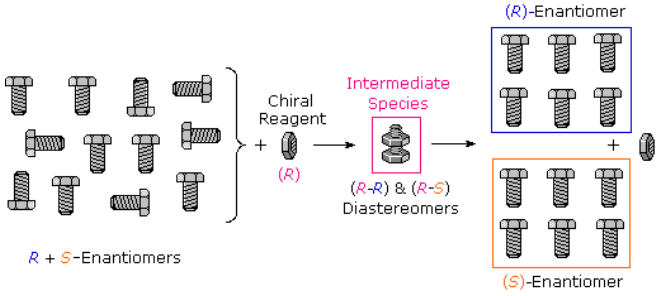


Figure 5.8.1:

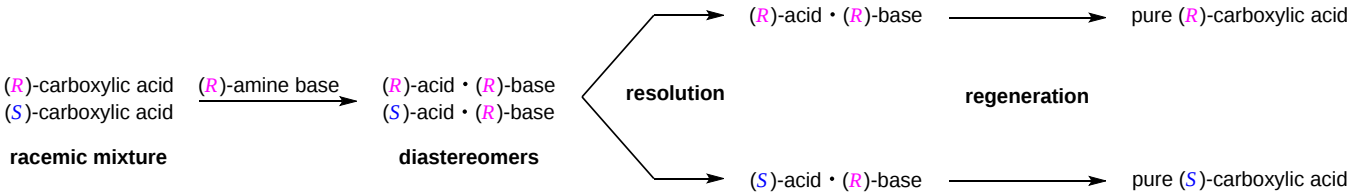
Many kinds of chemical and physical reactions, including salt formation, may be used to achieve the diastereomeric intermediates needed for separation. Figure 5.8.1 illustrates this general principle by showing how a nut having a right-handed thread (R) could serve as a

"reagent" to discriminate and separate a mixture of right- and left-handed bolts of identical size and weight. Only the two right-handed partners can interact to give a fully-threaded intermediate, so separation is fairly simple. The resolving moiety, i.e. the nut, is then removed, leaving the bolts separated into their right and left-handed forms. Chemical reactions of enantiomers are normally not so dramatically different, but a practical distinction is nevertheless possible.

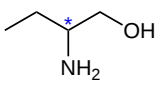
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution of enantiomers are based upon this fact. We include here a discussion of the primary methods of resolution.

CHIRAL AMINES AS RESOLVING AGENTS AND RESOLUTION OF RACEMIC ACIDS

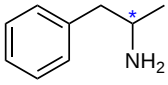
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or (*R*)/(*S*) mixture of enantiomers of a carboxylic acid and convert this to a salt with a chiral amine base having the (*R*) configuration, the salt will be a mixture of two diastereomers, ((*R*)-acid • (*R*)-base) and ((*S*)-acid • (*R*)-base). These diastereomeric salts are *not* identical and they are not mirror images. Therefore they will differ to some degree in their physical properties, and a separation by physical methods, such as crystallization, may be possible. If the diastereomeric salts can be completely separated, the carboxylic acid regenerated from each salt will be either exclusively the (*R*) or the (*S*) enantiomer.



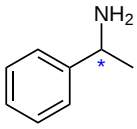
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino-1-butanol, amphetamine, and 1-phenylethanamine, also can be used, but first they must be resolved themselves.



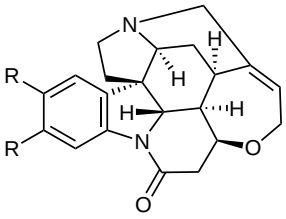
2-amino-1-butanol



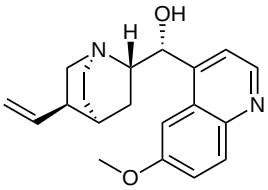
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



R = H,strychnine
R = OCH_3, brucine



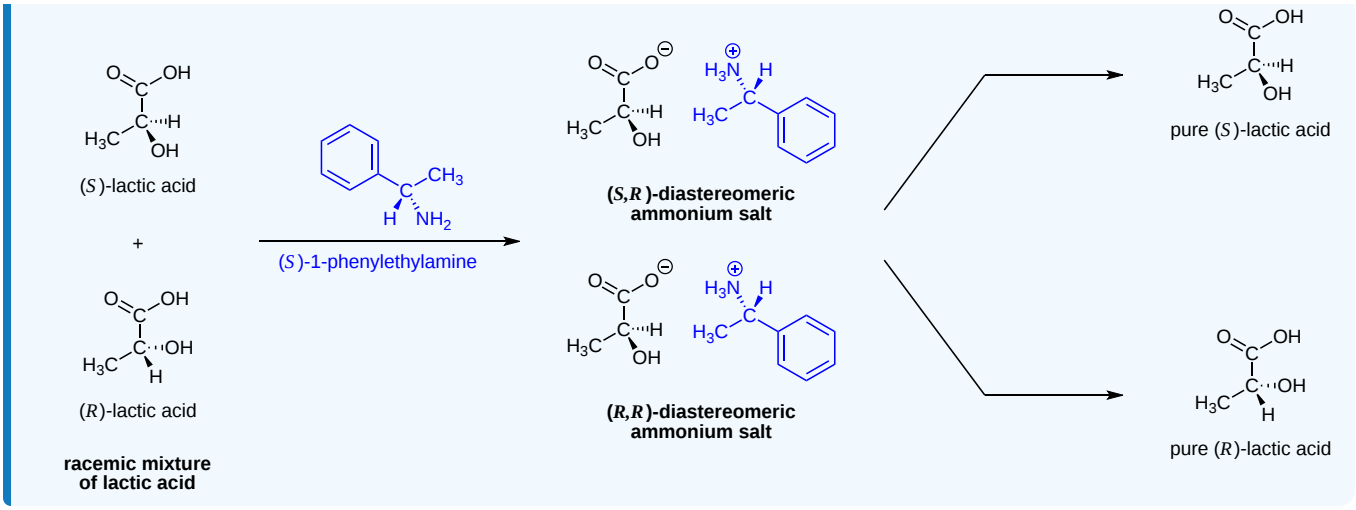
quinine
(antimicrobial)
(antimalarial)

? WORKED EXAMPLE 5.8.1

Show how (*S*)-1-phenylethylamine can be used to resolve a racemic mixture of lactic acid. Please draw all the structures involved.

Answer

https://chem.libretexts.org/@go/page/31427



RESOLUTION OF RACEMIC BASES

Chiral acids, such as (+)-tartaric acid, (-)-malic acid, (-)-mandelic acid, and (+)-camphor- 10-sulfonic acid, are used for the resolution of a racemic base.

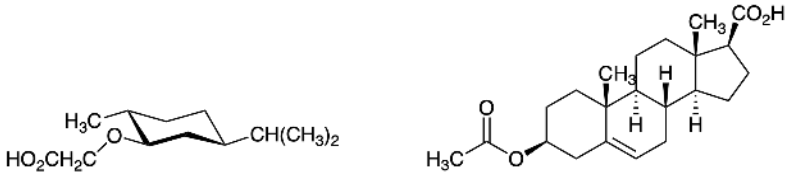


tartaric acid (2,3-dihydroxy-butanedioic acid) | malic acid (2-hydroxybutane-dioic acid) | mandelic acid (2-hydroxy-2-phenylethanoic acid) | camphor-10-sulfonic acid

The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind can be tedious, because numerous recrystallizations in different solvents may be necessary to progressively enrich the crystals in the less-soluble diastereomer. To determine when the resolution is complete, the mixture of diastereomers is recrystallized until there is no further change in the measured optical rotation of the crystals. At this stage it is hoped that the crystalline salt is a pure diastereomer from which one pure enantiomer can be recovered. The optical rotation of this enantiomer will be a maximum value if it is "optically" pure because any amount of the other enantiomer could only reduce the magnitude of the measured rotation α.

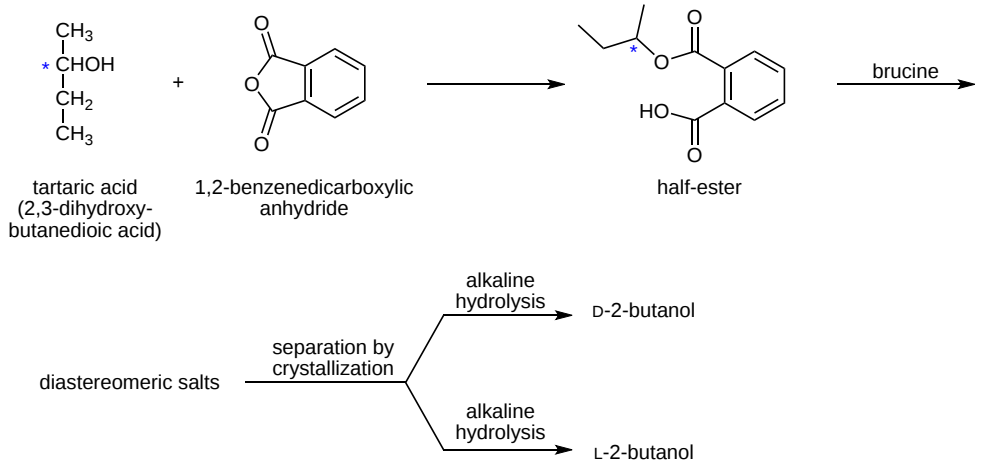
RESOLUTION OF RACEMIC ALCOHOLS

To resolve a racemic alcohol, a chiral acid can be used to convert the alcohol to a mixture of diastereomeric esters. This is not as generally useful as might be thought because esters tend to be liquids unless they are very high-molecularweight compounds. If the diastereomeric esters are not crystalline, they must be separated by some other method than fractional crystallization (for instance, by chromatography methods, Section 9-2). Two chiral acids that are useful resolving agents for alcohols are:



menthoxyethanoic acid | 3-β-acetoxy-Δ^5-etienic acid

The most common method of resolving an alcohol is to convert it to a half-ester of a dicarboxylic acid, such as butanedioic (succinic) or 1,2-benzenedicarboxylic (phthalic) acid, with the corresponding anhydride. The resulting half-ester has a free carboxyl function and may then be resolvable with a chiral base, usually brucine:



OTHER METHODS OF RESOLUTION

One of the major goals in the field of organic chemistry is the development of reagents with the property of "chiral recognition" such that they can affect a clean separation of enantiomers in one operation without destroying either of the enantiomers. We have not achieved that ideal yet, but it may not be far in the future. Chromatographic methods, whereby the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than the other, have been used to resolve racemic compounds, but such resolutions seldom have led to both pure enantiomers on a preparative scale. Other methods, called kinetic resolutions, are excellent when applicable. The procedure takes advantage of differences in reaction rates of enantiomers with chiral reagents. One enantiomer may react more rapidly, thereby leaving an excess of the other enantiomer behind. For example, racemic tartaric acid can be resolved with the aid of certain penicillin molds that consume the dextrorotatory enantiomer faster than the levorotatory enantiomer. As a result, almost pure (-)-tartaric acid can be recovered from the mixture:

(±)-tartaric acid + mold → (-)-tartaric acid + more mold

The crystallization procedure employed by Pasteur for his classical resolution of (±)-tartaric acid (**Section 5.4**) has been successful only in a very few cases. This procedure depends on the formation of individual crystals of each enantiomer. Thus if the crystallization of sodium ammonium tartrate is carried out below 27", the usual racemate salt does not form; a mixture of crystals of the (+) and (-) salts forms instead. The two different kinds of crystals, which are related as an object to its mirror image, can be separated manually with the aid of a microscope and subsequently may be converted to the tartaric acid enantiomers by strong acid. A variation on this method of resolution is the seeding of a saturated solution of a racemic mixture with crystals of one pure enantiomer in the hope of causing crystallization of just that one enantiomer, thereby leaving the other in solution. Unfortunately, very few practical resolutions have been achieved in this way.

PREDICATING THE CHIRALITY OF THE PRODUCT OF A REACTION

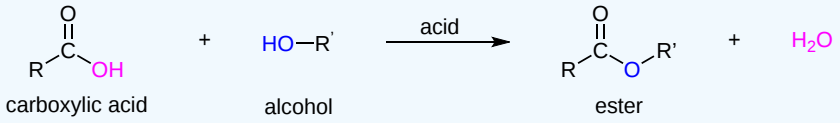
It important to understand the changes in chirality which occur during the formation of product during a reaction. A chiral reaction product, has the possibility of forming multiple stereoisomers which all need to be considered. Changes in chirality, if possible, will be discussed with each individual reaction as this textbook moves forward. Some possible situations which can occur are:

- **A new chiral carbon is formed during a reaction.** This commonly occurs when an sp^2 hybridized carbon in the reactant is converted to sp^3 hybridized chiral carbon in the product. When this occurs, a racemic mixture of the new chiral carbon is formed.
- **A chiral carbon is lost during a reaction.** This commonly occurs when an sp^3 hybridized chiral carbon in the reactant is converted to either a sp^2 or sp hybridized carbon in the product.
- **An enantiomerically pure starting material is converted to a racemic mixture in the product.** This commonly occurs when a sp^3 hybridized chiral carbon is temporarily converted to an sp^2 hybridized carbon during a reaction's mechanism. The chiral carbon is reformed as a racemic mixture.
- **Chiral carbons remain unchanged during a reaction.** If a chiral carbon is not directly involved in a reaction, it will move from a reactant to a product unchanged.

Determining if a chiral carbon is involved in a given reaction is vital for determining which of these four situations is occurring.

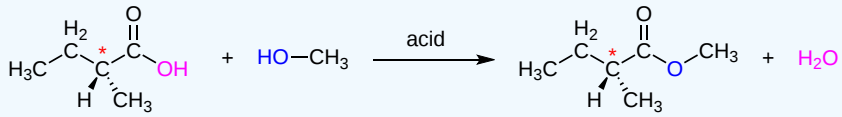
WORKED EXAMPLE 5.8.2

The following reaction involves the conversion of a carboxylic acid reacting with an alcohol to form an ester. If a pure sample of (R)-2-methylbutanoic acid is reacted with methanol to form an ester, what would be the stereochemistry of the product?



Answer

First it is important to identify the location of the chiral carbon and determine if it is directly involved in the reaction. In this case, the chiral carbon is not involved so the stereochemistry will be carried over into the product unchanged.



EXERCISE 5.8.1

Indicate the reagents you could use to resolve the following compounds. Show the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenyl-2-propanamine.

Answer

You could react the 1-phenyl-2-propanamine racemic mixture with a chiral acid such as (+)-tartaric acid (*R*, *R*). The reaction will produce a mixture of diastereomeric salts (i.e. *R*, *R*, *R* and *S*, *R*, *R*). You can separate the diastereomers through crystallization and treat the salt with a strong base (e.g. KOH) to recover the pure enantiomeric amine.

EXERCISE 5.8.2

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 2,3-pentadienedioic acid.

Answer

You could react the 2,3-pentadienedioic acid mixture with a chiral base such as (*R*)-1-phenylethylamine. The reaction will produce a mixture of diastereomeric salts. Separate the diastereomers through crystallization and treat the resulting salt with strong acid (e.g. HCl) to recover the pure enantiomeric acid.

EXERCISE 5.8.3

Indicate the reagents you would use to resolve the following and discuss the reactions involved and specify the physical method you believe would be the best to separate the diastereomers of 1 -phenylethanol.

Answer

You could react the 1-phenylethanol mixture with 1,2-benzenedicarboxylic anhydride. The reaction will produce a mixture of diastereomeric salts. You could then separate the diastereomers through crystallization and then alkaline hydrolysis treatment should recover the pure enantiomeric alcohol.

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5.9: A REVIEW OF ISOMERISM

OBJECTIVE

After completing this section, you should be able to explain the differences among constitutional (structural) isomers and stereoisomers (geometric isomers).

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- constitutional
- (structural) isomers
- stereoisomers

The following flow chart can be used to identify the relationship of two compounds with respect to isomerization:

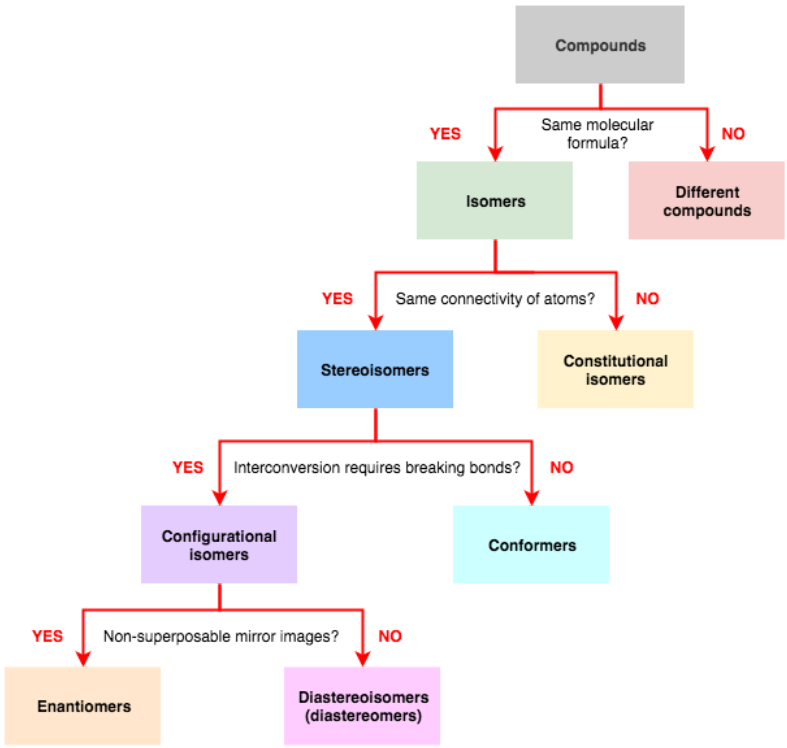
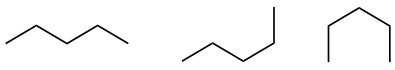


Figure 5.9.1: Different types of isomers. When using the flow chart, it is really important to remember that each decision on the flow chart is related to comparing two molecules, ie. it doesn't make sense to ask "what is compound A", but it does make sense to ask "how are compounds A and B related"? A molecule may be the enantiomer of another molecule, but a diastereomer of another. (CC-BY-SA 4.0; Mark Coster via StackExchange)

CONFORMATIONAL ISOMERS

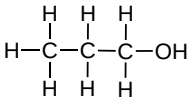
The C–C single bonds in ethane, propane, and other alkanes are formed by the overlap of an sp^3 hybrid orbital on one carbon atom with an sp^3 hybrid orbital on another carbon atom, forming a σ bond. Each sp^3 hybrid orbital is cylindrically symmetrical (all cross-sections are circles), resulting in a carbon–carbon single bond that is also cylindrically symmetrical about the C–C axis. Because rotation about the carbon–carbon single bond can occur without changing the overlap of the sp^3 hybrid orbitals, there is no significant electronic energy barrier to rotation. Consequently, many different arrangements of the atoms are possible, each corresponding to different degrees of rotation. Differences in three-dimensional structure resulting from rotation about a σ bond are called differences in conformation, and each different arrangement is called a conformational isomer (or conformer).



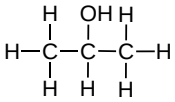
Conformational Isomers of Pentane

STRUCTURAL ISOMERS

Unlike conformational isomers, which do not differ in connectivity, structural isomers differ in connectivity, as illustrated here for 1-propanol and 2-propanol. Although these two alcohols have the same molecular formula (C_3H_8O), the position of the –OH group differs, which leads to differences in their physical and chemical properties.

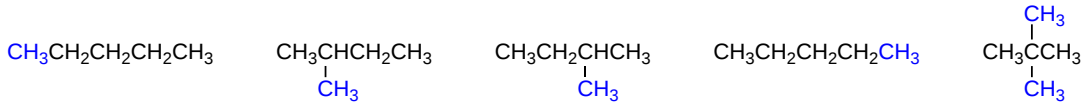


1-propanol (*n*-propanol)



2-propanol (isopropanol)

In the conversion of one structural isomer to another, at least one bond must be broken and reformed at a different position in the molecule. Consider, for example, the following five structures represented by the formula C_5H_{12}:



(a) (b) (c) (d) (e)

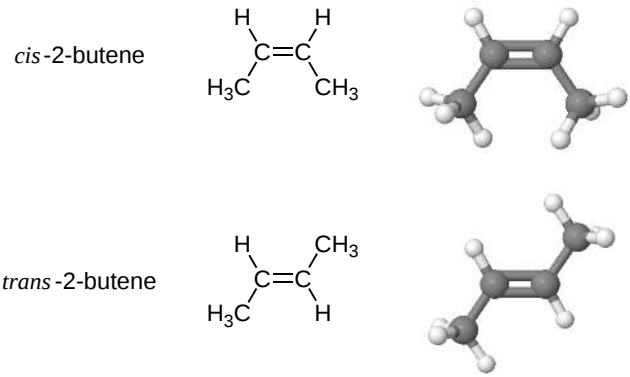
Of these structures, (a) and (d) represent the same compound, as do (b) and (c). No bonds have been broken and reformed; the molecules are simply rotated about a 180° vertical axis. Only three—n-pentane (a) and (d), 2-methylbutane (b) and (c), and 2,2-dimethylpropane (e)—are structural isomers. Because no bonds are broken in going from (a) to (d) or from (b) to (c), these alternative representations are not structural isomers. The three structural isomers—either (a) or (d), either (b) or (c), and (e)—have distinct physical and chemical properties.

STEREOISOMERS

Stereoisomers have the same connectivity in their atoms but a different arrangement in three-dimensional space. There are different classifications of stereoisomers depending on how the arrangements differ from one another. Notice that in the structural isomers, there was some difference in the connection of atoms. For example, 1-butene has a double bond followed by two single bonds while 2-butene has a single bond, then a double bond, then a single bond. A stereoisomer will have the same connectivity among all atoms in the molecule.

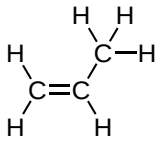
GEOMETRIC ISOMERS

With a molecule such as 2-butene, a different type of isomerism called geometric isomerism can be observed. **Geometric isomers** are isomers in which the order of atom bonding is the same but the arrangement of atoms in space is different. The double bond in an alkene is not free to rotate because of the nature of the bond. Therefore, there are two different ways to construct the 2-butene molecule (see figure below). The image below shows the two geometric isomers, called *cis*-2-butene and *trans*-2-butene.



Geometric Isomers of 2-Butene

The *cis* isomer has the two single hydrogen atoms on the same side of the molecule, while the *trans* isomer has them on opposite sides of the molecule. In both molecules, the bonding order of the atoms is the same. In order for geometric isomers to exist, there must be a rigid structure in the molecule to prevent free rotation around a bond. This occurs with a double bond or a ring. In addition, the two carbon atoms must each have two different groups attached in order for there to be geometric isomers. Propene (see figure below) has no geometric isomers because one of the carbon atoms (the one on the far left) involved in the double bond has two single hydrogens bonded to it.

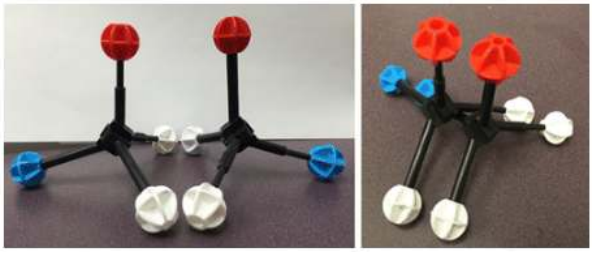


Physical and chemical properties of geometric isomers are generally different. As with alkenes, alkynes display structural isomerism beginning with 1-butyne and 2-butyne. However, there are no geometric isomers with alkynes because there is only one other group bonded to the carbon atoms that are involved in the triple bond.

OPTICAL ISOMERS

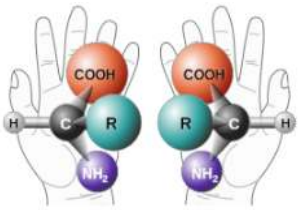
Stereoisomers that are not geometric isomers are known as optical isomers. Optical isomers differ in the placement of substituted groups around one or more atoms of the molecule. They were given their name because of their interactions with plane-polarized light. Optical isomers are labeled enantiomers or diastereomers.

Enantiomers are non-superimposable mirror images. A common example of a pair of enantiomers is your hands. Your hands are mirror images of one another but no matter how you turn, twist, or rotate your hands, they are not superimposable.



Two models that are mirror images and superimposable.

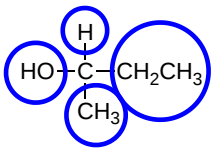
Since they are superimposable, they are the same molecule and are not isomers.



Your hands and some molecules are mirror images but are not superimposable.

These pairs of molecules are called enantiomers.

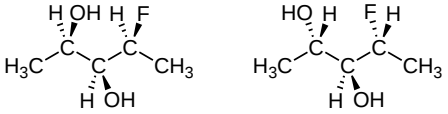
Objects that have non-superimposable mirror images are called **chiral**. When examining a molecule, carbon atoms with four unique groups attached are considered chiral. Look at the figure below to see an example of a chiral molecule. Note that we have to look beyond the first atom attached to the central carbon atom. The four circles indicate the four unique groups attached to the central carbon atom, which is chiral.



A chiral carbon has four unique groups attached to it

Another type of optical isomer are **diastereomers**, which are non-mirror image optical isomers. Diastereomers have a different arrangement around one or more atoms while some of the atoms have the same arrangement. As shown in the figure below, note that the orientation of

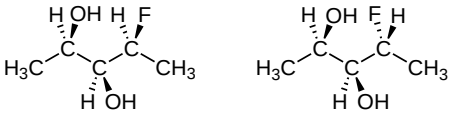
groups on the first and third carbons are different but the second one remains the same so they are not the same molecule. The solid wedge indicates a group coming out of the page/screen towards you and the dashed line indicates that a group is going away from you "behind" the page/screen.



Diastereomers differ at one or more atom. These molecules are not mirror images and they are not superimposable.

They are optical isomers because they have the same connectivity between atoms but a different arrangement of substituent groups.

Epimers are a sub-group of diastereomers that differ at only one location. All epimers are diastereomers but not all diastereomers are epimers.



Epimers have a different arrangement around one atom, while arrangements around the other atoms are the same

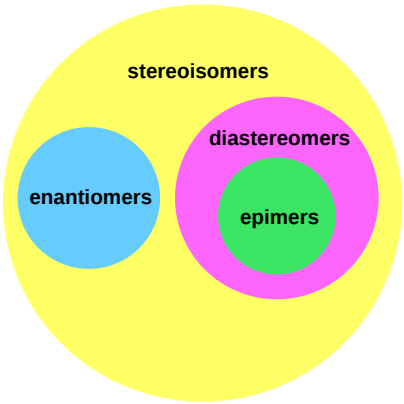
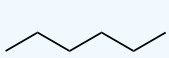
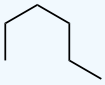
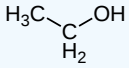
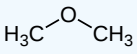


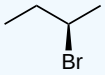
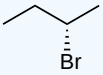
Diagram showing the division of stereoisomers (also known as optical isomers)

? EXERCISE 5.9.1

What kind of isomers are the following pairs?

a)  and 

b)  and 

c)  and 

Answer

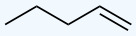
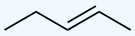
a. Since both structures have the same formula (C_6H_{12}) and they have the same connectivity, but are in a different arrangement of the atoms in space, they are conformational isomers.

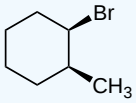
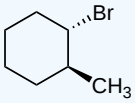
b. Since both structures have the same formula (C_2H_6O) but different connectivity, they are structural isomers.

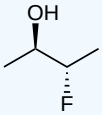
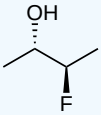
c. Since both structures have the same formula (C_3H_9Br) and the same connectivity but the structure on the left has *R* stereochemistry and the structure on the right has *S* stereochemistry, they are stereoisomers called enantiomers.

EXERCISE 5.9.2

What kind of isomers are the following pairs?

a)  and 

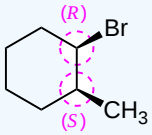
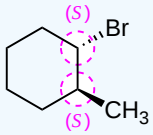
b)  and 

c)  and 

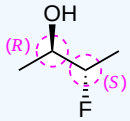
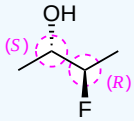
Answer

a) Since both structures have the same formula (C_2H_6O) but different connectivity of where the double bond is, they are structural isomers.

b) Both structures have the same formula and the same connectivity but the structure on the left has (*R*,*S*) stereochemistry and the structure on the right has (S,S) stereochemistry, they are stereoisomers that are diastereomers.

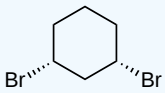
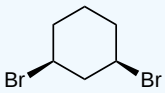
 

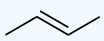
c) Both structures and have the same connectivity but their stereochemistry differs so they are stereoisomers. Since the one on the left is (R,S) and the one on the right is (S,R), they are non-super imposable mirror images of each other and enantiomers.

EXERCISE 5.9.3

What is the relationship between the following pairs?

a)  and 

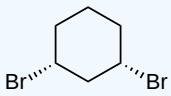
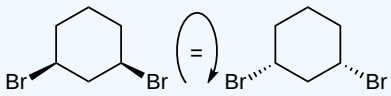
b)  and 

c) (*R*) – 2 chlorohexane & 1-chlorohexane

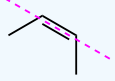
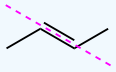
d) (2*R*, 3*R*) dichlorohexane & (2*S*, 3*R*) dichlorohexane

Answer

a) Both structures have the same connectivity and same chemical formula and when you rotate the structure on the right you can see that these are the same compound both with (R,S) stereochemistry.

 and 

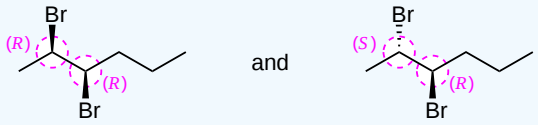
b)) Since both structures have the same formula (C_4H_8) and the same connectivity they are stereoisomers since they differ in what is known as cis/trans isomerism (covered more in Ch 7).Due to the pi bond between carbons 2 & 3, there is not free rotation between the C2-C3 bond so the structure on the left has the carbon chains on the same side of the double bond (cis) and the structure on the right has the carbon chains on opposite sides of the double bond (trans).

 and 

c) Looking at the structures below, you can see that they have the same formula ($C_6H_{13}Cl$) and different connectivity, so they are structural isomers.



d) Looking at the structures below, you can see that they have the same formula ($C_6H_{12}Br_2$) and the same connectivity, but the structure on the left is (*R*,*R*) and the structure on the right is (*S*,*R*) so since they differ by only one stereocenter, they are stereoisomers that are diastereomers (& epimers in this case).



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5.10: CHIRALITY AT NITROGEN, PHOSPHORUS, AND SULFUR

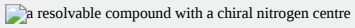
OBJECTIVES

After completing this section, you should be able to

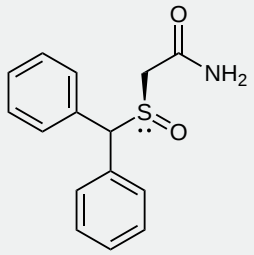
1. recognize that atoms other than carbon can be chiral centres.
2. explain why enantiomers of compounds such as ethylmethylamine cannot normally be isolated.

STUDY NOTES

The first example of a resolvable compound containing a chiral nitrogen atom was resolved by William Pope and Stanley Peachey in 1899. It had the structure shown below.



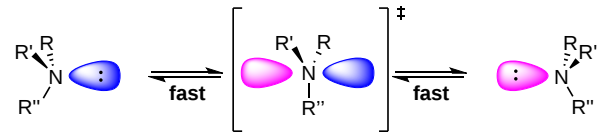
Chiral sulfoxides find application in certain drugs such as esomeprazole and armodafinil and are a good example of a stereogenic sulfur center.



armodafinil

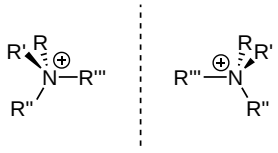
CHIRALITY AT NITROGEN

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of chiral amines cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp^3 hybridized amine momentarily rehybridizes to a sp^2 hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to tetrahedral sp^3 hybridization causing the lone pair electrons to enter to a hybrid orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer, analogous to the Walden inversion seen in S_N2 reactions. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic mixture of R and S configurations.



sp^3-hybridized (tetrahedral) | sp^2-hybridized (trigonal planar) | sp^3-hybridized (tetrahedral)

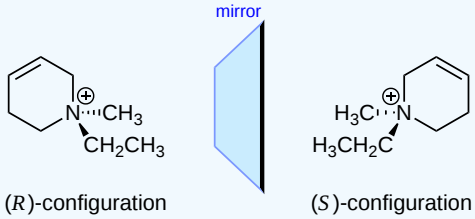
Quaternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quaternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.



enantiomers of a chiral quaternary amine

EXAMPLE 5.10.1

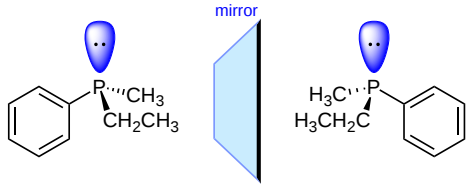
The Enantiomers of a chiral quaternary amine.



(*R*)-configuration (*S*)-configuration

CHIRALITY AT PHOSPHORUS

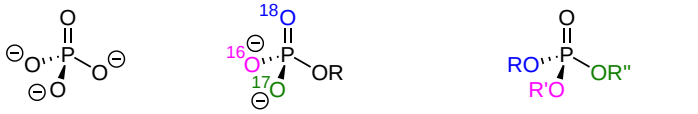
Trivalent phosphorus compounds called phosphines have a tetrahedral electron-group geometry which makes them structurally analogous to amines. The rate of inversion for phosphines are so much slower than amines that chiral phosphines can be isolated. In this case the set of lone pair electrons are considered a substituent and given the lowest Cahn-Ingold-Prelog priority.



(*R*)-configuration (*S*)-configuration

enantiomers of ethylmethylphenylphosphine

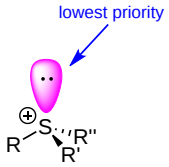
The phosphorus center of phosphate ions and organic phosphate esters is also tetrahedral, and thus potentially a stereocenter. In order to investigate the stereochemistry of reactions at the phosphate center, ^{17}O and ^{18}O isotopes of oxygen (the 'normal' isotope is ^{16}O) can be incorporated to create chiral phosphate groups. Phosphate triesters are chiral if the all four substituent groups are different (including the carbonyl oxygen).



phosphate (achiral) labeled phosphate ester (chiral) a chiral phosphate triester

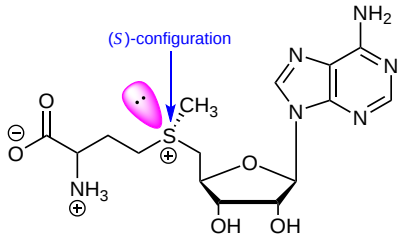
CHIRALITY AT SULFUR

Trivalent sulfur compounds called sulfonium salts (R_3S^+) have a tetrahedral electron-group geometry similar to amines and can be chiral if the R groups are all different. In a similar fashion as phosphorus, the inversion rates are slow enough for chiral sulfonium salts to be isolated. Here again the set of lone pair electrons are considered a substituent and given the lowest CIP priority. Sulfonium salts will be discussed in greater detail in **Section 18.8**.



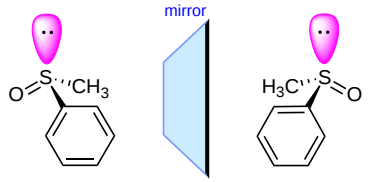
a chiral sulfur in the form of a sulfonium ion

An excellent example of a chiral sulfonium salt in biological systems is the coenzyme (*S*)-adenosylmethionine (SAM). The presence of a sulfonium allows SAM to be a biological methyl group donor in many metabolic pathways. Note that SAM has an (*S*) configuration at the sulfur atom.



(*S*)-S-adenosylmethionine

The sulfur in sulfoxides (R'SOR") can be chiral if both R groups are different. Here again the inversion rate is slow enough to allow chiral sulfoxides to be isolated. An excellent example is methyl phenyl sulfoxide. Sulfoxides will also be discussed in greater detail in **Section 18.8**.



(*R*)-configuration (*S*)-configuration

enantiomers of methyl phenyl sulfoxide

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5.11: PROCHIRALITY

OBJECTIVES

After completing this section, you should be able to

1. identify a compound as being prochiral.
2. identify the *Re* and *Si* faces of prochiral sp^2 centre.
3. identify atoms (or groups of atoms) as *pro-R* or *pro-S* on a prochiral sp^3 centre.

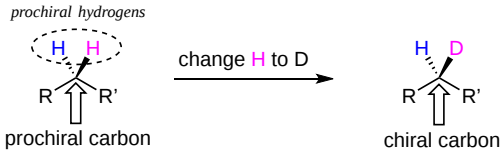
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- prochiral
- *pro-R*
- *pro-S*
- *Re*
- *Si*

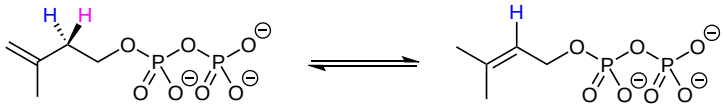
PROCHIRAL CARBONS

When a tetrahedral carbon can be converted to a chiral center by changing only one of the attached groups, it is referred to as a '**prochiral**' carbon. The two hydrogens on the prochiral carbon can be described as 'prochiral hydrogens'.



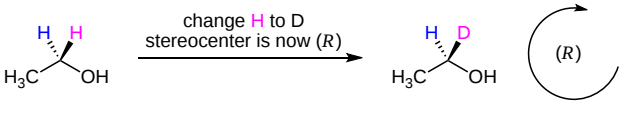
Note that if, in a 'thought experiment', we were to change either one of the prochiral hydrogens on a prochiral carbon center to a deuterium (the ^{2}H isotope of hydrogen), the carbon would now have four different substituents and thus would be a chiral center.

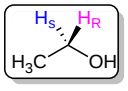
Prochirality is an important concept in biological chemistry, because enzymes can distinguish between the two 'identical' groups bound to a prochiral carbon center due to the fact that *they occupy different regions in three-dimensional space*. Consider the isomerization reaction below, which is part of the biosynthesis of isoprenoid compounds. We do not need to understand the reaction itself (it will be covered in chapter 14); all we need to recognize at this point is that the isomerase enzyme is able to distinguish between the prochiral 'red' and the 'blue' hydrogens on the isopentenyl diphosphate (IPP) substrate. In the course of the left to right reaction, IPP specifically loses the 'red' hydrogen and keeps the 'blue' one.



isopentenyl diphosphate dimethylallyl diphosphate

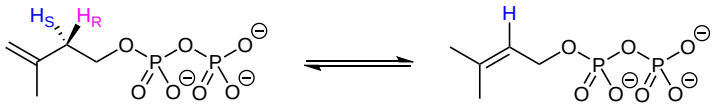
Prochiral hydrogens can be unambiguously designated using a variation on the *R/S* system for labeling chiral centers. For the sake of clarity, we'll look at a very simple molecule, ethanol, to explain this system. To name the 'red' and 'blue' prochiral hydrogens on ethanol, we need to engage in a thought experiment. If we, in our imagination, were to arbitrarily change red H to a deuterium, the molecule would now be chiral and the chiral carbon would have the *R* configuration (D has a higher priority than H).





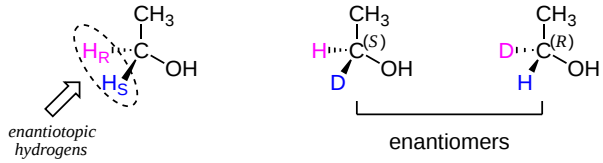
For this reason, we can refer to the red H as the *pro-R* hydrogen of ethanol, and label it H_R. Conversely, if we change the blue H to D and leave red H as a hydrogen, the configuration of the molecule would be *S*, so we can refer to blue H as the *pro-S* hydrogen of ethanol, and label it H_S.

Looking back at our isoprenoid biosynthesis example, we see that it is specifically the *pro-R* hydrogen that the isopentenyl diphosphate substrate loses in the reaction.



isopentenyl diphosphate dimethylallyl diphosphate

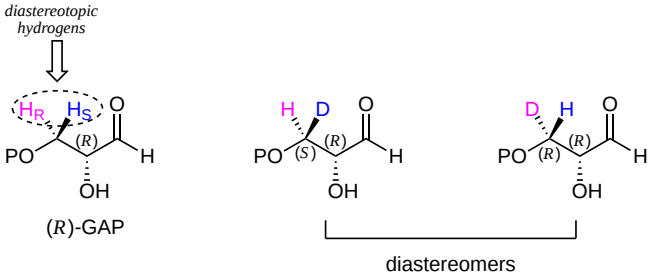
Prochiral hydrogens can be designated either enantiotopic or diastereotopic. If either H_R or H_S on ethanol were replaced by a deuterium, the two resulting isomers would be enantiomers (because there are no other stereocenters anywhere on the molecule).



enantiotopic hydrogens enantiomers

Thus, these two hydrogens are referred to as **enantiotopic**.

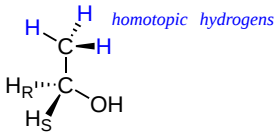
In (*R*)-glyceraldehyde-3-phosphate ((*R*)-GAP), however, we see something different:



diastereotopic hydrogens (*R*)-GAP diastereomers

R)-GAP already has one chiral center. If either of the prochiral hydrogens H_R or H_S is replaced by a deuterium, a second chiral center is created, and the two resulting molecules will be diastereomers (one is *S*,*R*, one is *R*,*R*). Thus, in this molecule, H_R and H_S are referred to as **diastereotopic** hydrogens.

Finally, hydrogens that can be designated neither enantiotopic nor diastereotopic are called **homotopic**. If a homotopic hydrogen is replaced by deuterium, a chiral center is *not* created. The three hydrogen atoms on the methyl (CH_3) group of ethanol (and on *any* methyl group) are homotopic. An enzyme cannot distinguish among homotopic hydrogens.

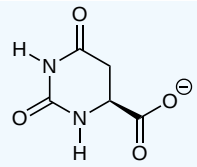


homotopic hydrogens

? EXAMPLE 5.11.1

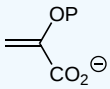
Identify in the molecules below all pairs/groups of hydrogens that are homotopic, enantiotopic, or diastereotopic. When appropriate, label prochiral hydrogens as H_R or H_S.

a)



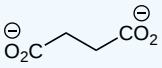
dihydroorotate
(a nucleotide biosynthesis intermediate)

b)



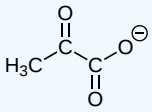
phosphoenolpyruvate
(a glycolysis intermediate)

c)



succinate
(a citric acid cycle intermediate)

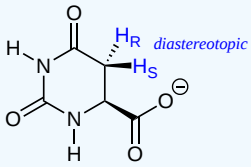
d)



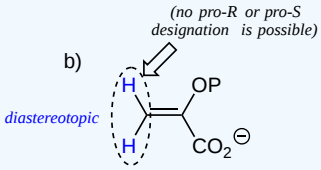
pyruvate
(endpoint of glycolysis)

Answer

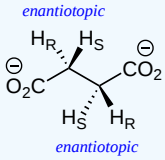
a)



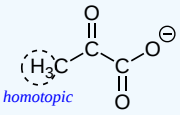
b)



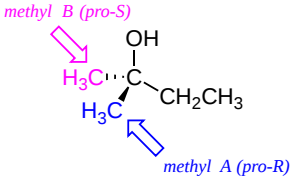
c)



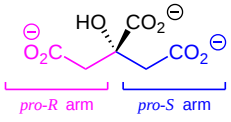
d)



Groups other than hydrogens can be considered prochiral. The alcohol below has two prochiral methyl groups - the red one is *pro-R*, the blue is *pro-S*. How do we make these designations? Simple - just arbitrarily assign the red methyl a higher priority than the blue, and the compound now has the *R* configuration - therefore red methyl is *pro-R*.

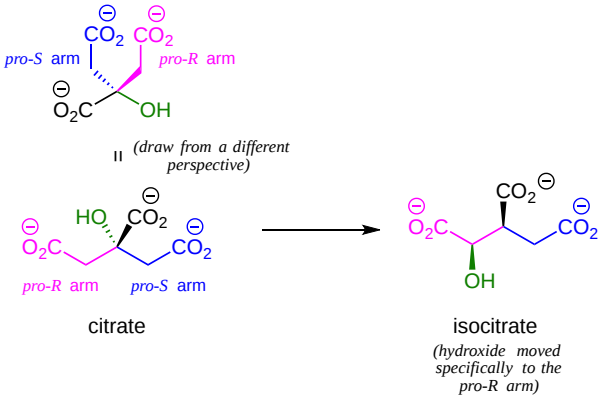


Citrate is another example. The central carbon is a prochiral center with two 'arms' that are identical except that one can be designated *pro-R* and the other *pro-S*.



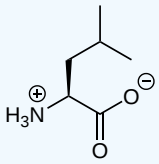
citrate

In an isomerization reaction of the citric acid (Krebs) cycle, a hydroxide is shifted specifically to the *pro-R* arm of citrate to form isocitrate: again, the enzyme catalyzing the reaction distinguishes between the two prochiral arms of the substrate (we will study this reaction in chapter 13).



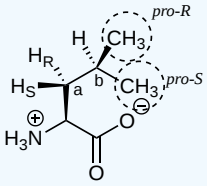
EXERCISE 5.11.1

Assign *pro-R* and *pro-S* designations to all prochiral groups in the amino acid leucine. (*Hint*: there are two pairs of prochiral groups!). Are these prochiral groups diastereotopic or enantiotopic?



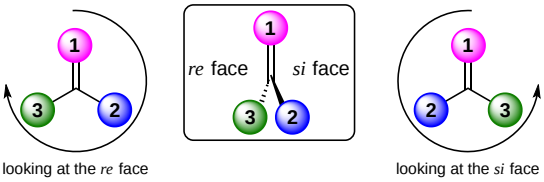
leucine

Answer

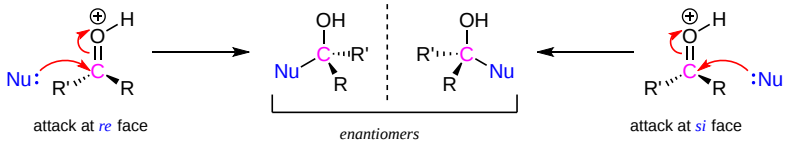


PROCHIRAL CARBONYL AND IMINE GROUPS

Trigonal planar, sp^2-hybridized carbons are not, as we well know, chiral centers– but they can be prochiral centers if they are bonded to three different substitutuents. We (and the enzymes that catalyze reactions for which they are substrates) can distinguish between the two planar 'faces' of a prochiral sp^2 - hybridized group. These faces are designated by the terms ***re*** and ***si***. To determine which is the *re* and which is the *si* face of a planar organic group, we simply use the same priority rankings that we are familiar with from the R/S system, and trace a circle: *re* is clockwise and *si* is counterclockwise.

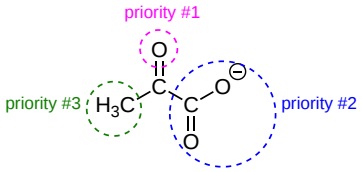


When the two groups adjacent to a carbonyl (C=O) are not the same, we can distinguish between the re and si 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Nucleophilic additions to carbonyls will be covered in greater detail in **Chapter 19**. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.

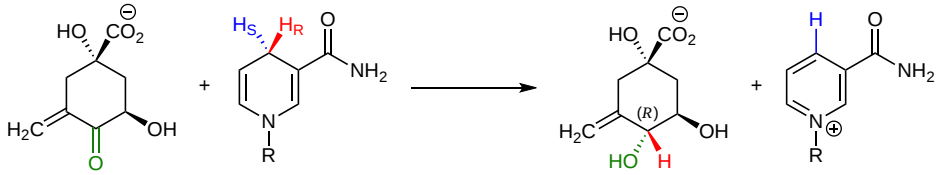


Note: R is higher priority than R'

Below, for example, we are looking down on the *re* face of the ketone group in pyruvate. If we flipped the molecule over, we would be looking at the *si* face of the ketone group. Note that the carboxylate group does not have *re* and *si* faces, because two of the three substituents on that carbon are identical (when the two resonance forms of carboxylate are taken into account).



As we will see in chapter 10, enzymes which catalyze reactions at carbonyl carbons act specifically from one side or the other.

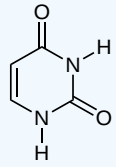


*looking at the **si** face of the ketone*

We need not worry about understanding the details of the reaction pictured above at this point, other than to notice the stereochemistry involved. The *pro-R* hydrogen (along with the two electrons in the C-H bond) is transferred to the *si* face of the ketone (in green), forming, in this particular example, an alcohol with the *R* configuration. If the transfer had taken place at the *re* face of the ketone, the result would have been an alcohol with the *S* configuration.

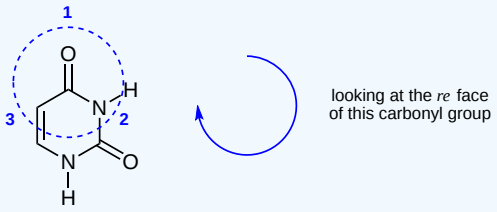
EXERCISE 5.11.2

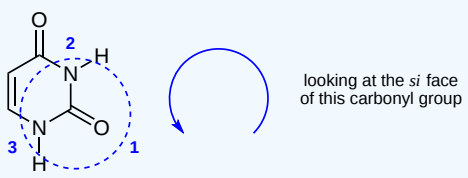
For each of the carbonyl groups in uracil, state whether we are looking at the *re* or the *si* face in the structural drawing below.



uracil

Answer





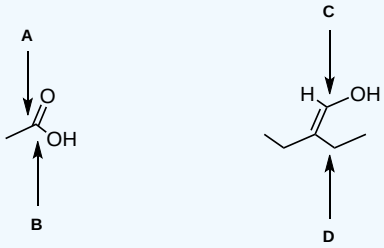
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EXERCISE 5.11.3

a) State which of the following hydrogen atoms are *pro-R* or *pro-S*.



b) Identify which side is Re or Si.



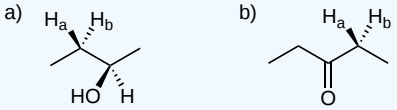
Answer

a) Left compound: H_a = *pro-S* and H_b = *pro-R*; Right compound: H_a = *pro-R* and H_b = *pro-S*

b) A – Re; B – Si; C – Re; D – Si\)

EXERCISE 5.11.4

State whether the H's indicated below are pro-*R* or pro-*S* for the following structures.



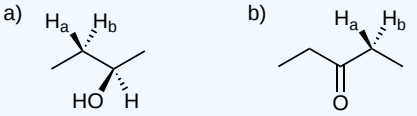
Answer

a) H_a is pro-R; H_b is pro-S

H_a is pro-R; H_b is pro-S

EXERCISE 5.11.5

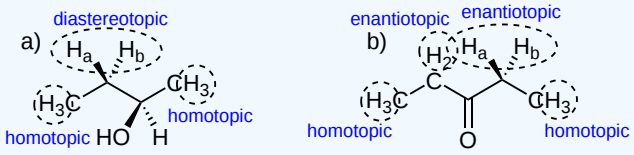
In the structures below, determine if the H's are homotopic, enantiotopic, or diastereotopic.



Answer

In a), the CH_2 is diastereotopic since there is another chiral center on the molecule. Both CH_3's are homotopic since replacing one of them doesn't create a chiral center.

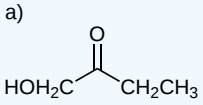
IN b), the CH_2's are enantiotopic since it would create the only chiral center on the molecule. Both CH_3's are homotopic since replacing one of them doesn't create a chiral center.

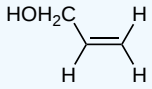


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EXERCISE 5.11.6

State whether you are looking down at the molecule from the re face or si face.

a) 

b) 

Answer

a. You are looking at the **si face**. The re face would be if you were facing the molecule from the back.

b. You are looking at the **re face**. The si face would be if you were facing the molecule from the back.

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5.12: CHIRALITY IN NATURE AND CHIRAL ENVIRONMENTS

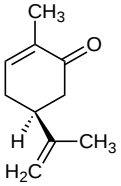
OBJECTIVE

After completing this section, you should be able to explain how chiral molecules in nature can have such dramatically different biological properties.

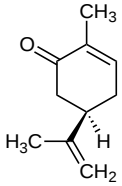
SOME CHIRAL ORGANIC MOLECULES

There are a number of important biomolecules that could occur as enantiomers, including amino acids and sugars. In most cases, only one enantiomer occurs naturally (although some fungi, for example, are able to produce mirror-image forms of these compounds). We will look later at some of these biomolecules, but first we will look at a compound that occurs naturally in both enantiomeric forms.

Carvone is a secondary metabolite. That means it is a naturally-occurring compound that is not directly connected to the very basic functions of a cell, such as self-replication or the production of energy. The role of secondary metabolites in nature is often difficult to determine. However, these compounds often play roles in self-defense, acting as deterrents against competitor species in a sort of small-scale chemical warfare scenario. They are also frequently used in communications; this role has been studied most extensively among insects, which use lots of compounds to send information to each other.



(*S*)-carvone
oil at 25 °C
bp: 230-231 °C
d: 0.965 g/mL
n: 1.4988
insol H_2O, misc EtOH, MeOH
$[\alpha]_D$ = +61.2°



(*R*)-carvone
oil at 25 °C
bp: 230-231 °C
d: 0.965 g/mL
n: 1.4988
insol H_2O, misc EtOH, MeOH
$[\alpha]_D$= −62.46°

Figure **5.12.1**: The two naturally-occurring enantiomers of carvone.

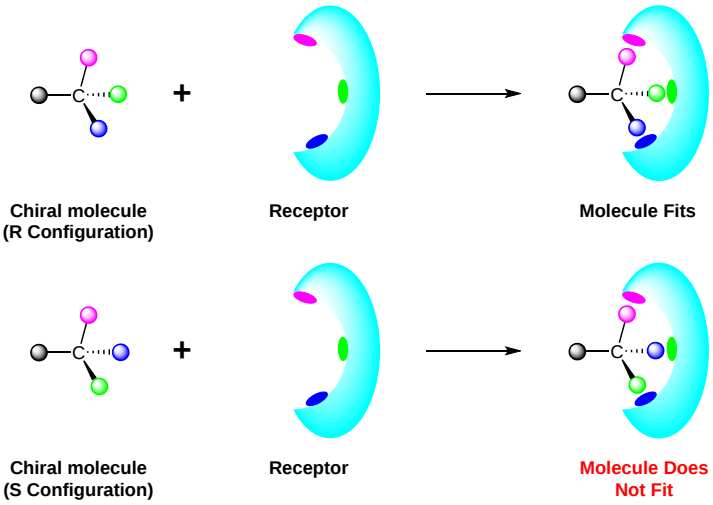
Carvone is produced in two enantiomeric forms. One of these forms, called (-)-carvone, is found in mint leaves, and it is a principal contributor to the distinctive odor of mint. The other form, (+)-carvone, is found in caraway seeds. This form has a very different smell, and is typically used to flavor rye bread and other Eastern European foods.

Note that (+)-carvone is another name for (S)-carvone. The (+) designation is based on its positive optical rotation value, which is experimentally measured. This means the (-)-carvone is (R)-carvone and would have a negative optical rotation value.

How different, exactly, are these two compounds, (+)- and (-)-carvone? Are they completely different isomers, with different physical properties? In most ways, the answer is no. These two compounds have the same appearance (colorless oil), the same boiling point (230 °C), the same refractive index (1.499) and specific gravity (0.965). However, they have optical rotations that are almost exactly opposite values.

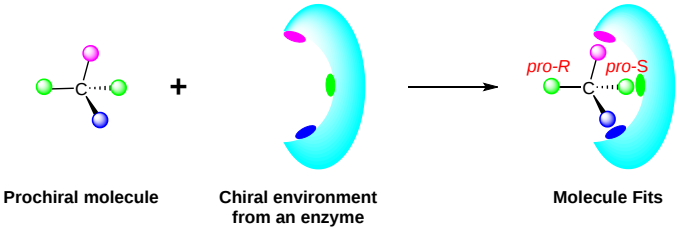
- Two enantiomers have the same physical properties.
- Enantiomers have opposite optical rotations.

Clearly they have different biological properties; since they have slightly different odors, they must fit into slightly different nasal receptors, signaling to the brain whether the person next to you is chewing a stick of gum or a piece of rye bread. This is much like how a left hand only fits into a left handed baseball glove and not into a right handed one. Receptors which allow for a biological effect, in this case to perceive a certain smell, are often chiral and will only allow one enantiomer of a chiral substrate to fit. An example of this is shown in the figure below. The receptor as a complementary three-dimension shape to allow the R configuration of the chiral substrate to fit. When the S configuration of the chiral substrate attempts to fit the configuration does not match that of the receptor as shown in the second drawing where the bottom two groups do not fit the receptor site.



CHIRAL ENVIRONMENTS

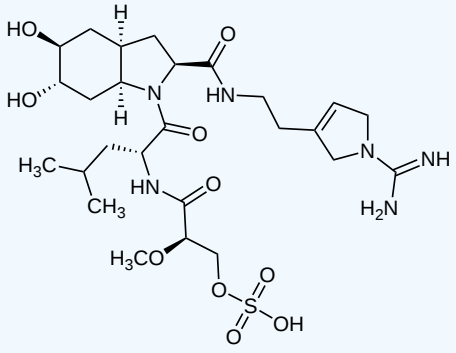
In the previous section, enzymes were shown to be capable of converting a prochiral substrate into a single enantiomer product. Enzymes can provides such an effect because they create a **chiral environment**. The figure below shows a prochiral substrate. The magenta and blue balls represent substituents while the two green balls represent two of the same substituent which is available for a given reaction. One of these substituents is *pro*-R and the other is *pro*-S. Without the presence of a chiral environment the two green substituents are chemically identical. However, as the prochiral molecule interacts with the chiral environment provided by an enzyme the two green substituents become chemically distinct. Despite being achiral, the prochiral molecule can only interact with the chiral environment in one specific position. The figure below shows that the *pro*-S green substituent of the prochiral molecule is protected by the enzyme, while the pro-R green substituent is exposed and can undergo a reaction. In this case the enzyme would provide a product that is predominantly the R enantiomer.



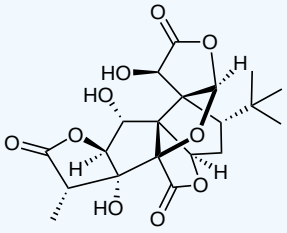
? EXERCISE 5.12.1

The following are three molecules found in nature. Please identify four chiral centers in each, mark them with asterisks, and identify each center as having a R or S configuration. Each molecule contains more than four chiral centers.

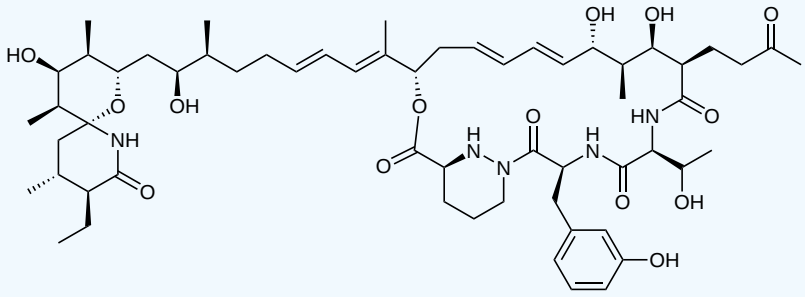
a) The following is the structure of dysinosin A, a potent thrombin inhibitor that consequently prevents blood clotting.



b) Ginkgolide B (below) is a secondary metabolite of the ginkgo tree, extracts of which are used in Chinese medicine.

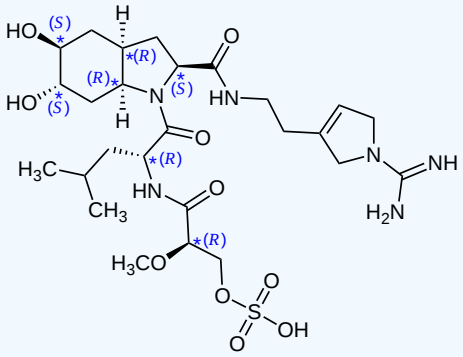


c) Sanglifehrin A, shown below, is produced by a bacteria that may be found in the soil of coffee plantations in Malawi. It is also a promising candidate for the treatment of organ transplant patients owing to its potent immuno-suppressant activity.

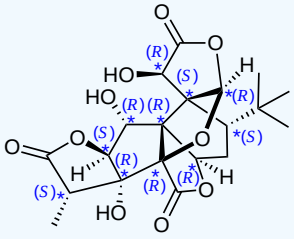


Answer

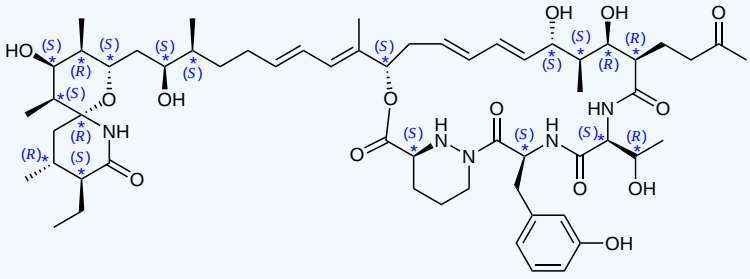
a)



b)



c)



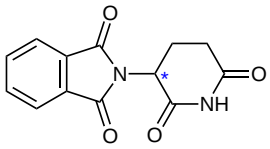


Figure \(\PageIndex{2}\): Thalidomide.

There are other reasons that we might concern ourselves with an understanding of enantiomers, apart from dietary and olfactory preferences. Perhaps the most dramatic example of the importance of enantiomers can be found in the case of thalidomide. Thalidomide was a drug commonly prescribed during the 1950's and 1960's in order to alleviate nausea and other symptoms of morning sickness. In fact, only one enantiomer of thalidomide had any therapeutic effect in this regard. The other enantiomer, apart from being therapeutically useless in this application, was subsequently found to be a teratogen, meaning it produces pronounced birth defects. This was obviously not a good thing to prescribe to pregnant women. Workers in the pharmaceutical industry are now much more aware of these kinds of consequences, although of course not all problems with drugs go undetected even through the extensive clinical trials required in the United States. Since the era of thalidomide, however, a tremendous amount of research in the field of synthetic organic chemistry has been devoted to methods of producing only one enantiomer of a useful compound and not the other. This effort probably represents the single biggest aim of synthetic organic chemistry through the last quarter century.

- Enantiomers may have very different biological properties.
- Obtaining enantiomerically pure compounds is very important in medicine and the pharmaceutical industry.

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5.S: STEREOCHEMISTRY AT TETRAHEDRAL CENTERS (SUMMARY)

CONCEPTS & VOCABULARY

5.1: Enantiomers and the Tetrahedral Carbon

- Every molecule is either **chiral** (not superimposable on its mirror image) or **achiral** (superimposable on its mirror image).
- **Chiral** molecules do not have a plane of symmetry, while **achiral** molecules have one or more **planes of symmetry**.
- **Stereoisomers** vary by spatial arrangement of atoms but have the same atom connectivity.
- **Stereoisomers** that are mirror images of one another but are not superimposable are called **enantiomers**.

5.2: The Reason for Handedness in Molecules - Chirality

- A Tetrahedral carbon atom bonded to four different substituents is an **asymetric** carbon (also called a **stereocenter** or **chiral** carbon), which typically leads to a **chiral** molecule (meso compounds are the exception in section 5.7).

5.3: Optical Activity

- **Enantiomers** cause rotation of plane-polarized light in equal amounts in opposite directions. This is called **optical activity.** Clockwise rotation is called d**extrorotatory** (+) and counter-clockwise is called **levorotatory** (-).
- **Specific rotation** is the amount that a sample of a chemical rotates planne-polarized light. It can be used to calculate the purity of a mixture of **enantiomers** called the **enantiomeric excess**.
- **Resolution** is the separation of a mixture of **enatiomers**.
- **Racemates** are defined as a 50:50 mixture of **enantiomers**, resulting in a sample that is not **optically active**. The process of forming a **racemic** mixture is called **racemization**.

5.4: Pasteur's Discovery of Enantiomers

5.5: Sequence Rules for Specifying Configuration

- Use the CIP rules to determine the priority of each substituent attached to a **chiral** carbon to determine whether configuration is **R** or **S**. With the lowest priority group facing away from you, draw an arc connecting groups 1-2-3. If that arc is clockwise, the configuration is **R**. If counterclockwise, the configuration is **S**.

5.6: Diastereomers

- **Stereoisomers** that are not mirror images of one another are called **diastereomers**.
- **Diastereomers** have two or more **stereocenters**. The configurations of the **stereocenters** cannot be inverse of each other (example R,R and S,S) because that defines a pair of **enantiomers**.

5.7: Meso Compounds

- **Meso** compounds are **achiral** but have **chiral** centers. This is caused by having an internal **plane of symmetry** that allows the two molecules to be superimposable on one another and be **optically inactive**.

5.8: Racemic Mixtures and the Resolution of Enantiomers

- Each component of a **racemic** mixture rotates plane polarized light an equal amount in opposite directions, so there is no **optical activity**.
- **Racemic** mixtures can be separated into the component **enantiomers** by reaction with a **chiral** reagent, which will form **diastereomer** intermediates of the molecules which can then be separated. Following separation the **chiral** reagent is removed to yield the two pure **enantiomers**.

5.9: A Review of Isomerism

- There are several categories of **isomers** with the largest distinction between:
  - constitutional (structural) isomers that contain the same number of each atom but differ in connectivity
  - **stereoisomers** that have all the same atoms with the same connectivity, but only differ in how the atoms are arranged three dimensionally
- In addition to the **diastereomers** and **enantiomers** that have been discussed at length in this chapter, **stereoisomers** can also be:
  - cis/trans or E/Z isomers which differ by spatial arrangement around a double bond
  - conformational **isomers** (conformers) which occur due to free rotation of sigma bonds

5.10: Chirality at Nitrogen, Phosphorus, and Sulfur

- Nitrogen when bonded to three different atoms is **chiral**, however the lone pair of electrons moves freely between positions on the Nitrogen causing these molecules to become a **racemic** mixture.
- When bonded to four different atoms in quaternary ammonium salts, nitrogen atoms lead to **chiral** molecules.
- Organic phosphates with four different groups can also be **chiral**.

5.11: Prochirality

- When a carbon can be converted to a **chiral** center by changing only one of its attached groups, it is called **prochiral**.
- If a molecule has two hydrogens on the same atom and replacement of either one with deuterium would lead to **enantiomers**, the hydrogens are **enantiotopic**.
- Similarly if this replacement would lead to **diastereomer** molecules, the hydrogens are **diastereotopic**.
- If replacement of a hydrogen would not lead to a chiral center being created, they are termed **homotopic**.

5.12: Chirality in Nature and Chiral Environments

SKILLS TO MASTER

- Skill 5.1 Identify stereocenters in molecular structures.
- Skill 5.2 Identify whether two structures are identical (not meso), constitutional isomers, enantiomers, diastereomers or meso and identical.
- Skill 5.3 Explain how plane polarized light is used to show optical activity.
- Skill 5.4 Calculate specific rotation from experimental data.
- Skill 5.5 Calculate optical purity and enantiomeric excess from experimental data.
- Skill 5.6 Determine configuration of stereocenters as R or S.
- Skill 5.7 Draw the enantiomer and diastereomers of a given compound with one or more stereocenters.
- Skill 5.8 Identify planes of symmetry in meso compounds.
- Skill 5.9 Describe a process for separating a mixture of enantiomers.
- Skill 5.10 Explain why racemic mixtures are optically inactive.
- Skill 5.11 Explain the difference between constitutional and stereoisomers.
- Skill 5.12 Give an example of a chiral center that is not carbon.

MEMORIZATION TASKS

MT 5.1 Memorize the rules for determining R and S configuration.

MT 5.2 Memorize the types of isomers and how to identify them.

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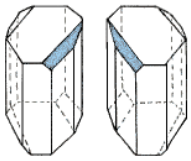
5.XX: ENANTIOMERS AND DIASTEREOMERS

OBJECTIVE

After completing this section, you should be able to discuss how the results of work carried out by Biot and Pasteur contributed to the development of the concept of the tetrahedral carbon atom.

Because enantiomers have identical physical and chemical properties in achiral environments, separation of the stereoisomeric components of a racemic mixture or racemate is normally not possible by the conventional techniques of distillation and crystallization. In some cases, however, the crystal habits of solid enantiomers and racemates permit the chemist (acting as a chiral resolving agent) to discriminate enantiomeric components of a mixture. As background for the following example, it is recommended that the section on crystal properties be reviewed.

Tartaric acid, its potassium salt known in antiquity as "tartar", has served as the locus of several landmark events in the history of stereochemistry. In 1832 the French chemist Jean Baptiste Biot observed that tartaric acid obtained from tartar was optically active, rotating the plane of polarized light clockwise (dextrorotatory). An optically inactive, higher melting, form of tartaric acid, called racemic acid was also known. A little more than a decade later, young Louis Pasteur conducted a careful study of the crystalline forms assumed by various salts of these acids. He noticed that under certain conditions, the sodium ammonium mixed salt of the racemic acid formed a mixture of enantiomorphic hemihedral crystals; a drawing of such a pair is shown on the right. Pasteur reasoned that the dissymmetry of the crystals might reflect the optical activity and dissymmetry of its component molecules. After picking the different crystals apart with a tweezer, he found that one group yielded the known dextrorotatory tartaric acid measured by Biot; the second led to a previously unknown levorotatory tartaric acid, having the same melting point as the dextrorotatory acid. Today we recognize that Pasteur had achieved the first resolution of a racemic mixture, and laid the foundation of what we now call stereochemistry.



Optical activity was first observed by the French physicist Jean-Baptiste Biot. He concluded that the change in direction of plane-polarized light when it passed through certain substances was actually a rotation of light, and that it had a molecular basis. His work was supported by the experimentation of Louis Pasteur. Pasteur observed the existence of two crystals that were mirror images in tartaric acid, an acid found in wine. Through meticulous experimentation, he found that one set of molecules rotated polarized light clockwise while the other rotated light counterclockwise to the same extent. He also observed that a mixture of both, a *racemic mixture* (or *racemic modification*), did not rotate light because the optical activity of one molecule canceled the effects of the other molecule. Pasteur was the first to show the existence of chiral molecules.

? EXERCISE 5.*xx*.1

When you have one enantiomer that rotates plane polarized light clockwise, why does a racemic mixture of that compound not rotate plane polarized light?

Answer

Since a racemic mixture consists of equal amounts of both enantiomers, one enantiomer will rotate plane polarized light clockwise, while the other enantiomer will rotate plane polarized light counterclockwise an equal amount, causing them to cancel out, and the racemic mixture being not optically active.

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CHAPTER OVERVIEW

6: AN OVERVIEW OF ORGANIC REACTIONS

LEARNING OBJECTIVES

After you have completed Chapter 6, you should be able to

1. fulfill the detailed objectives listed under each individual section.
2. identify the polarity pattern in the common functional groups, and explain the importance of being able to do so.
3. describe the essential differences between polar and radical reactions, and assign a given reaction to one of these two categories.
4. discuss how kinetic and thermodynamic factors determine the rate and extent of a chemical reaction.
5. use bond dissociation energies to calculate the $\Delta H°$ of simple reactions, and *vice versa*.
6. draw and interpret reaction energy diagrams.
7. define, and use in context, the new key terms.

This chapter is designed to provide a gentle introduction to the subject of reaction mechanisms. Two types of reactions are introduced—polar reactions and radical reactions. The chapter briefly reviews a number of topics you should be familiar with, including rates and equilibria, elementary thermodynamics and bond dissociation energies. You must have a working knowledge of these topics to obtain a thorough understanding of organic reaction mechanisms. Reaction energy diagrams are used to illustrate the energy changes that take place during chemical reactions, and to emphasize the difference between a reaction intermediate and a transition state.

6.0: Chapter Objectives
6.1: Kinds of Organic Reactions
6.2: How Organic Reactions Occur - Mechanisms
6.3: Radical Reactions
6.4: Polar Reactions
6.5: An Example of a Polar Reaction - Addition of HBr to Ethylene
6.6: Using Curved Arrows in Polar Reaction Mechanisms
6.7: Describing a Reaction - Equilibria, Rates, and Energy Changes
6.8: Describing a Reaction - Bond Dissociation Energies
6.9: Describing a Reaction - Energy Diagrams and Transition States
6.10: Describing a Reaction - Intermediates
6.11: A Comparison between Biological Reactions and Laboratory Reactions
6.S: An Overview of Organic Reactions (Summary)

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6.0: CHAPTER OBJECTIVES

Organic reactions form the backbone of organic chemistry, defining how molecules interact and transform into new compounds. These reactions involve the breaking and formation of chemical bonds between carbon atoms and other elements, leading to the synthesis of complex molecules with diverse functionalities. Understanding organic reactions is essential for designing synthetic pathways, predicting chemical behavior, and elucidating the mechanisms underlying biological processes. An overview of some key categories of organic reactions include:

1. **Substitution Reactions**: In substitution reactions, one functional group in a molecule is replaced by another. This can occur through either nucleophilic or electrophilic substitution mechanisms. Examples include S_N1 (nucleophilic substitution, unimolecular), S_N2 (nucleophilic substitution, bimolecular), and electrophilic aromatic substitution.
2. **Addition Reactions**: Addition reactions involve the addition of atoms or groups to carbon-carbon multiple bonds (such as alkenes or alkynes). Examples include hydration (addition of water), hydrogenation (addition of hydrogen), and halogenation (addition of halogens).
3. **Elimination Reactions**: In elimination reactions, a molecule loses atoms or functional groups to form a double or triple bond. Common examples include dehydration (loss of water), dehydrohalogenation (loss of a hydrogen halide), and beta-elimination reactions.
4. **Oxidation-Reduction (Redox) Reactions**: Redox reactions involve the transfer of electrons between reactants. Oxidation involves the loss of electrons, while reduction involves the gain of electrons. Organic redox reactions often involve the conversion of functional groups, such as alcohols to ketones/aldehydes or alkenes to diols.
5. **Acid-Base Reactions**: Acid-base reactions involve the transfer of a proton (H+) from an acid to a base. In organic chemistry, this can occur between molecules containing acidic or basic functional groups, such as carboxylic acids and amines.
6. **Condensation Reactions**: Condensation reactions involve the combination of two molecules with the loss of a small molecule, often water. Examples include esterification (formation of esters from carboxylic acids and alcohols) and peptide bond formation (condensation of amino acids to form peptides and proteins).
7. **Functional Group Transformation Reactions**: These reactions involve the conversion of one functional group into another through a series of chemical steps. Examples include hydrolysis (cleavage of esters, amides, etc., by water), reduction of carbonyl compounds to alcohols, and Grignard reactions (formation of carbon-carbon bonds).

Organic reactions can be classified based on various criteria, including reaction mechanism, types of reactants and products, and the nature of the functional groups involved. Mastery of organic reactions is essential for synthetic chemists, medicinal chemists, and biochemists alike, enabling the design and manipulation of molecules for a wide range of applications in industry, medicine, and materials science.

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6.1: KINDS OF ORGANIC REACTIONS

OBJECTIVE

After completing this section, you should be able to list and describe the four important “kinds” of reactions that occur in organic chemistry.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- addition reaction
- elimination reaction
- rearrangement reaction
- substitution reaction

STUDY NOTES

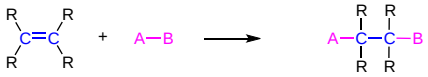
It is sufficient that you know the general form of each kind of reaction. However, given a chemical equation, you should be able to recognize which kind of reaction it involves.

If you scan any organic textbook you will encounter what appears to be a very large, often intimidating, number of reactions. These are the "tools" of a chemist, and to use these tools effectively, we must organize them in a sensible manner and look for patterns of reactivity that permit us make plausible predictions. Most of these reactions occur at special sites of reactivity known as functional groups, and these constitute one organizational scheme that helps us catalog and remember reactions.

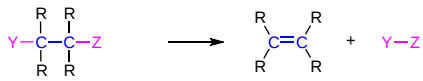
> *Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.*

First, we identify four broad classes of reactions based solely on the **structural change** occurring in the reactant molecules. This classification does not require knowledge or speculation concerning reaction paths or mechanisms. The four main reaction classes are additions, eliminations, substitutions, and rearrangements.

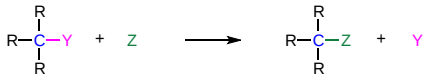
Addition Reaction



Elimination Reaction



Substitution Reaction



Rearrangement Reaction

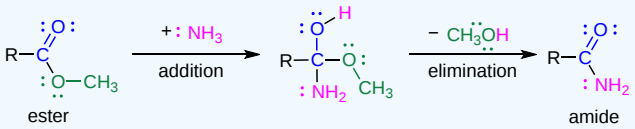


In an **addition** reaction the number of σ-bonds in the substrate molecule increases, usually at the expense of one or more π-bonds. The reverse is true of **elimination** reactions, *i.e.*the number of σ-bonds in the substrate decreases, and new π-bonds are often formed. **Substitution** reactions, as the name implies, are characterized by replacement of an atom or group (Y) by another atom or group (Z). Aside from these groups, the number of bonds does not change. A **rearrangement** reaction generates an isomer, and again the number of bonds normally does not change.

The examples illustrated above involve simple alkyl and alkene systems, but these reaction types are general for most functional groups, including those incorporating carbon-oxygen double bonds and carbon-nitrogen double and triple bonds. Some common reactions may actually be a combination of reaction types.

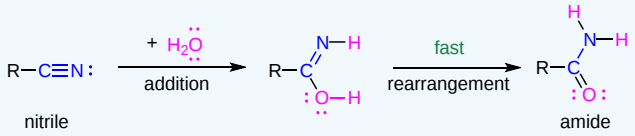
EXAMPLE 6.1.1: REACTION OF AN ESTER WITH AMMONIA

The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



EXAMPLE 6.1.2: THE ADDITION OF WATER TO A NITRILE

The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



EXERCISE 6.1.3

Classify each reaction as addition, elimination, substitution, or rearrangement.

A) $CH_3CH_2Br + LiOH \longrightarrow CH_3CH_2OH + LiBr$

B) $CH_3CH_2CH_2Cl \longrightarrow CH_3CH{=}CH_2 + HCl$

C) $CH_3CH{=}CH_2 + H_2 \longrightarrow CH_3CH_2CH_3$

Answer

A = Substitution; B = Elimination; C = Addition

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6.2: HOW ORGANIC REACTIONS OCCUR - MECHANISMS

OBJECTIVES

After completing this section, you should be able to

- explain the difference between heterolytic and homolytic bond breakage, and between heterogenic and homogenic bond formation.
- state the two reaction types involved in symmetrical and unsymmetrical processes.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- heterogenic
- heterolytic
- homogenic
- homolytic
- polar reaction
- radical reaction
- reaction mechanism

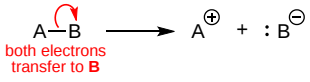
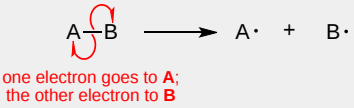
STUDY NOTES

Upon first reading first four key terms, it is easy to be puzzled. The ending of the word tells you whether a bond is being formed (-genic) or broken (-lytic), while the root of the word describes the nature of that formation or decomposition. So hetero (meaning different) reactions involve asymmetrical bond making (or breaking) and homo (meaning same) involve symmetrical processes.

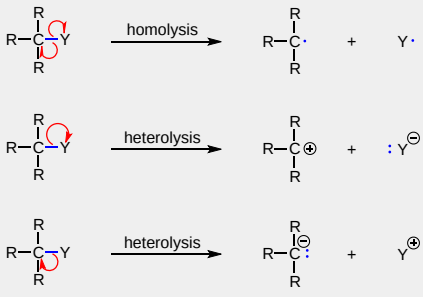
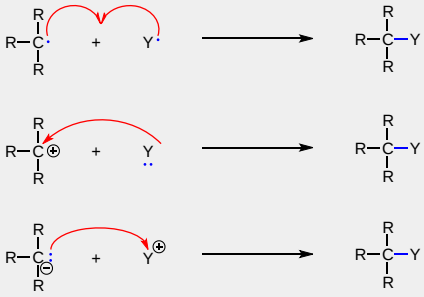
Because one pair of electrons constitutes a single bond, the unsymmetrical making or breaking of that bond in a hetero processes are described as polar reactions. Similarly, symmetrical homo processes of bond making and breaking are called radical reactions. Radicals (sometimes referred to as free radicals) are highly reactive neutral chemical species with one unpaired electron. In later sections we discuss radical and polar reactions in more detail.

THE ARROW NOTATION IN MECHANISMS

Since chemical reactions involve the breaking and making of bonds, a consideration of the movement of bonding (and non-bonding) valence shell electrons is essential to this understanding. It is now common practice to show the movement of electrons with curved arrows, and a sequence of equations depicting the consequences of such electron shifts is termed a **mechanism**. In general, two kinds of curved arrows are used in drawing mechanisms:

A full head on the arrow indicates the movement or shift of an electron pair:		
A partial head (fishhook) on the arrow indicates the shift of a single electron:		

The use of these symbols in bond-breaking and bond-making reactions is illustrated below. If a covalent single bond is broken so that one electron of the shared pair remains with each fragment, as in the first example, this bond-breaking is called **homolysis**. If the bond breaks with both electrons of the shared pair remaining with one fragment, as in the second and third examples, this is called **heterolysis**.

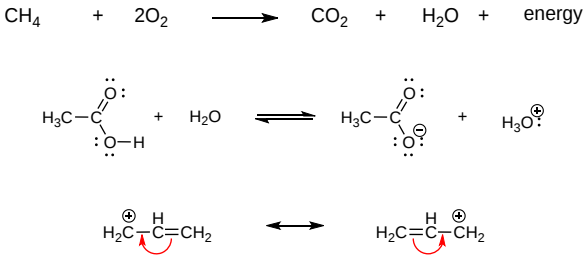
Bond-Breaking	Bond-Making
	

OTHER ARROW SYMBOLS

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

The Reaction Arrow	The Equilibrium Arrow	The Resonance Arrow
		

The following equations illustrate the proper use of these symbols:



REACTIVE INTERMEDIATES

The products of bond breaking, shown above, are not stable in the usual sense, and cannot be isolated for prolonged study. Such species are referred to as **reactive intermediates**, and are believed to be transient intermediates in many reactions. The general structures and names of four such intermediates are given below.

Charged Intermediates	Uncharged Intermediates
 a carbocation	 a radical
 a carbanion	 a carbene

A pair of widely used terms, related to the Lewis acid-base notation, should also be introduced here.

- Electrophile: An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile.
- Nucleophile: An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile (or Lewis acid).

Using these definitions, it is clear that carbocations (called carbonium ions in the older literature) are electrophiles and carbanions are nucleophiles. Carbenes have only a valence shell sextet of electrons and are therefore electron deficient. In this sense they are electrophiles, but the non-bonding electron pair also gives carbenes nucleophilic character. As a rule, the electrophilic character dominates carbene reactivity. Carbon radicals have only seven valence electrons, and may be considered electron deficient; however, they do not in general bond to nucleophilic electron pairs, so their chemistry exhibits unique differences from that of conventional electrophiles. Radical intermediates are often called **free radicals**.

The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, since ionic reactants or products are often involved. Some common examples of ionic reactions and their mechanisms may be examined below.

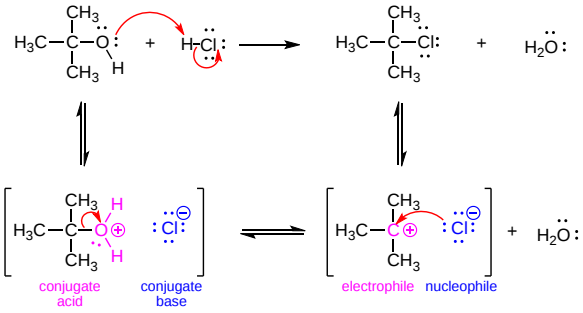
The shapes ideally assumed by these intermediates becomes important when considering the stereochemistry of reactions in which they play a role. A simple tetravalent compound like methane, CH_4, has a tetrahedral configuration. Carbocations have only three bonds to the charge bearing carbon, so it adopts a planar trigonal configuration. Carbanions are pyramidal in shape (tetrahedral if the electron pair is viewed as a substituent), but these species invert rapidly at room temperature, passing through a higher energy planar form in which the electron pair occupies a p-orbital. Radicals are intermediate in configuration, the energy difference between pyramidal and planar forms being very small. Since three points determine a plane, the shape of carbenes must be planar; however, the valence electron distribution varies.

IONIC REACTIONS

The principles and terms introduced in the previous sections can now be summarized and illustrated by the following three examples. Reactions such as these are called **ionic** or **polar** reactions, because they often involve charged species and the bonding together of **electrophiles and nucleophiles**. Ionic reactions normally take place in liquid solutions, where solvent molecules assist the formation of charged intermediates.

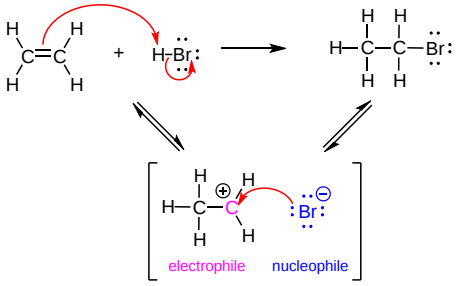
SUBSTITUTION REACTION

The substitution reaction shown below can be viewed as taking place in three steps. The first is an acid-base equilibrium, in which HCl protonates the oxygen atom of the alcohol. The resulting conjugate acid then loses water in a second step to give a carbocation intermediate. Finally, this electrophile combines with the chloride anion nucleophile to give the final product.



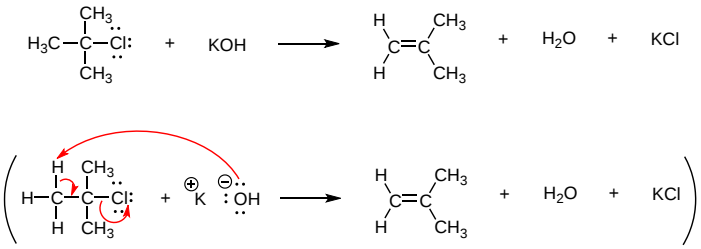
ADDITION REACTION

The addition reaction shown below can be viewed as taking place in two steps. The first step can again be considered an acid-base equilibrium, with the pi-electrons of the carbon-carbon double bond functioning as a base. The resulting conjugate acid is a carbocation, and this electrophile combines with the nucleophilic bromide anion.



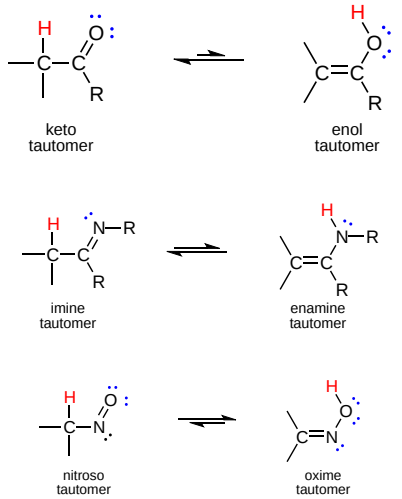
ELEMINATION REACTION

The elimination reaction shown below takes place in one step. The bond breaking and making operations that take place in this step are described by the curved arrows. The initial stage may also be viewed as an acid-base interaction, with hydroxide ion serving as the base and a hydrogen atom component of the alkyl chloride as an acid. **rearrangement** (tautomerism)



TAUTOMERIZATION REACTION

There are many kinds of molecular rearrangements. The examples shown below are from an important class called **tautomerization** or, more specifically, keto-enol tautomerization. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidence for the presence of the minor tautomer comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are generally present in most chemical samples.



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6.3: RADICAL REACTIONS

OBJECTIVES

After completing this section, you should be able to

- give an example of a radical substitution reaction.
- identify the three steps (initiation, propagation and termination) that occur in a typical radical substitution reaction.
- write out the steps involved in a simple radical substitution reaction, such as the chlorination of methane.
- explain why the halogenation of an alkane is not a particularly useful method of preparing specific alkyl halides.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chain reaction
- initiation step
- propagation step
- radical substitution
- termination step

STUDY NOTES

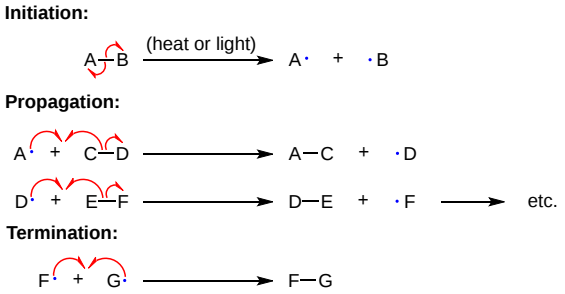
A *radical substitution reaction* is a reaction which occurs by a free radical mechanism and results in the substitution of one or more of the atoms or groups present in the substrate by different atoms or groups.

The *initiation step* in a radical chain reaction is the step in which a free radical is first produced. A *termination step* of a radical chain reaction is one in which two radicals react together in some way so that the chain can no longer be propagated.

While radical halogenation of very simple alkanes can be an effective synthetic strategy, it cannot be employed for larger more complex alkanes to yield specific alkyl halides, since the reactive nature of radicals always leads to mixtures of single- and multiple-halogenated products.

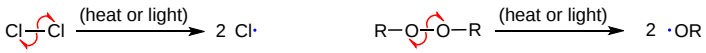
THE THREE PHASES OF RADICAL CHAIN REACTIONS

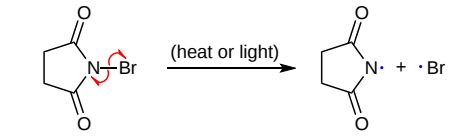
Because of their high reactivity, free radicals have the potential to be both extremely powerful chemical tools and extremely harmful contaminants. Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction fashion. **Radical chain reactions** have three distinct phases: initiation, propagation, and termination.



The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage event, and takes place very rarely due to the high energy barriers involved. Often the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

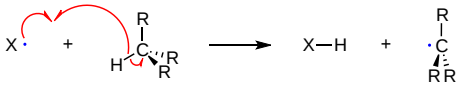
Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups which also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).

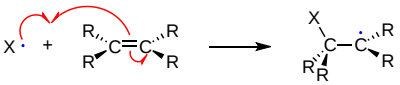




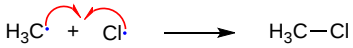
N-bromosuccinimide
(NBS)

The **propagation phase** describes the 'chain' part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. Propagation steps often involve hydrogen abstraction or addition of the radical to double bonds.





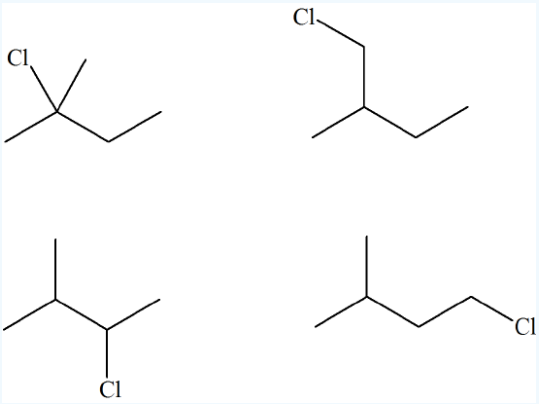
Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. In other words, the Gibbs free energy barrier is very high for this reaction, mostly due to entropic rather than enthalpic considerations. The active sites of enzymes, of course, can evolve to overcome this entropic barrier by positioning two radical intermediates adjacent to one another.



? EXERCISE 6.3.1

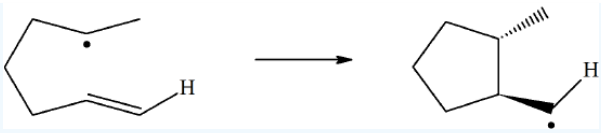
Radical chlorination of alkanes are not useful due to uncontrolled substitution. Draw the mono-substituted products of Cl_2 reacting with 2-methylbutane.

Answer



? EXERCISE 6.3.2

Propose a radical mechanism for the following reaction:



Answer



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6.4: POLAR REACTIONS

OBJECTIVES

After completing this section, you should be able to

- identify the positive and negative ends of the bonds present in the common functional groups.
- explain how bond polarity can be enhanced by the interaction of a functional group with a solvent, metal cation or acid.
- explain how the polarizability of an atom can be an important factor in determining the reactivity of a bond.
- describe the heterolytic bond-breaking process.
- use curved (curly) arrows to indicate the movement of electron pairs during bond breakage and bond formation.
- predict whether a given species (compound or ion) is likely to behave as a nucleophile or as an electrophile.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electrophile
- nucleophile
- polar reaction
- polarizability

STUDY NOTES

You may wish to review Section 2.1 before you begin this section. The relative electronegativities of the elements shown in the periodic table should already be familiar. Remember that it is the relative electronegativities that are important, not the actual numerical values.

Make sure that you understand the polarity patterns of the common functional groups. Do not try to memorize these polarities; rather, concentrate on why they arise. You will encounter these group polarities so frequently that they will soon become “second nature” to you.

HALOGENS AND THE CHARACTER OF THE CARBON-HALOGEN BOND

With respect to electronegativity, most halogens are more electronegative than carbon. This results in a carbon-halogen bond that is polarized. As shown in the image below, the carbon atom has a partial positive charge, while the halogen has a partial negative charge.



The following table shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

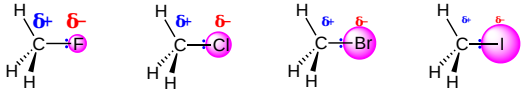
Electronegativity	I < Br < Cl < F

The following table shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.

Bond length	C–F < C–Cl < C–Br < C–I
Bond strength	C–I < C–Br < C–Cl < C–F
Molecular size	F < Cl < Br < I

THE INFLUENCE OF BOND POLARITY

Of the four halogens, fluorine is the most electronegative and iodine the least. That means that the electron pair in the carbon-fluorine bond will be dragged most towards the halogen end. Looking at the methyl halides as simple examples:



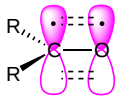
The electronegativities of carbon and iodine are not very different, and so there will be little separation of charge on the bond. One of the important set of reactions of alkyl halides involves replacing the halogen by something else - substitution reactions. These reactions can involve the carbon-halogen bond breaking to give positive and negative ions. The ion with the positively charged carbon atom then reacts with something either fully or slightly negatively charged. Alternatively, something either fully or negatively charged is attracted to the slightly positive carbon atom and pushes off the halogen atom.

You might have thought that either of these would be more effective in the case of the carbon-fluorine bond with the quite large amounts of positive and negative charge already present. But that's not so - quite the opposite is true! The thing that governs the reactivity is the strength of the bonds which have to be broken. It is difficult to break a carbon-fluorine bond, but easy to break a carbon-iodine one.

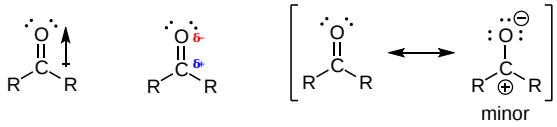
THE CARBONYL GROUP

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.

Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming overlaps with orbitals on the oxygen and on the two carbon or hydrogen atoms. These three bonds adopt trigonal planar geometry. The remaining unhybridized 2p orbital on the central carbonyl carbon is perpendicular to this plane, and forms a ‘side-by-side’ pi bond with a 2p orbital on the oxygen.

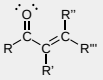


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and the carbonyl carbon a partial positive charge.



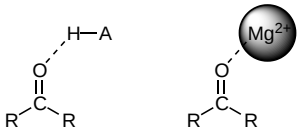
A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pbond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.

SOME CARBONYL COMPOUNDS

Compound	aldehyde	ketone	formaldehyde	carboxylic acid	ester	amide	enone	acyl halide	acid anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R"	RC(O)C(R')CR"R"'	RCOX	RCO_2COR'

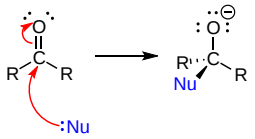
NUCLEOPHILIC ADDITION TO ALDEHYDES AND KETONES

The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond’s polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen.

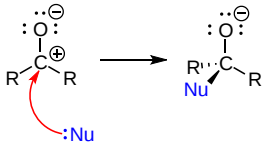


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen. Unlike the situation in a nucleophilic substitution reaction, when a nucleophile attacks an aldehyde or ketone carbon there is no leaving group – the incoming

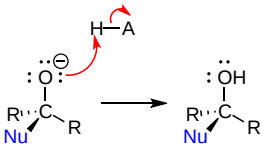
nucleophile simply ‘pushes’ the electrons in the pi bond up to the oxygen.



Alternatively, if you start with the minor resonance contributor, you can picture this as an attack by a nucleophile on a carbocation.



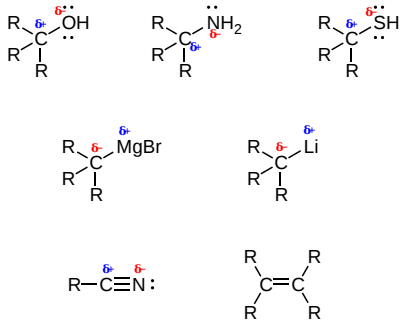
After the carbonyl is attacked by the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. However, most commonly the oxygen acts instead as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site.



This very common type of reaction is called a **nucleophilic addition**. In many biologically relevant examples of nucleophilic addition to carbonyls, the nucleophile is an alcohol oxygen or an amine nitrogen, or occasionally a thiol sulfur. In one very important reaction type known as an aldol reaction, the nucleophile attacking the carbonyl is a resonance-stabilized carbanion. In this chapter, we will concentrate on reactions where the nucleophile is an oxygen or nitrogen.

1. Nucleophilic Addition to Aldehydes and Ketones
2. Nucleophilic Substitution of RCOZ (Z = Leaving Group)
3. General reaction
4. General mechanism

POLARITY PATTERNS IN OTHER COMMON FUNCTIONAL GROUPS



NUCLEOPHILE?

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

More specifically in laboratory reactions, halide and azide (N_3^-) anions are commonly seen acting as nucleophiles.

Of course, carbons can also be nucleophiles - otherwise how could new carbon-carbon bonds be formed in the synthesis of large organic molecules like DNA or fatty acids? Enolate ions (section 7.5) are the most common carbon nucleophiles in biochemical reactions, while the cyanide ion (CN^-) is just one example of a carbon nucleophile commonly used in the laboratory. Reactions with carbon nucleophiles will be dealt with in chapters 13 and 14, however - in this chapter and the next, we will concentrate on non-carbon nucleophiles.

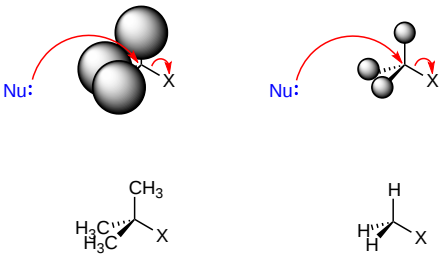
When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

Neutral Nucleophiles	Charged Nucleophiles
H_2O, NH_3, RNH_2, R_2NH, R_3N, ROH, RCOOH, RSH, and PR_3	$^{\ominus}OH$, $^{\ominus}OR$, $^{\ominus}NH_2$, $^{\ominus}NHR$, $^{\ominus}NR_2$, $^{\ominus}SH$, $^{\ominus}SR$, $^{\ominus}SeR$, $^{\ominus}Cl$, $^{\ominus}Br$, $^{\ominus}I$, $^{\ominus}F$, $^{\ominus}CN$, $RCOO^{\ominus}$

ELECTROPHILES

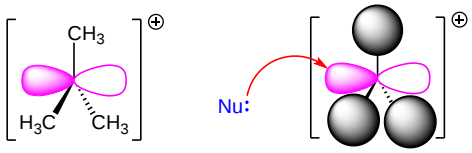
In the vast majority of the nucleophilic substitution reactions you will see in this and other organic chemistry texts, the electrophilic atom is a carbon which is bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom is an attractive target for something that is electron-rich, *i.e.* a nucleophile. However, we must also consider the effect of steric hindrance on electrophilicity. In addition, we must discuss how the nature of the electrophilic carbon, and more specifically the stability of a potential carbocationic intermediate, influences the S_N1 vs. S_N2 character of a nucleophilic substitution reaction.

Consider two hypothetical S_N2 reactions: one in which the electrophile is a methyl carbon and another in which it is tertiary carbon.



Because the three substituents on the methyl carbon electrophile are tiny hydrogens, the nucleophile has a relatively clear path for backside attack. However, backside attack on the tertiary carbon is blocked by the bulkier methyl groups. Once again, steric hindrance - this time caused by bulky groups attached to the electrophile rather than to the nucleophile - hinders the progress of an associative nucleophilic (S_N2) displacement.

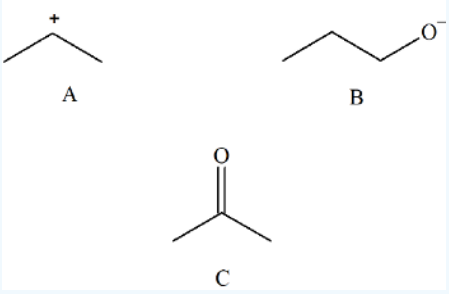
The factors discussed in the above paragraph, however, do not prevent a sterically-hindered carbon from being a good electrophile - they only make it less likely to be attacked in a *concerted S_N2 reaction*. Nucleophilic substitution reactions in which the electrophilic carbon is sterically hindered are more likely to occur by a two-step, dissociative (S_N1) mechanism. This makes perfect sense from a geometric point of view: the limitations imposed by sterics are significant mainly in an S_N2 displacement, when the electrophile being attacked is a sp^3-hybridized tetrahedral carbon with its relatively 'tight' angles of 109.4°. Remember that in an S_N1 mechanism, the nucleophile attacks an sp^2-hybridized carbocation intermediate, which has trigonal planar geometry with 'open' 120 angles.



With this open geometry, the empty p orbital of the electrophilic carbocation is no longer significantly shielded from the approaching nucleophile by the bulky alkyl groups. A carbocation is a very potent electrophile, and the nucleophilic step occurs very rapidly compared to the first (ionization) step.

? EXERCISE 6.4.1

Label the following either an electrophile or a nucleophile.



Answer

A = Electrophile

B = Nucleophile

C = Both (carbonyl carbon is electrophile and oxygen is nucleophile)

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6.5: AN EXAMPLE OF A POLAR REACTION - ADDITION OF HBR TO ETHYLENE

OBJECTIVES

After completing this section, you should be able to

- give an example of a simple polar reaction (e.g., a electrophilic addition).
- identify the electrophile and nucleophile in a simple polar reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electrophilic addition
- carbocation

STUDY NOTES

The curved arrows introduced in this section are used throughout the course to indicate the movement of electron pairs. It takes practice for the beginning student to feel comfortable using these arrows. Remember that the head of the arrow indicates where the electron pair moves to; its tail shows where the electron pair comes from. (Chemists often refer to the use of curved arrows as “electron pushing.")

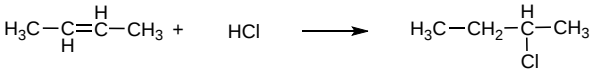
This page looks at the reaction of the carbon-carbon double bond in alkenes such as ethene with hydrogen halides such as hydrogen chloride and hydrogen bromide. Symmetrical alkenes (like ethene or but-2-ene) are dealt with first. These are alkenes where identical groups are attached to each end of the carbon-carbon double bond.

ADDITION TO SYMMETRICAL ALKENES

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other. For example, with ethene and hydrogen chloride, you get chloroethane:



With but-2-ene you get 2-chlorobutane:

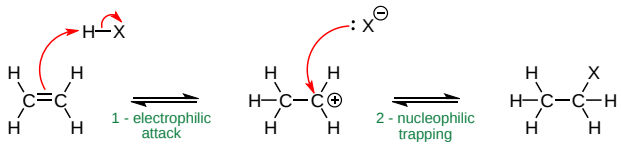


What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space. That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

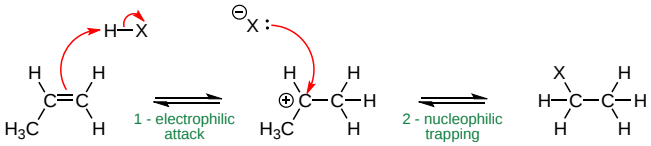
MECHANISM

The addition of hydrogen halides is one of the easiest electrophilic addition reactions because it uses the simplest electrophile: the proton. Hydrogen halides provide both an electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of pi electrons, attaching it to the molecule (1). This is basically the reverse of the last step in the E1 reaction (deprotonation step). The resulting molecule will have a single carbon-carbon bond with a positive charge on one of them (carbocation). The next step is when the nucleophile (halide) bonds to the carbocation, producing a new molecule with both the original hydrogen and halide attached to the organic reactant (2). The second step will only occur if a good nucleophile is used.

Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene



Mechanism of Electrophilic Addition of Hydrogen Halide to Propene

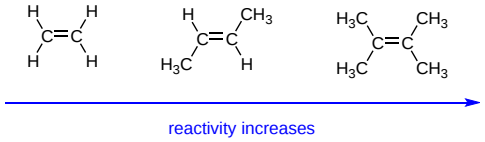


All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

REACTION RATES

Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions. When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

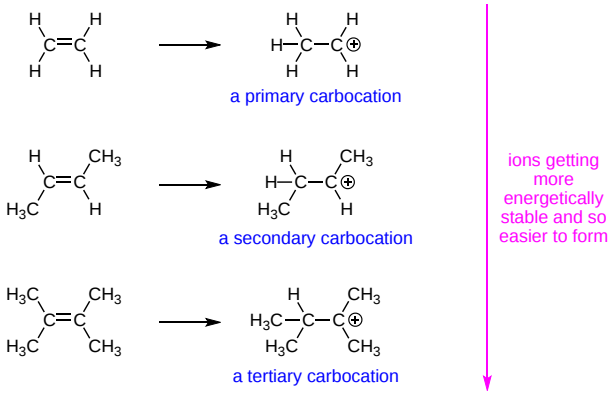
This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be. Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:



There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this. Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes.

The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride. The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:

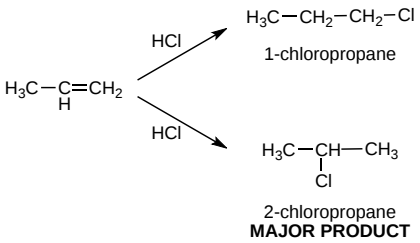


The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

ADDITION TO UNSYMMETRICAL ALKENES

In terms of reaction conditions and the factors affecting the rates of the reaction, there is no difference whatsoever between these alkenes and the symmetrical ones described above. The problem comes with the orientation of the addition - in other words, which way around the hydrogen and the halogen add across the double bond.

If HCl adds to an unsymmetrical alkene like propene, there are two possible ways it could add. However, in practice, there is only one major product.



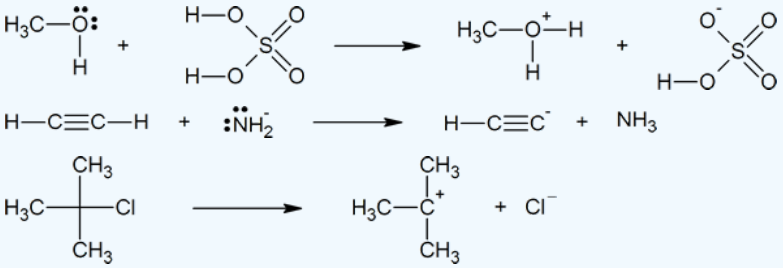
This is in line with Markovnikov's Rule which says:

> When a compound HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already.

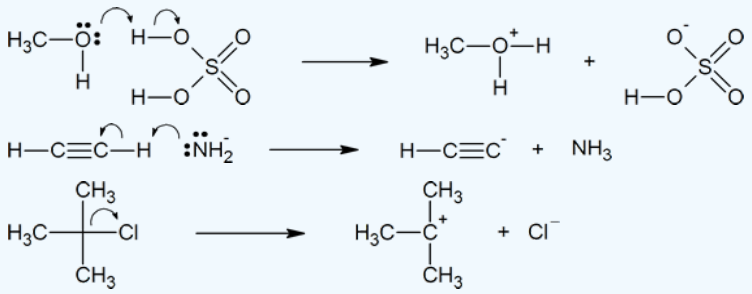
In this case, the hydrogen becomes attached to the CH_2 group, because the CH_2 group has more hydrogens than the CH group. Notice that only the hydrogens directly attached to the carbon atoms at either end of the double bond count. The ones in the CH_3 group are totally irrelevant.

EXERCISE 6.5.1

Supply the missing curved arrows in the equations given below.

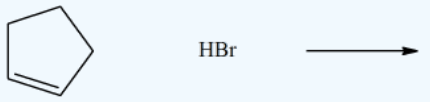


Answer



EXERCISE 6.5.2

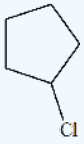
Predict the product of the following reactions:





Answer





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6.6: USING CURVED ARROWS IN POLAR REACTION MECHANISMS

OBJECTIVE

After completing this section, you should be able to use curved (curly) arrows, in conjunction with a chemical equation, to show the movement of electron pairs in a simple polar reaction, such as electrophilic addition.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electrophlic
- nucleophlic

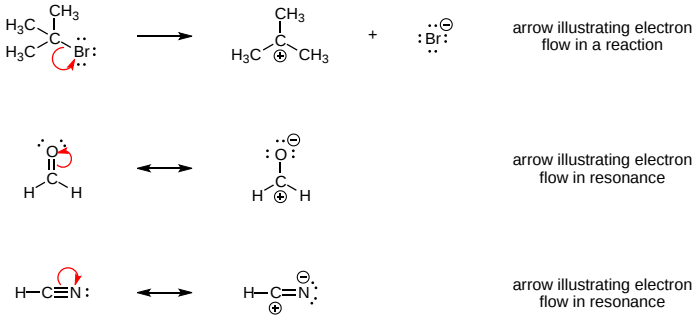
PUSHING ELECTRONS AND CURVED ARROWS

Understanding the location of electrons and being able to draw the curved arrows that depict the mechanisms by which the reactions occur is one of the most critical tools for learning organic chemistry since they allow you to understand what controls reactions, and how reactions proceed.

Before you can do this you need to understand that a **bond** is due to a pair of electrons shared between atoms. When asked to draw a mechanism, curved arrows should be used to show all the bonding changes that occur. A few simple lessons that illustrate these concepts can be found below.

LESSON 1

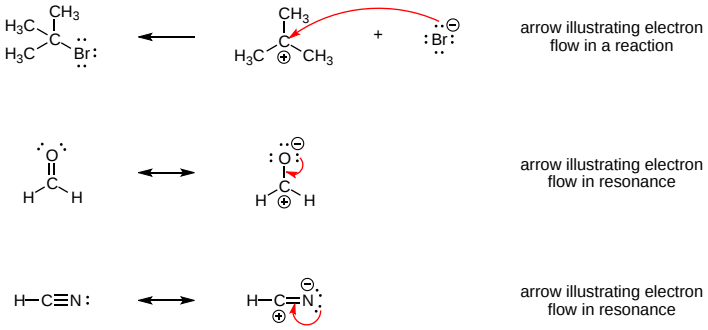
If we remove the pair of electrons in a bond, then we BREAK that bond. This is true for single and multiple bonds as shown below:



Notice that since the starting materials were *neutral*, the products are also *neutral*. In general terms, the *sum of the charges* on the starting materials MUST equal the *sum of the charges* on the products since we have the **same number of electrons**.

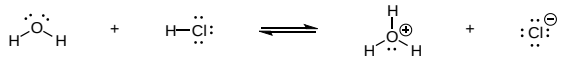
The first example is a REACTION since we broke a sigma bond. In the second two examples, we moved pi electrons into long pairs. This is RESONANCE.

If we move electrons between two atoms, then we MAKE a new bond:

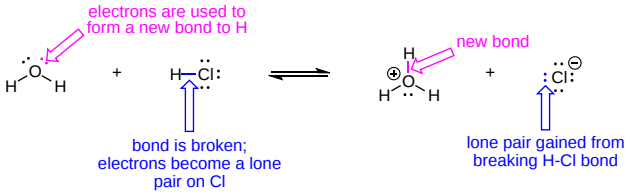


We always show electrons moving from **electron rich** to **electron poor**.

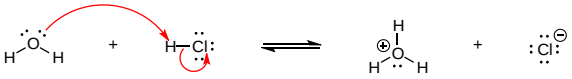
LESSON 2



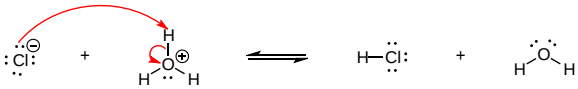
This is a simple acid/base reaction, showing the formation of the hydronium ion produced when hydrochloric acid is dissolved in water. It is useful to analyze the bond changes that are occurring. Water is functioning as a **base** and hydrochloric acid as an **acid**. Consider the differences in bonding between the starting materials and the products:



One of the lone pairs on the oxygen atom of water was used to form a bond to a hydrogen atom, creating the hydronium ion (H_3O^+) seen in the products. The hydrogen-chlorine bond of HCl was broken, and the electrons in this bond became a lone pair on the chlorine atom, thus generating a chloride ion. We can illustrate these changes in bonding using the curved arrows shown below.



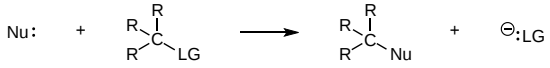
Note that in this diagram, the overall charge of the reactants is the same as the overall charge of the products. We can also show the curved arrows for the reverse reaction:



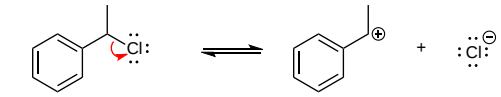
This shows the formation of the new H-Cl bond by using a lone pair of electrons from the electron-rich chloride ion to form a bond to an electron poor hydrogen atom of the hydronium ion. Because hydrogen can only form one bond, the oxygen-hydrogen bond is broken and its electrons become a lone pair on the electron-poor oxygen atom. Notice that the charges balance!

LESSON 3

In this section, we will look at the curved arrows for some nucleophilic substitution reactions. Overall, the processes involved are similar to those for the acid/base reactions described above. In a nucleophilic substitution reaction, an electron-rich nucleophile (Nu) becomes bonded to an electron-poor carbon atom, and a leaving group (LG) is displaced. In bonding terms, we must *make* a Nu-C bond and *break* a C-LG bond.

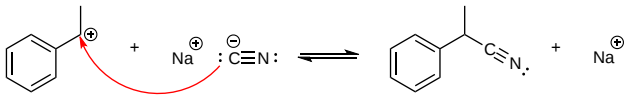


Let's consider the stepwise S_N1 reaction between (1-chloroethyl)benzene and sodium cyanide. The first step of this process is breaking the C-Cl bond, where the electrons in that bond become a lone pair on the chlorine atom. The carbon atom has lost electrons and therefore becomes positive, generating a secondary carbocation. Because the chlorine atom gained an additional lone pair of electrons, it becomes a negatively charged chloride ion.

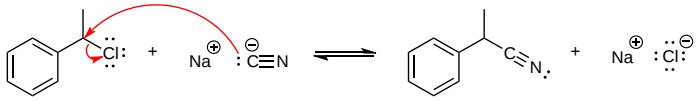


(1-chloroethyl)benzene

In the second step, the electron-rich nucleophile donates electrons to form a new C-C bond with the electron-poor secondary carbocation.



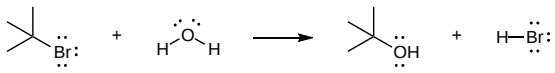
In an S_N2 reaction, the bond forming and breaking processes occur simultaneously. The scheme below shows the Nu donating electrons to form a new C-C bond at the same time that the C-Cl bond is breaking. The electrons in the C-Cl bond become a long pair on the chlorine atom, generating a chloride ion. Forming and breaking the bonds simultaneously allows carbon to obey the octet rule throughout this process.



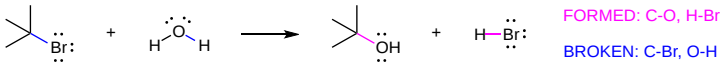
Notice that in all steps for the processes above, the overall charges of the starting materials match those of the products.

LESSON 4

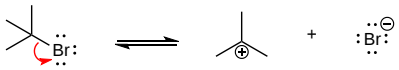
This section will dissect another substitution reaction, although it is more involved. Let's consider the S_N1 reaction of *tert*-butyl bromide with water.



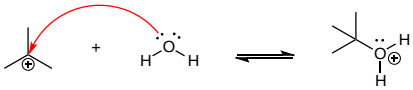
It can be helpful to take inventory of which bonds have been formed, and which bonds have been broken.



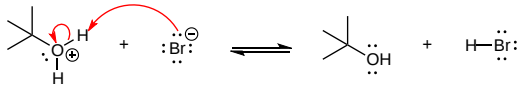
The curved arrows we draw must account for ALL of these bonding changes. Since we are dealing with an S_N1 reaction process, the first step will be cleavage of the C-Br bond to give a carbocation and and a bromide anion.



Water then acts as a nucleophile, using one of its lone pairs to form a bond to the electron-poor *t*-butyl cation. This generates an oxonium ion, where oxygen has three bonds and a positive formal charge.

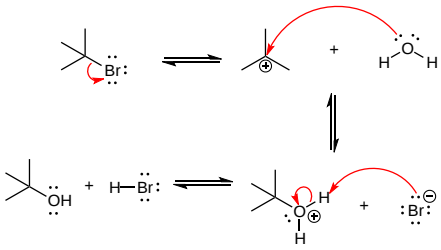


The final step is an acid/base reaction between the bromide anion generated in step 1 and the oxonium product of step 2. The bromide anion acts as a base, using a lone pair to form a bond to one of the hydrogen atoms. The O-H bond then breaks, and its electrons become a lone pair on oxygen. This gives the final products of HBr and *t*-butyl alcohol.

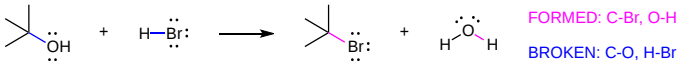


Notice that in each of the mechanistic steps above, the overall charge of the reactant side balances with the overall charge of the product side.

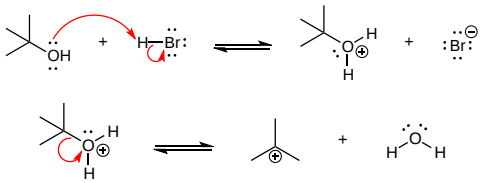
While the above process was broken down into distinct steps, however it is important to note that mechanisms are almost always shown as a continuous process. The overall mechanism for this processes can be found below:



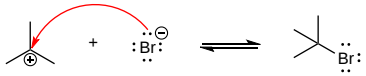
Now consider the reverse reaction, i.e. the reaction of *t*-butyl alcohol with hydrobromic acid to generate *t*-butyl bromide and water. The scheme is shown below, along with an analysis of the bonds formed and broken in this process:



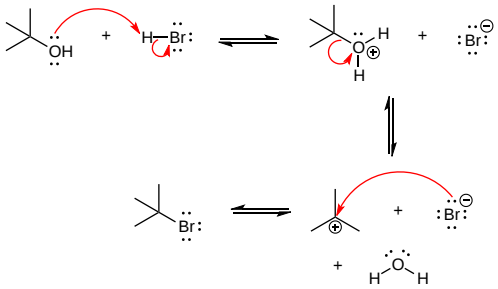
The mechanism must occur via the same pathway as shown above (Law of Macroscopic Reversibility), however this mechanism can still be deduced without knowing that. First, it is known that HBr is a strong acid and can donate a proton to a base. The most basic sites in the whole system are the lone pairs on the oxygen atom of *t*-butanol. Since the lone pairs are the electron-rich area of the molecule, the arrow starts at a lone pair and ends at the proton of HBr. The H-Br bond breaks, pushing its electrons onto the bromine atom and generating a bromide ion.



The bromide ion generated in the first step can then react with the *t*-butyl cation to generate *t*-butyl bromide.



Once again, the above the overall process is broken down into individual steps, however it is more common to illustrate this as one overall process:

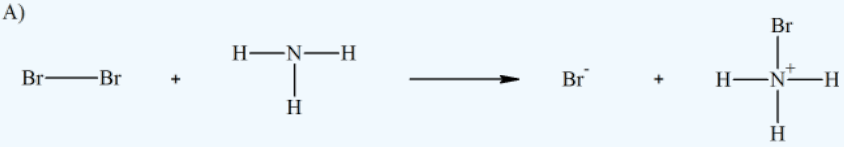


CURVED ARROW SUMMARY

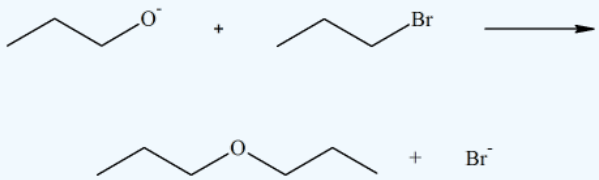
- Curved arrows flow from electron rich to electron poor.
- Therefore they start from lone pairs or bonds.
- The charges in any particular step should always be balanced.
- Remember to obey the rules of valence (*eg*. octet rule for C,N,O,F *etc*.)
- If electrons are taken out of a bond, then that bond is broken.
- If electrons are placed between two atoms then it implies a bond is being made.

EXERCISE 6.6.1

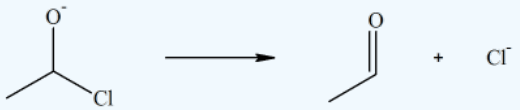
A)



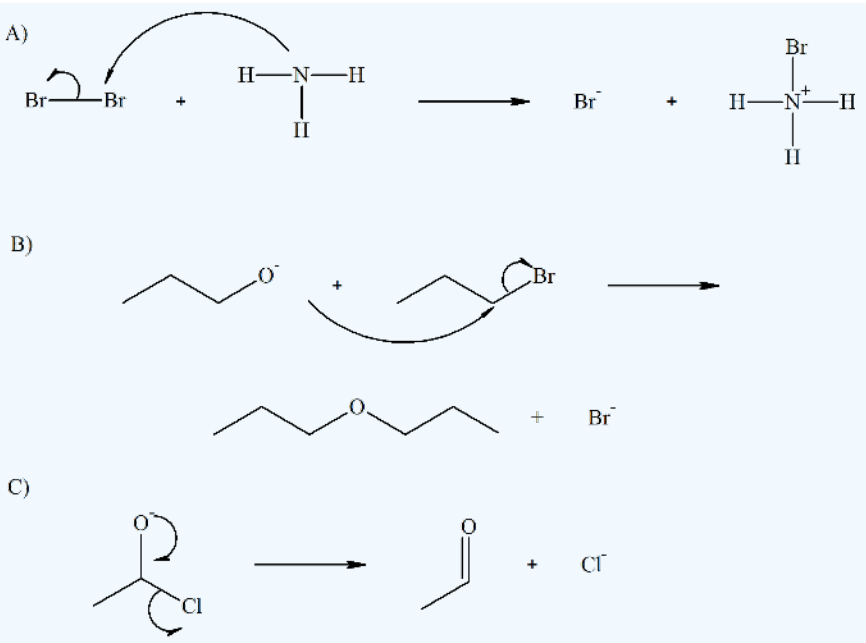
B)



C)



Answer



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6.7: DESCRIBING A REACTION - EQUILIBRIA, RATES, AND ENERGY CHANGES

OBJECTIVES

After completing this section, you should be able to

- write the equilibrium constant expression for a given reaction.
- assess, qualitatively, how far a reaction will proceed in a given direction, given the value of K_{eq}.
- explain the difference between rate and equilibrium.
- state the relationship between $\Delta G°$ and K_{eq}, and use this relationship to determine the value of either of the two variables, given the other.
- state the relationship between Gibbs free-energy, enthalpy and entropy, and use the relationship to calculate any one of $\Delta G°$, $\Delta H°$ and $\Delta S°$, given the other two.
- make a qualitative assessment of whether $\Delta S°$ for a given process is expected to be positive or negative.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- exergonic
- endergonic
- exothermic
- endothermic
- enthalpy change (heat of reaction), $\Delta H°$
- entropy change, $\Delta S°$
- reaction mechanism
- standard Gibbs free-energy change, $\Delta G°$

STUDY NOTES

Throughout this course you will be paying a great deal of attention to the mechanisms of the reactions that you study. Some students see this as a laborious task of little practical use. However, you will find that a knowledge of reaction mechanisms can help reduce the number of reactions to memorize, provide a connecting link between apparently unrelated reactions, and enable someone with a basic knowledge of organic chemistry to deduce how a previously unseen reaction might proceed. The investigation of reaction mechanisms is a popular research area for organic chemists.

EQUILIBRIUM CONSTANT

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b}$$

The notation [A] signifies the molar concentration of species A. An alternative expression for the equilibrium constant involves partial pressures:

$$K_P = \frac{P_C^c P_D^d}{P_A^a P_B^b}$$

Note that the expression for the equilibrium constant includes only solutes and gases; pure solids and liquids do not appear in the expression. For example, the equilibrium expression for the reaction

$$\mathrm{CaH_2\,(s) + 2\,H_2O\,(g) \rightleftharpoons Ca(OH)_2\,(s) + 2\,H_2\,(g)}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2}$$

Observe that the gas-phase species H_2O and H_2 appear in the expression but the solids CaH_2 and $Ca(OH)_2$ do not appear.

The equilibrium constant is most readily determined by allowing a reaction to reach equilibrium, measuring the concentrations of the various solution-phase or gas-phase reactants and products, and substituting these values into the Law of Mass Action.

FREE ENERGY

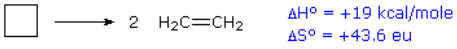
The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called Free Energy (or Gibbs Free Energy), symbol ΔG, is defined as shown in the first equation below. Two things should be apparent from this equation. First, in cases where the entropy change is small, $\Delta G \cong \Delta H$. Second, the importance of ΔS in determining ΔG increases with increasing temperature.

$$\Delta G^o = \Delta H^o - T\Delta S^o$$

where the temperature is measured in absolute temperature (K).

The free energy function provides improved insight into the thermodynamic driving forces that influence reactions. A negative ΔG^o is characteristic of an **exergonic reaction**, one which is thermodynamically favorable and often spontaneous, as is the melting of ice at 1 ºC. Likewise a positive ΔG^o is characteristic of an **endergonic reaction**, one which requires an input of energy from the surroundings.

For an example of the relationship of free energy to enthalpy consider the decomposition of cyclobutane to ethene, shown in the following equation. The standard state for all the compounds is gaseous.



This reaction is endothermic, but the increase in number of molecules from one (reactants) to two (products) results in a large positive ΔSº.

At 25 ºC (298 K):

ΔGº = 19 kcal/mol – 298(43.6) cal/mole = 19 – 13 kcal/mole = +6 kcal/mole.

Thus, the entropy change opposes the enthalpy change, but is not sufficient to change the sign of the resulting free energy change, which is endergonic. Indeed, cyclobutane is perfectly stable when kept at room temperature.

Because the entropy contribution increases with temperature, this energetically unfavorable transformation can be made favorable by raising the temperature. At 200 ºC (473 K),

$$\Delta G^o = 19\,kcal/mol - 473(43.6)\,cal/mole \quad (6.7.1)$$
$$= 19 - 20.6\,kcal/mole \quad (6.7.2)$$
$$= -1.6 kcal/mole. \quad (6.7.3)$$

This is now an **exergonic reaction**, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

$$\Delta G^o = -RT \ln K = -2.303 RT \log_{10} K \quad (6.7.4)$$

where R = 1.987 cal/ K mole T = temperature in K and K = equilibrium constant

NOTE

Equation 6.7.4 is important because it demonstrates the fundamental relationship of ΔG^o to the equilibrium constant, K. Because of the negative logarithmic relationship between these variables, a negative ΔGº generates a K>1, whereas a positive ΔGº generates a K<1. When ΔGº = 0, K = 1. Furthermore, small changes in ΔGº produce large changes in K. A change of 1.4 kcal/mole in ΔGº changes K by approximately a factor of 10. This interrelationship may be explored with the calculator on the right. Entering free energies outside the range -8 to 8 kcal/mole or equilibrium constants outside the range 10^{-6} to 900,000 will trigger an alert, indicating the large imbalance such numbers imply.

? EXERCISE 6.7.1

At 155°C, the equilibrium constant, K_{eq}, for the reaction

CH3CO2H + CH3CH2OH <=> CH3CO2CH2CH3 + H2O

has a value of 4.0. Calculate $\Delta G°$ for this reaction at 155°C.

EXERCISE 6.7.2

Acetylene (C_2H_2) can be converted into benzene (C_6H_6) according to the equation:

You can't use 'macro parameter character #' in math mode

At 25°C, $\Delta G°$ for this reaction is −503 kJ and $\Delta H°$ is −631 kJ. Determine $\Delta S°$ and indicate whether the size of $\Delta S°$ agrees with what you would have predicted simply by looking at the chemical equation.

Answer

The entropy change is negative, as one would expect from looking at the chemical equation, since three moles of reactants yield one mole of product; that is, the system becomes much more “ordered” as it goes from reactants to products.

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6.8: DESCRIBING A REACTION - BOND DISSOCIATION ENERGIES

OBJECTIVES

After completing this section, you should be able to

- predict the value of $\Delta H°$ for a gas-phase reaction, given the necessary bond dissociation energy data.
- predict the dissociation energy of a particular bond, given $\Delta H°$ for a reaction involving the bond and any other necessary bond dissociation energy data.
- outline the limitations of using bond dissociation energies to predict whether or not a given reaction will occur.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bond dissociation energy
- solvation

STUDY NOTES

The idea of calculating the standard enthalpy of a reaction from the appropriate bond dissociation energy data should be familiar to you from your first-year chemistry course.

Solvation is the interaction between solvent molecules and the ions or molecules dissolved in that solvent.

The homolytic bond dissociation energy is the amount of energy needed to break apart one mole of covalently bonded gases into a pair of radicals. The SI units used to describe bond energy are kiloJoules per mole of bonds (kJ/Mol). It indicates how strongly the atoms are bonded to each other.

INTRODUCTION

Breaking a covalent bond between two partners, A-B, can occur either heterolytically, where the shared pair of electron goes with one partner or another

$$A-B \rightarrow A^{+} + B:^{-}$$

or

$$A-B \rightarrow A:^{-} + B^{+}$$

or homolytically, where one electron stays with each partner.

$$A-B \rightarrow A^{\bullet} + B^{\bullet}$$

The products of homolytic cleavage are radicals and the energy that is required to break the bond homolytically is called the Bond Dissociation Energy (BDE) and is a measure of the strength of the bond.

CALCULATION OF THE BDE

The BDE for a molecule A-B is calculated as the difference in the enthalpies of formation of the products and reactants for homolysis

$$BDE = \Delta_f H(A^{\bullet}) + \Delta_f H(B^{\bullet}) - \Delta_f H(A-B)$$

Officially, the IUPAC definition of bond dissociation energy refers to the energy change that occurs at 0 K, and the symbol is D_o. However, it is commonly referred to as BDE, the bond dissociation energy, and it is generally used, albeit imprecisely, interchangeably with the bond dissociation *enthalpy*, which generally refers to the enthalpy change at room temperature (298K). Although there are technically differences between BDEs at 0 K and 298 K, those difference are not large and generally do not affect interpretations of chemical processes.

BOND BREAKAGE/FORMATION

Bond dissociation energy (or enthalpy) is a state function and consequently does not depend on the path by which it occurs. Therefore, the specific mechanism in how a bond breaks or is formed does not affect the BDE. Bond dissociation energies are useful in assessing the

energetics of chemical processes. For chemical reactions, combining bond dissociation energies for bonds formed and bonds broken in a chemical reaction using Hess's Law can be used to estimate reaction enthalpies.

EXAMPLE 6.8.1: CHLORINATION OF METHANE

Consider the chlorination of methane

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

the overall reaction thermochemistry can be calculated exactly by combining the BDEs for the bonds broken and bonds formed

$$CH_4 \rightarrow CH_3\bullet + H\bullet \quad BDE(CH_3\text{-}H)$$

$$Cl_2 \rightarrow 2Cl\bullet \quad BDE(Cl_2) \nonumber \]$$

$$H\bullet + Cl\bullet \rightarrow HCl \quad -BDE(HCl)$$

$$CH_3\bullet + Cl\bullet \rightarrow CH_3Cl \quad -BDE(CH_3\text{-}Cl)$$

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$$

$$\Delta H = BDE(R-H) + BDE(Cl_2) - BDE(HCl) - BDE(CH_3-Cl)$$

Because reaction enthalpy is a state function, it does not matter what reactions are combined to make up the overall process using Hess's Law. However, BDEs are convenient to use because they are readily available.

Alternatively, BDEs can be used to assess individual steps of a mechanism. For example, an important step in free radical chlorination of alkanes is the abstraction of hydrogen from the alkane to form a free radical.

$$RH + Cl\bullet \rightarrow R\bullet + HCl$$

The energy change for this step is equal to the difference in the BDEs in RH and HCl

$$\Delta H = BDE(R-H) - BDE(HCl)$$

This relationship shows that the hydrogen abstraction step is more favorable when BDE(R-H) is smaller. The difference in energies accounts for the selectivity in the halogenation of hydrocarbons with different types of C-H bonds.

Table 6.8.1: Representative C-H BDEs in Organic Molecules

R-H	D_o, kJ/mol	D_{298}, kJ/mol	R-H	D_o, kJ/mol	D_{298}, kJ/mol
CH_3-H	432.7±0.1	439.3±0.4	H_2C=CH-H	456.7±2.7	463.2±2.9
CH_3CH_2-H		423.0±1.7	C_6H_5-H	465.8±1.9	472.4±2.5
$(CH_3)_2$CH-H		412.5±1.7	HCCH	551.2±0.1	557.8±0.3
$(CH_3)_3$C-H		403.8±1.7			
			H_2C=CHCH_2-H		371.5±1.7
HC(O)-H		368.6±0.8	$C_6H_5CH_2$-H		375.3±2.5
CH_3C(O)-H		374.0±1.2			

TRENDS IN C-H BDES

It is important to remember that C-H BDEs refer to the energy it takes to break the bond, and is the difference in energy between the reactants and the products. Therefore, it is not appropriate to interpret BDEs solely in terms of the "stability of the radical products" as is often done.

Analysis of the BDEs shown in the table above shows that there are some systematic trends:

1. **BDEs vary with hybridization:** Bonds with sp^3 hybridized carbons are weakest and bonds with sp hybridized carbons are much stronger. The vinyl and phenyl C-H bonds are similar, reflecting their sp^2 hybridization. The correlation with hybridization can be viewed as a reflection of the C-H bond lengths. Longer bonds formed with sp^3 orbitals are consequently weaker. Shorter bonds formed with orbitals that have more s-character are similarly stronger.
2. **C-H BDEs vary with substitution:** Among sp^3 hybridized systems, methane has the strongest C-H bond. C-H bonds on primary carbons are stronger than those on secondary carbons, which are stronger than those on tertiary carbons.

INTERPRETATION OF C-H BDES FOR SP^3 HYBRIDIZED CARBONS

The interpretation of the BDEs in saturated molecules has been subject of recent controversy. As indicated above, the variation in BDEs with substitution has traditionally been interpreted as reflecting the stabilities of the alkyl radicals, with the assessment that more highly substituted radicals are more stable, as with carbocations. Although this is a popular explanation, it fails to account fo the fact the bonds to groups other than H do not show the same types of variation.

R	BDE(R-CH_3)	BDE(R-Cl)	BDE(R-Br)	BDE(R-OH)
CH_3-	377.0±0.4	350.2±0.4	301.7±1.3	385.3±0.4
CH_3CH_2-	372.4±1.7	354.8±2.1	302.9±2.5	393.3±1.7
$(CH_3)_2CH$-	370.7±1.7	356.5±2.1	309.2±2.9	399.6±1.7
$(CH_3)_3C$-	366.1±1.7	355.2±2.9	303.8±2.5	400.8±1.7

Therefore, although C-CH_3 bonds get weaker with more substitution, the effect is not nearly as large as that observed with C-H bonds. The strengths of C-Cl and C-Br bonds are not affected by substitution, despite the fact that the same radicals are formed as when breaking C-H bonds, and the C-OH bonds in alcohols actually *increase* with more substitution.

Gronert has proposed that the variation in BDEs is alternately explained as resulting from destabilization of the reactants due to steric repulsion of the substituents, which is released in the nearly planar radicals.[1] Considering that BDEs reflect the relative energies of reactants and products, either explanation can account for the trend in BDEs.

Another factor that needs to be considered is the electronegativity. The Pauling definition of electronegativity says that the bond dissociation energy between unequal partners is going to be dependent on the difference in electrongativities, according to the expression

$$D_o(A-B) = \frac{D_o(A-A) + D_o(B-B)}{2} + (X_A - X_B)^2$$

where X_A and X_B are the electronegativities and the bond energies are in eV. Therefore, the variation in BDEs can be interpreted as reflecting variation in the electronegativities of the different types of alkyl fragments.

There is likely some merit in all three interpretations. Since Gronert's original publication of his alternate explanation, there have been many desperate attempts to defend the radical stability explanation.

? EXERCISE 6.8.1

Given that $\Delta H°$ for the reaction

$CH_4\,(g) + 4F_2\,(g) \rightarrow CF_4\,(g) + 4HF\,(g)$

is −1936 kJ, use the following data to calculate the average bond energy of the C-F bonds in CF_4.

Bond	Average Bond Energy
C – H	413 kJ · mol^{-1}
F – F	155 kJ · mol^{-1}
H – F	567 kJ · mol^{-1}

Answer

Bonds broken:

4 mol C-H bonds $\times \frac{(413\ \text{kJ})}{(1\ \text{mol})} = 1652\ \text{kJ}$

4 mol F-F bonds $\times \frac{(155\ \text{kJ})}{(1\ \text{mol})} = 620\ \text{kJ}$

Bonds formed:

4 mol CF bonds $\times \frac{(x\ \text{kJ})}{(1\ \text{mol})} = 4x\ \text{kJ}$

(where x = the average energy of one mole of C-F bonds in CF_4, expressed in kJ)

4 mol H-F bonds $\times \frac{(567\ \text{kJ})}{(1\ \text{mol})} = 2268\ \text{kJ}$

$\Delta H° = \Delta H°(\text{bonds broken}) - \Delta H°(\text{bonds formed}) = (1652\ \text{kJ} + 620\ \text{kJ}) - (4x + 2268\ \text{kJ}) = 1652\ \text{kJ} + 620\ \text{kJ} - 4x - 2268\ \text{kJ} = -1936\ \text{kJ}$

Thus,

$$4x = 1936\ \text{kJ} - 2268\ \text{kJ} + 620\ \text{kJ} + 1652\ \text{kJ}$$
$$= 1940\ \text{kJ}$$

and

$$x = \frac{1940\ \text{kJ}}{4\ \text{mol}}$$
$$= 385\ \text{kJ} \cdot \text{mol}^{-1}$$

The average energy of a C-F bond in CF_4 is 385 kJ · mol^{-1}

? EXERCISE 6.8.1

Calculate $\Delta H°$ for the reactions given below. [Access bond energy tables via left-hand blue column Resources > Reference Tables > Reference Tables > Thermodynamic Tables > T3: Bond Energies]

a. $CH_3CH_2OCH_3$ + HI -> CH_3CH_2OH + CH_3I
b. CH_3Cl + NH_3 -> CH_3NH_2 + HCl

Answer

$CH_3CH_2OCH_3 + HI \rightarrow CH_3CH_2OH + CH_3I$

Reactant bonds broken	D		Product bonds formed	D
$CH_3CH_2O-CH_3$	339 kJ/mol		CH_3CH_2O-H	438 kJ/mol
H–I	298 kJ/mol	$$ $$	CH_3-I	238 kJ/mol
	637 kJ/mol			676 kJ/mol

$$\Delta H° = D_{\text{bonds broken}} + D_{\text{bonds formed}}$$
$$= 637\ \text{kJ/mol} - 676\ \text{kJ/mol}$$
$$= -39\ \text{kJ/mol}$$

$CH_3Cl + NH_3 \rightarrow CH_3NH_2 + HCl$

Reactant bonds broken	D		Product bonds formed	D
CH_3-Cl	356 kJ/mol		CH_3-NH_2	364 kJ/mol
NH_2-H	450 kJ/mol	$$ $$	H–Cl	432 kJ/mol
	806 kJ/mol			796 kJ/mol

$$\Delta H° = D_{\text{bonds broken}} + D_{\text{bonds formed}}$$
$$= 806\ \text{kJ/mol} - 796\ \text{kJ/mol}$$
$$= +10\ \text{kJ/mol}$$

REFERENCES

1. Gronert, S. *J. Org. Chem.* **2006**, *13*, 1209

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6.9: DESCRIBING A REACTION - ENERGY DIAGRAMS AND TRANSITION STATES

OBJECTIVES

After completing this section, you should be able to

- sketch the reaction energy diagram for a single-step reaction, given some indication of whether the reaction is fast or slow, exothermic or endothermic.
- interpret the reaction energy diagram for a single-step process (e.g., use the diagram to decide whether the reaction is exothermic or endothermic).
- suggest possible transition-state structures for simple one-step processes.
- assess the likelihood of a reaction occurring at room temperature, given the value of the activation energy $\Delta G^{\ddagger}$.

KEY TERMS

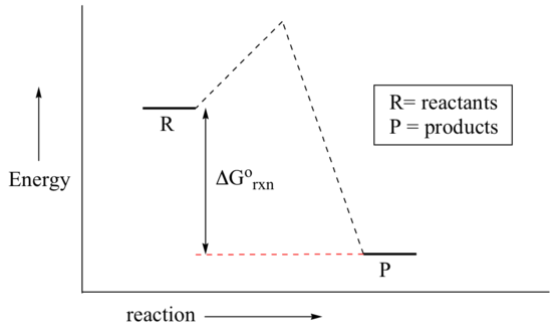
Make certain that you can define, and use in context, the key terms below.

- activation energy, $\Delta G^{\ddagger}$
- reaction energy diagram
- transition state

STUDY NOTES

You may have been taught to use the term "activated complex" rather than "transition state," as the two are often used interchangeably. Similarly, the activation energy of a reaction is often represented by the symbol E_{act} or E_a.

You may recall from general chemistry that it is often convenient to describe chemical reactions with energy diagrams. In an energy diagram, the vertical axis represents the overall energy of the reactants, while the horizontal axis is the 'reaction coordinate', tracing from left to right the progress of the reaction from starting compounds to final products. The energy diagram for a typical one-step reaction might look like this:



Despite its apparent simplicity, this energy diagram conveys some very important ideas about the thermodynamics and kinetics of the reaction. Recall that when we talk about the **thermodynamics** of a reaction, we are concerned with the difference in energy between reactants and products, and whether a reaction is 'downhill' (exergonic, energy releasing) or 'uphill (endergonic, energy absorbing). When we talk about **kinetics**, on the other hand, we are concerned with the *rate* of the reaction, regardless of whether it is uphill or downhill thermodynamically.

First, let's review what this energy diagram tells us about the thermodynamics of the reaction illustrated by the energy diagram above. The energy level of the products is *lower* than that of the reactants. This tells us that the change in standard Gibbs Free Energy for the reaction (ΔG°_{rnx}) is negative. In other words, the reaction is exergonic, or 'downhill'. Recall that the ΔG°_{rnx} term encapsulates both ΔH°_{rnx}, the change in enthalpy (heat) and ΔS°_{rnx} , the change in entropy (disorder):

$$\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$$

where T is the absolute temperature in Kelvin. For chemical processes where the entropy change is small (~0), the enthalpy change is essentially the same as the change in Gibbs Free Energy. Energy diagrams for these processes will often plot the enthalpy (H) instead of Free Energy for simplicity.

The standard Gibbs Free Energy change for a reaction can be related to the reaction's equilibrium constant (\(K_{eq}_) by a simple equation:

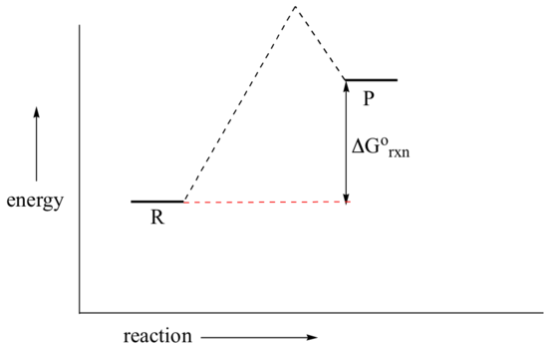
$$\Delta G^\circ = -RT \ln K_{eq}$$

where:

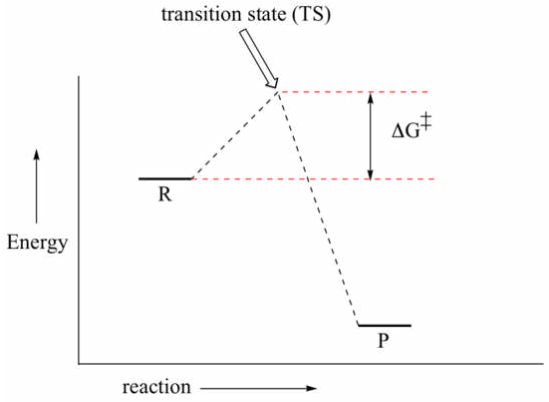
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 $J \times K^{-1} \times mol^{-1}$ *or* 1.987 $cal \times K^{-1} \times mol^{-1}$
- T = temperature in Kelvin (K)

If you do the math, you see that a negative value for ΔG°_{rnx} (an exergonic reaction) corresponds - as it should by intuition - to K_{eq} being greater than 1, an equilibrium constant which favors product formation.

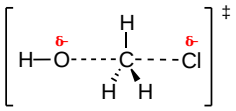
In a hypothetical endergonic (energy-absorbing) reaction the products would have a higher energy than reactants and thus ΔG°_{rnx} would be positive and K_{eq} would be less than 1, favoring reactants.



Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



First, an 'energy barrier' must be overcome to get to the product side. The height of this energy barrier, you may recall, is called the '**activation energy'** ($\Delta G^{\ddagger}$). The activation energy is what determines the kinetics of a reaction: the higher the energy hill, the slower the reaction. At the very top of the energy barrier, the reaction is at its **transition state** (TS), which is the point at which the bonds are in the process of breaking and forming. The transition state is an '**activated complex'**: a transient and dynamic state that, unlike more stable species, does not have any definable lifetime. It may help to imagine a transition state as being analogous to the exact moment that a baseball is struck by a bat. Transition states are drawn with dotted lines representing bonds that are in the process of breaking or forming, and the drawing is often enclosed by brackets. Here is a picture of a likely transition state for a substitution reaction between hydroxide and chloromethane:



Note that this species is absent from the chemical equation (that is it is neither a reactant nor product)

$$\mathrm{CH_3Cl + HO^- \rightarrow CH_3OH + Cl^-}$$

This reaction involves a collision between *two* molecules: for this reason, we say that it has **second order kinetics**. The **rate expression** for this type of reaction is:

$$\mathrm{rate} = k[\mathrm{reactant\ 1}][\mathrm{reactant\ 2}]$$

... which tells us that the rate of the reaction depends on the **rate constant** k as well as on the concentration of *both* reactants. The rate constant can be determined experimentally by measuring the rate of the reaction with different starting reactant concentrations. The rate constant depends on the activation energy, of course, but also on temperature: a higher temperature means a higher k and a faster reaction, all else being equal. This should make intuitive sense: when there is more heat energy in the system, more of the reactant molecules are able to get over the energy barrier.

Here is one more interesting and useful expression. Consider a simple reaction where the reactants are **A** and **B**, and the product is **AB** (this is referred to as a **condensation reaction**, because two molecules are coming together, or condensing). If we know the rate constant k for the forward reaction and the rate constant $k_{reverse}$ for the reverse reaction (where AB splits apart into **A** and **B**), we can simply take the quotient to find our equilibrium constant K_{eq}:

$$A + B \rightleftharpoons AB$$

with

$$K_{eq} = \frac{[AB]}{[A][B]} = \frac{k_{\mathrm{forward}}}{k_{\mathrm{reverse}}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

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6.10: DESCRIBING A REACTION - INTERMEDIATES

OBJECTIVES

After completing this section, you should be able to

- explain the difference between a transition state and an intermediate.
- draw a reaction energy diagram for a given multistep process.
- interpret the reaction energy diagram of a multistep process (e.g., determine which of the steps is rate-determining).

KEY TERMS

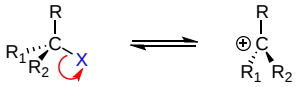
Make certain that you can define, and use in context, the key term below.

- reaction intermediate

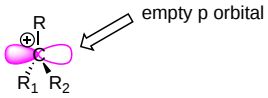
STUDY NOTES

Each step in a multistep reaction has its own activation energy. The overall activation energy is the difference in energy between the reactants and the transition state of the slowest (rate-determining) step. The rate-determining step, that is, the one that controls the overall rate of reaction, is the step with the highest activation energy.

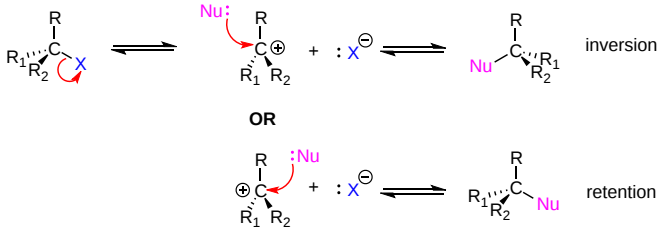
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism: in this picture, the C-X bond breaks *first*, before the nucleophile approaches:



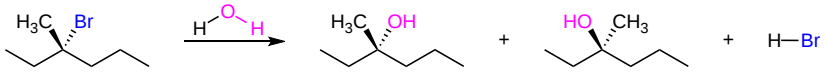
This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry.



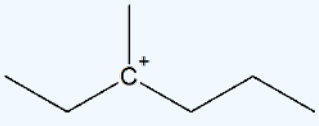
We saw that S_N2 reactions result specifically in inversion of stereochemistry at the electrophilic carbon center. What about the stereochemical outcome of S_N1 reactions? In the model S_N1 reaction shown above, the leaving group dissociates completely from the vicinity of the reaction before the nucleophile begins its attack. Because the leaving group is no longer in the picture, the nucleophile is free to attack from either side of the planar, sp^2-hybridized carbocation electrophile. This means that about half the time the product has the same stereochemical configuration as the starting material (retention of configuration), and about half the time the stereochemistry has been inverted. In other words, *racemization* has occurred at the carbon center. As an example, the tertiary alkyl bromide below would be expected to form a racemic mix of *R* and *S* alcohols after an S_N1 reaction with water as the incoming nucleophile.



EXERCISE 6.10.1

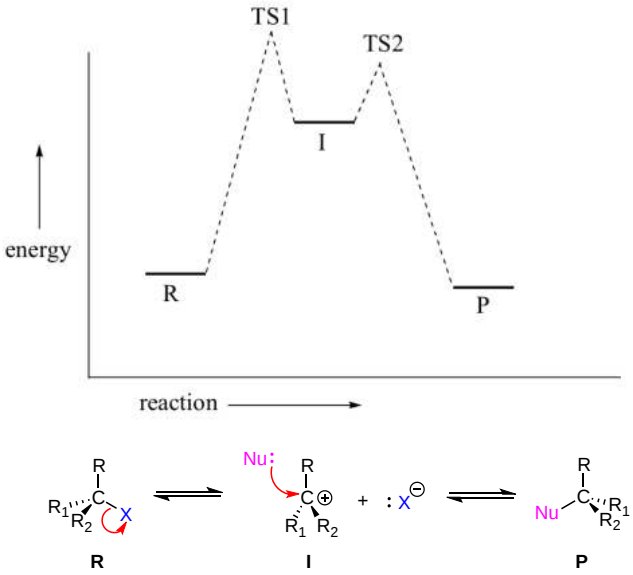
Draw the structure of the intermediate in the two-step nucleophilic substitution reaction above.

Answer



S_N1 intermediate (sp^2)

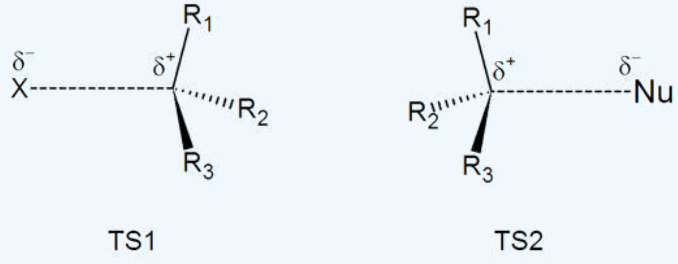
The S_N1 reaction we see an example of a **reaction intermediate**, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation **intermediate** can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states.



EXERCISE 6.10.2

Draw structures representing TS1 and TS2 in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Answer

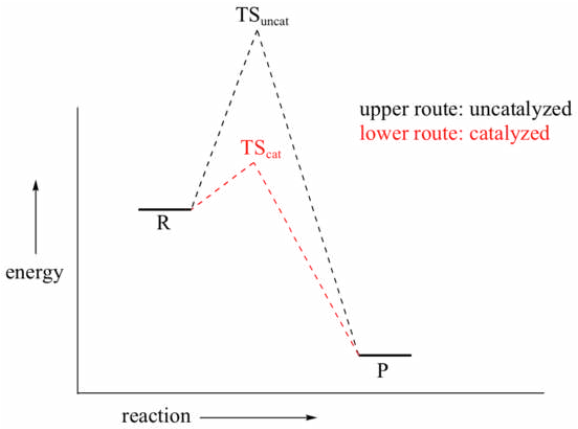


Recall that the first step of the reaction above, in which two charged species are formed from a neutral molecule, is much the slower of the two steps, and is therefore rate-determining. This is illustrated by the energy diagram, where the activation energy for the first step is higher

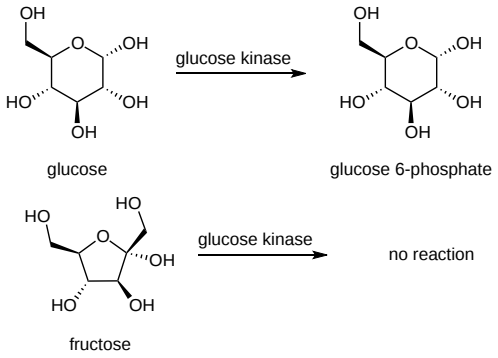
than that for the second step. Also recall that an S_N1 reaction has *first order* kinetics, because the rate determining step involves one molecule splitting apart, not two molecules colliding

We come now to the subject of catalysis. Our hypothetical bowl of sugar (from section 6.2) is still stubbornly refusing to turn into carbon dioxide and water, even though by doing so it would reach a much more stable energy state. There are, in fact, two ways that we could speed up the process so as to avoid waiting several millennia for the reaction to reach completion. We could supply enough energy, in the form of heat from a flame, to push some of the sugar molecules over the high energy hill. Heat would be released from the resulting exothermic reaction, and this energy would push more molecules over their energy hills, and so on - the sugar would literally burn up.

A second way to make the reaction go faster is to employ a **catalyst**. You probably already know that a catalyst is an agent that causes a chemical reaction to go faster by lowering its activation energy.



How might you catalyze the conversion of sugar to carbon dioxide and water? It's not too hard – just eat the sugar, and let your digestive enzymes go to work catalyzing the many biochemical reactions involved in breaking it down. Enzymes are proteins, and are very effective catalysts. 'Very effective' in this context means very specific, and very fast. Most enzymes are very selective with respect to reactant molecules: they have evolved over millions of years to catalyze their specific reactions. An enzyme that attaches a phosphate group to glucose, for example, will not do anything at all to fructose (the details of these reactions are discussed in section 10.2B).



Glucose kinase is able to find and recognize glucose out of all of the other molecules floating around in the 'chemical soup' of a cell. A different enzyme, fructokinase, specifically catalyzes the phosphorylation of fructose.

We have already learned (section 3.9) that enzymes are very specific in terms of the stereochemistry of the reactions that they catalyze . Enzymes are also highly **regiospecific**, acting at only one specific part of a molecule. Notice that in the glucose kinase reaction above only one of the alcohol groups is phosphorylated.

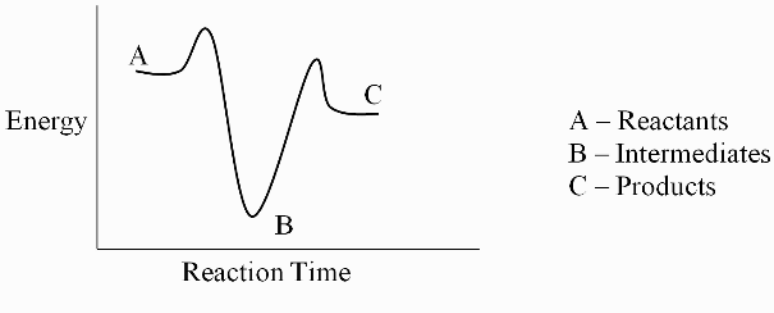
Finally, enzymes are capable of truly amazing rate acceleration. Typical enzymes will speed up a reaction by anywhere from a million to a billion times, and the most efficient enzyme currently known to scientists is believed to accelerate its reaction by a factor of about 10^{17} (see *Chemical and Engineering News*, March 13, 2000, p. 42 for an interesting discussion about this enzyme, orotidine monophosphate decarboxylase).

We will now begin an exploration of some of the basic ideas about how enzymes accomplish these amazing feats of catalysis, and these ideas will be revisited often throughout the rest of the text as we consider various examples of enzyme-catalyzed organic reactions. But in order to begin to understand how enzymes work, we will first need to learn (or review, as the case may be) a little bit about protein structure.

EXERCISE 6.10.3

Draw an energy diagram with a exergonic first step and an endergonic second step. Label the diagram.

Answer



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6.11: A COMPARISON BETWEEN BIOLOGICAL REACTIONS AND LABORATORY REACTIONS

OBJECTIVES

- No objectives have been identified for this section

KEY TERMS

Make certain that you can define, and use in context, the key term below.

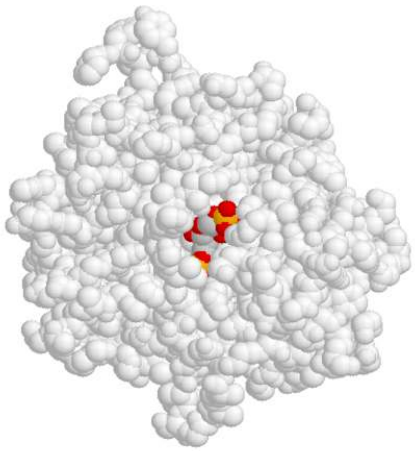
- enzyme

STUDY NOTES

This section is a brief (but perhaps interesting) overview of some of the key differences between reactions performed in the lab and those in living systems. At this point, do not concern yourself with memorizing large biological molecules and reactions.

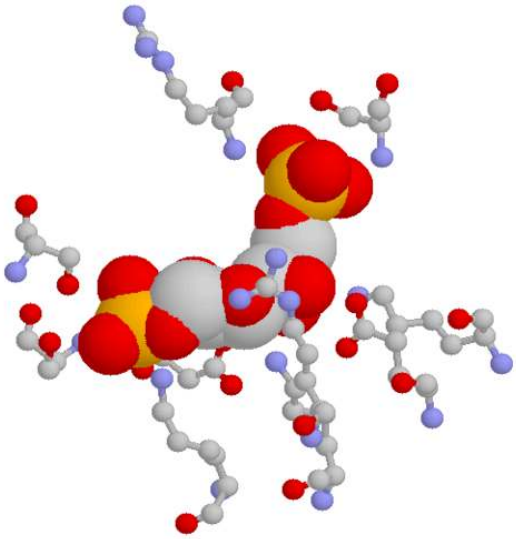
THE ACTIVE SITE

A critical element in the three-dimensional structure of any enzyme is the presence of an '**active site'**, which is a pocket, usually located in the interior of the protein, that serves as a docking point for the enzyme's **substrate**(s) ('substrate' is the term that biochemists use for a reactant molecule in an enzyme-catalyzed reaction). It is inside the active site pocket that enzymatic catalysis occurs. Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase, with its substrate bound inside the active site pocket.

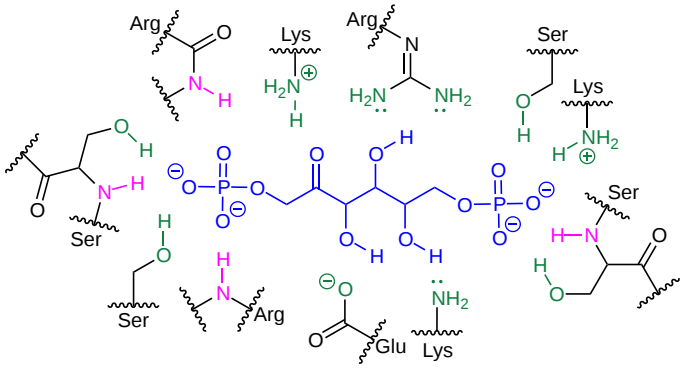


When the substrate binds to the active site, a large number of noncovalent interactions form with the amino acid residues that line the active site. The shape of the active site, and the enzyme-substrate interactions that form as a result of substrate binding, are *specific to the substrate-enzyme pair*: the active site has evolved to 'fit' one particular substrate and to catalyze one particular reaction. Other molecules do not fit in this active site nearly so well as fructose 1,6-bisphosphate.

Here are two close-up views of the same active site pocket, showing some of the specific hydrogen-bonding interactions between the substrate and active site amino acids. The first image below is a three-dimensional rendering directly from the crystal structure data. The substrate is shown in 'space-filling' style, while the active site amino acids are shown in the 'ball and stick' style. Hydrogens are not shown. The color scheme is grey for carbon, red for oxygen, blue for nitrogen, and orange for phosphorus.



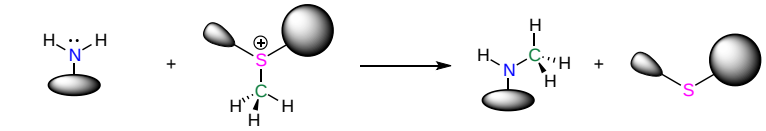
Below is a two-dimensional picture of the substrate (colored blue) surrounded by hydrogen-bonding active site amino acids. Notice that both main chain and side chain groups contribute to hydrogen bonding: in this figure, main chain H-bonding groups are colored purple, and side chain H-bonding groups are colored green.



Looking at the last three images should give you some appreciation for the specific manner in which a substrate fits inside its active site.

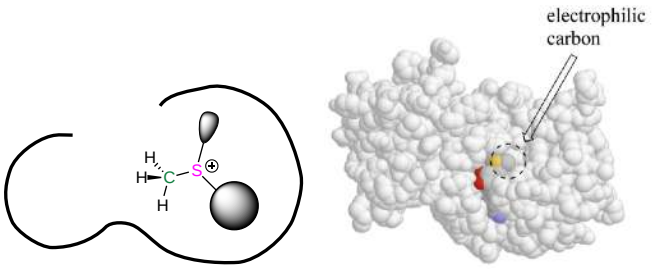
TRANSITION STATE STABILIZATION

One of the most important ways that an enzyme catalyzes any given reaction is through entropy reduction: by bringing order to a disordered situation (remember that entropy is a component of Gibbs Free Energy, and thus a component of the activation energy). Let's turn again to our previous example (from section 6.1C) of a biochemical nucleophilic substitution reaction, the methylation of adenosine in DNA. The reaction is shown below with non-reactive sections of the molecules depicted by variously shaped 'bubbles' for the sake of simplicity.



In order for this reaction to occur, the two substrates (reactants) must come into contact in precisely the right way. If they are both floating around free in solution, the likelihood of this occurring is very small – the entropy of the system is simply too high. In other words, this reaction takes place *very* slowly without the help of a catalyst.

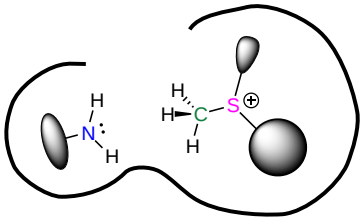
Here's where the enzyme's active site pocket comes into play. It is lined with various functional groups from the amino acid main and side chains, and has a very specific three-dimensional architecture that has evolved to bind to both of the substrates. If the SAM molecule, for example, diffuses into the active site, it can replace its (favorable) interactions with the surrounding water molecules with (even more favorable) new interactions with the functional groups lining the active site.



Depiction of SAM bound in active site of enzyme

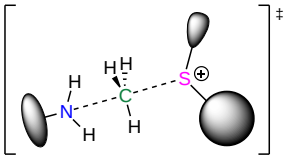
In a sense, SAM is moving from one solvent (water) to another 'solvent' (the active site), where many new energetically favorable interactions are possible. Remember: these new contacts between SAM and the active site groups are *highly specific* to SAM and SAM alone – no other molecule can 'fit' so well in this precise active site environment, and thus no other molecule will be likely to give up its contacts to water and bind to the active site.

The second substrate also has a specific spot reserved in the active site. (Because in this case the second substrate is a small segment of a long DNA molecule, the DNA-binding region of the active site is more of a 'groove' than a 'pocket').



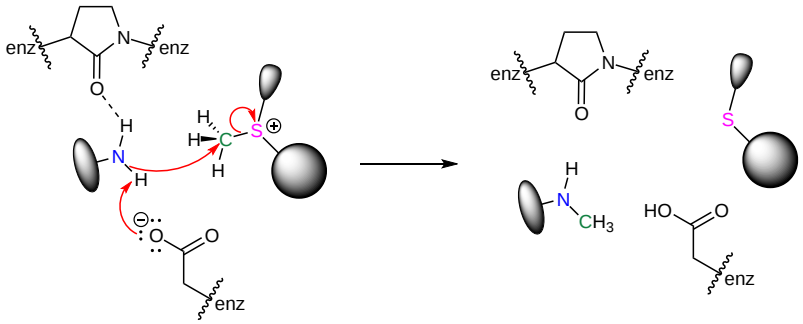
So now we have both substrates bound in the active site. But they are not just bound in any random orientation – they are specifically positioned relative to one another so that the nucleophilic nitrogen is held very close to the electrophilic carbon, with a free path of attack. What used to be a very disordered situation – two reactants diffusing freely in solution – is now a very highly ordered situation, with everything set up for the reaction to proceed. This is what is meant by entropy reduction: the entropic component of the energy barrier has been lowered.

Looking a bit deeper, though, it is not really the noncovalent interaction between enzyme and *substrate* that are responsible for catalysis. Remember: all catalysts, enzymes included, accelerate reactions by lowering the energy of the *transition state*. With this in mind, it should make sense that the primary job of an enzyme is to maximize favorable interactions with the transition state, *not* with the starting substrates. This does not imply that enzyme-substrate interactions are not strong, rather that enzyme-TS interactions are far *stronger*, often by several orders of magnitude. Think about it this way: if an enzyme were to bind to (and stabilize) its substrate(s) more tightly than it bound to (and stabilized) the transition state, it would actually *slow down* the reaction, because it would be *increasing* the energy difference between starting state and transition state. ***The enzyme has evolved to maximize favorable noncovalent interactions to the transition state***: in our example, this is the state in which the nucleophilic nitrogen is already beginning to attack the electrophilic carbon, and the carbon-sulfur bond has already begun to break.

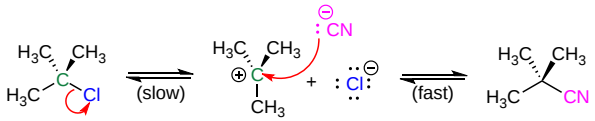


enzyme binds best to
the transition state

In many enzymatic reactions, certain active site amino acid residues contribute to catalysis by *increasing the reactivity of the substrates*. Often, the catalytic role is that of acid and/or base. In our DNA methylation example, the nucleophilic nitrogen is deprotonated by a nearby aspartate side chain as it begins its nucleophilic attack on the methyl group of SAM. We will study nucleophilicity in greater detail in chapter 8, but it should make intuitive sense that deprotonating the amine increases the electron density of the nitrogen, making it *more nucleophilic*. Notice also in the figure below that the main chain carbonyl of an active site proline forms a hydrogen bond with the amine, which also has the effect of increasing the nitrogen's electron density and thus its nucleophilicity (*Nucleic Acids Res.* **2000**, *28*, 3950).

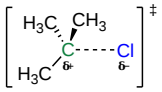


How does our picture of enzyme catalysis apply to multi-step reaction mechanisms? Although the two-step nucleophilic substitution reaction between 2-chloro-2-methylpropane and the cyanide anion is not a biologically relevant process, let's pretend just for the sake of illustration that there is a hypothetical enzyme that catalyzes this reaction.

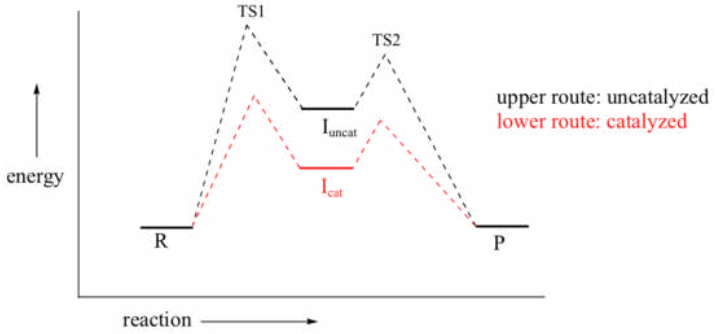


The same basic principles apply here: the enzyme binds best to the transition state. But therein lies the problem: there are two transition states! To which TS does the enzyme maximize its contacts?

Recall that the first step – the loss of the chloride leaving group to form the carbocation intermediate – is the slower, rate-limiting step. It is this step that our hypothetical enzyme needs to accelerate if it wants to accelerate the overall reaction, and it is thus the energy of TS1 that needs to be lowered.



By Hammond's postulate, we also know that the intermediate I is a close approximation of TS1. So the enzyme, by stabilizing the intermediate, will also stabilize TS1 (as well as TS2) and thereby accelerate the reaction.



If you read scientific papers about enzyme mechanisms, you will often see researchers discussing how an enzyme stabilizes a reaction intermediate. By virtue of Hammond's postulate, they are, at the same time, talking about how the enzyme lowers the energy of the transition state.

An additional note: although we have in this section been referring to SAM as a 'substrate' of the DNA methylation reaction, it is also often referred to as a **coenzyme**, or **cofactor**. These terms are used to describe small (relative to protein and DNA) biological organic molecules that bind specifically in the active site of an enzyme and help the enzyme to do its job. In the case of SAM, the job is methyl group donation. In addition to SAM, we will see many other examples of coenzymes in the coming chapters, a number of which - like ATP (adenosine triphosphate), coenzyme A, thiamine, and flavin - you have probably heard of before. The full structures of some common coenzymes are shown in table 6 in the tables section.

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6.S: AN OVERVIEW OF ORGANIC REACTIONS (SUMMARY)

CONCEPTS & VOCABULARY

6.1: Kinds of Organic Reactions

- **Addition** reactions increase the number of sigma bonds in a molecule.
- **Elimination** reactions reduce the number of sigma bonds in a molecule.
- **Substitution** reactions incorporate replacement of an atom or group with another.
- **Rearrangement** reactions cause a molecule to be converted to a constitutional isomer without gaining or losing any atoms.

6.2: How Organic Reactions Occur: Mechanisms

- A reaction **mechanism** describes movement of electrons by using curved arrows to show bonds that are breaking and forming.
- **Homolysis** occurs when a bond breaks with each atom keeping one electron.
- **Heterolysis** occurs when a bond breaks and both electrons remain with one of the atoms.
- Some reactions occur in more than one step with a **reactive intermediate** formed briefly on the way to the new product.
- **Reactive intermediates** can be charged species such as carbocations and carbanions or uncharged species such as **radicals**.
- In organic chemistry Lewis acids are more often referred to as **electrophiles**, having an affinity for an electron pair.
- In organic chemistry Lewis bases are more often referred to as **nucleophiles**, having an electron pair that is available to bond to an **electrophile**.
- **Ionic** reactions involve charged species.
- **Polar** reactions involve bonds with unequally shared electrons.

6.3: Radical Reactions

- **Radical chain reactions** have three distinct phases: initiation, propagation and termination.
  - Initiation causes radicals to be created from non-radical species.
  - During the Propagation phase, radicals react with stable molecules to form new radicals.
  - Termination occurs when two radicals react together to form a stable molecule.

6.4: Polar Reactions

- Carbon when bonded to a halogen, oxygen, nitrogen, sulfur, or metal has a partial positive charge. This allows these carbons to react with many **nucleophiles**.
- For carbonyl groups bond polarity is reinforced by resonance making the carbon even more positive than in other molecules. This makes carbonyl groups prone to addition and substitution reactions with **nucleophiles**.
- **Nucleophiles** have electron rich atoms that are able to donate a pair of electrons.
- In nucleophilic substitution reactions, the **electrophile** is typically carbon bonded to a more electronegative atom.

6.5: An Example of a Polar Reaction: Addition of HBr to Ethylene

- Alkene addition reaction with HBr occurs through the pi bond reacting as a nucleophile and abstracting a proton from the acid. This creates a carbocation intermediate which reacts with the bromide ion to form the final product.
- Reaction rates for this alkene addition reaction increase with larger halogens and more substituted alkenes.
- Markovnikov's Rule states that addition reactions of unsymmetrical alkenes yield the more substituted product.

6.6: Using Curved Arrows in Polar Reaction Mechanisms

- Curved arrows in mechanism drawings always represent electrons moving, starting at either a bond or lone pair of electrons.
- Electrons flow from electron rich to electron poor.

6.7: Describing a Reaction: Equilibria, Rates, and Energy Changes

- **Exergonic reactions** have a negative free energy meaning they are thermodynamically favorable and give off energy.
- **Endergonic reactions** have a positive free energy and require energy from the surroundings to occur.

6.8: Describing a Reaction: Bond Dissociation Energies

- **Bond dissociation energy** for a molecule is the difference in enthalpy of formation (**homolytic**) for the products and reactants.
- **Bond dissociation energies** are independent of path of reaction, so they do not give direct information on mechanisms. However, they can be used to evaluate the results of individual steps of a mechanism.
- **Bond dissociation energies** show that sigma bonds formed with sp hybridized carbon are stronger than sp^2 which are stronger than bonds formed with sp^3 carbons.

- **Bond dissociation energies** show that carbon-hydrogen bonds on primary carbons are stronger than secondary, which are stronger than tertiary.

6.9: Describing a Reaction: Energy Diagrams and Transition States

- **Reaction coordinate** diagrams are a special type of energy diagram that has the reaction coordinate (or reaction progress) on the x-axis.
- **Thermodynamics** of a reaction is conveyed on a reaction coordinate diagram by the difference in energy between the reactants and products.
- **Activation energy** is the energy barrier to a reaction occurring.
- A **transition state** is the highest energy point during the process of bonds forming and breaking in a reaction step.
- **Kinetics** of a reaction is conveyed on a **reaction coordinate** diagram by the difference in energy between the reactants and transition state.
- A r**ate expression** relates rate to the **rate constant** and concentration of reactants.

6.10: Describing a Reaction: Intermediates

- A **reaction intermediate** is a short-lived species that goes on to react in a subsequent reaction step.
- **Reaction intermediates** appear as a local minimum (or valley) on a reaction coordinate diagram.
- **Catalysts** cause reaction rates to increase by lowing activation energy.

6.11: A Comparison between Biological Reactions and Laboratory Reactions

- An enzyme **active site** is the location where the enzyme interacts with its **substrate** and where **catalysis** occurs.
- **Substrates** are reactant molecules in enzymatic reactions.

SKILLS TO MASTER

- Skill 6.1 Identify organic reactions by type (addition, elimination, substitution, rearrangement).
- Skill 6.2 Draw homolytic and heterolytic bond breaking as part of reaction mechanisms.
- Skill 6.3 Identify radical and ionic reactions.
- Skill 6.4 Identify and write out steps in a typical radical substitution reaction (initiation, propagation, termination).
- Skill 6.5 Identify polarity of bonds in organic molecules.
- Skill 6.6 Use curved arrows to indicate movement of electrons in resonance and reaction mechanisms.
- Skill 6.7 Predict whether a chemical species will act as an electrophile or nucleophile.
- Skill 6.8 Write an equilibrium expression for a reaction.
- Skill 6.9 Determine the direction of a reaction based on the equilibrium constant.
- Skill 6.10 Explain how rate and equilibrium are related to ΔG^o and K_{eq}.
- Skill 6.11 Calculate bond dissociation energy given enthalpies of formation for reactants and products.
- Skill 6.12 Describe order of bond strength based on bond dissociation energy.
- Skill 6.13 Explain activation energy, kinetics, thermodynamics and transition states based on energy diagrams (reaction coordinate diagrams).
- Skill 6.14 Predict possible transition state structures for single reaction steps.
- Skill 6.15 Differentiate between transition states and intermediates.
- Skill 6.16 Draw a reaction coordinate diagram for a given multi-step process.
- Skill 6.17 Interpret a reaction coordinate diagram for a multi-step process.
- Skill 6.18 Briefly explain how enzymes catalyze reactions.

MEMORIZATION TASKS

MT 6.1 Memorize that arrows in reaction mechanisms always define movement of electrons.

MT 6.2 Memorize the relative electronegativities of common atoms (necessary for determining polarity of bonds).

MT 6.3 Memorize the equations that relate equilibrium, free energy, enthalpy and entropy.

$\Delta G^o = -RT\ln K$

$\Delta G^o = \Delta H^o - T\Delta S^o$

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CHAPTER OVERVIEW

7: ALKENES- STRUCTURE AND REACTIVITY

LEARNING OBJECTIVES

After you have completed Chapter 7, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. describe the importance of alkenes to the chemical industry.
3. use the concept of “degree of unsaturation” in determining chemical structures.
4. describe the electronic structure and geometry of alkenes.
5. describe the factors that influence alkene stability, and determine the relative stability of a number of given alkenes.
6. write the IUPAC name of a given alkene, and draw the structure of any alkene, given its IUPAC name.
7. determine whether a given alkene has an *E* configuration or a *Z* configuration.
8. explain why alkenes are more reactive than alkanes.
9. describe the reaction between an alkene and a hydrogen halide, and explain why one product is formed rather than another. Base your explanation on the concepts of carbocation stability and the Hammond postulate.
10. define, and use in context, the key terms introduced in this chapter.

This, the first of two chapters devoted to the chemistry of alkenes, describes how certain alkenes occur naturally, then shows the industrial importance of ethylene and propylene (the simplest members of the alkene family). The electronic structure of alkenes is reviewed, and their nomenclature discussed in detail. After dealing with the question of cis-trans isomerism in alkenes, Chapter 7 introduces the reactivity of the carbon-carbon double bond. The chapter then focuses on one specific reaction—the addition of hydrogen halides to alkenes—to raise a number of important concepts, including carbocation stability and the Hammond postulate.

7.0: Chapter Objectives
7.1: Introduction to Alkenes
7.2: Industrial Preparation and Use of Alkenes
7.3: Calculating Degree of Unsaturation
7.4: Naming Alkenes
7.5: Cis-Trans Isomerism in Alkenes
7.6: Sequence Rules - The E,Z Designation
7.7: Stability of Alkenes
7.8: Electrophilic Addition Reactions of Alkenes
7.9: Orientation of Electrophilic Additions - Markovnikov's Rule
7.10: Carbocation Structure and Stability
7.11: The Hammond Postulate
7.12: Evidence for the Mechanism of Electrophilic Additions - Carbocation Rearrangements
7.S: Alkenes- Structure and Reactivity (Summary)

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7.0: CHAPTER OBJECTIVES

Alkenes are a fundamental class of organic compounds characterized by the presence of a carbon-carbon double bond, which gives them unique structural and reactivity properties. In this introduction to Alkenes, we'll delve into their structure and reactivity, exploring the foundational concepts that define their behavior in chemical reactions.

Structure of Alkenes: At the heart of alkenes is the carbon-carbon double bond, consisting of one sigma (σ) bond and one pi (π) bond. This double bond imparts significant structural rigidity and planarity to alkenes. Due to the presence of this double bond, alkenes often adopt a trigonal planar geometry around the carbon atoms involved in the double bond.

Naming Alkenes: In the IUPAC nomenclature system, alkenes are named by identifying the longest continuous carbon chain containing the double bond. The suffix "-ene" is added to the end of the alkane name corresponding to the same number of carbon atoms, and the position of the double bond is indicated by the lowest numbered carbon atom involved in the double bond.

Reactivity of Alkenes: Alkenes exhibit rich reactivity owing to the presence of the π bond. The π bond is relatively weak compared to the σ bond, making it susceptible to various types of reactions, including addition reactions, polymerization, and elimination reactions.

Addition Reactions: One of the most common reactions involving alkenes is addition reactions, where atoms or groups are added to the carbon atoms of the double bond. Examples include hydrogenation, halogenation, hydration, and hydrohalogenation.

Polymerization: Alkenes readily undergo polymerization, a process where monomers containing double bonds join together to form long-chain polymers. This process is crucial in the production of various synthetic materials, such as plastics and synthetic rubbers.

Elimination Reactions: Elimination reactions involve the removal of atoms or groups from adjacent carbon atoms of a molecule, resulting in the formation of a double bond. The most common elimination reaction involving alkenes is the dehydrohalogenation of alkyl halides to form alkenes.

Understanding the structure and reactivity of alkenes is foundational in organic chemistry, as they serve as important intermediates and reactants in numerous synthetic pathways. In the subsequent discussions, we will explore these concepts in greater detail, elucidating the mechanisms and applications of various reactions involving alkenes.

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7.1: INTRODUCTION TO ALKENES

OBJECTIVE

After completing this section, you should be able to give an example of a naturally occurring compound that contains at least one double bond.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- olefin

STUDY NOTES

Alkenes are a class of hydrocarbons (i.e., containing only carbon and hydrogen). They are unsaturated compounds with at least one carbon-to-carbon double bond. The double bond makes Alkenes more reactive than alkanes. Olefin is another term used to describe alkenes.

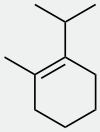
The graphic shows three alkenes. The more complex alkene is commonly known as 1-menthene, but its full proper IUPAC name is 1-methyl-2-(1-methylethyl)-cyclohexene.



ethene



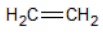
1,3-cyclopentadiene



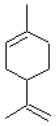
1-menthene
(peppermint fragrance)

ALKENES

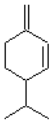
Alkenes are a class of hydrocarbons (i.e., containing only carbon and hydrogen). They are unsaturated compounds with at least one carbon-to-carbon double bond. The double bond makes alkenes more reactive than alkanes. Olefin is another term used to describe alkenes. The alkene group can also be called a vinyl group and the carbons sharing the double bond can be called vinyl carbons.



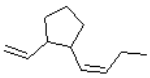
fruit ripening hormone



oil of eucalyptus



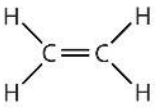
limonene



sex attractanct of brown algae

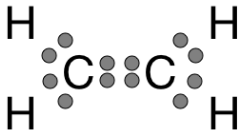
STRUCTURE OF ETHENE - THE SIMPLEST ALKENE

Ethene is often written as CH_2=CH_2 which stands for:

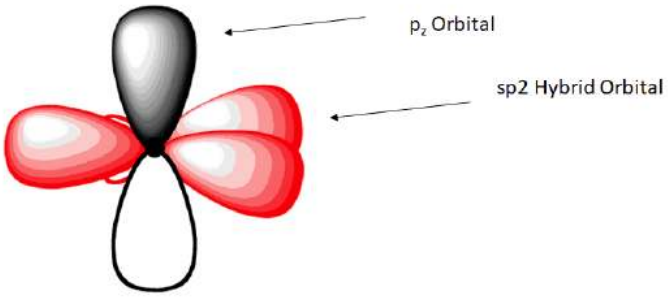


The double bond is shared by the two carbon atoms and does not involve the hydrogen atoms, although the condensed formula does not make this point obvious. Note that the molecular formula for ethene is C_2H_4, whereas that for ethane is C_2H_6.

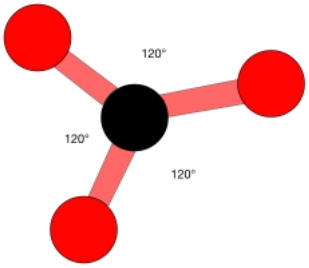
Ethene is not a very complicated molecule. It is made up of four $1s^1$ hydrogen atoms and two $2s^2$ $2p_x^1$ $2p_y^1$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight (octet) in the valence shell. Having eight valence electrons around carbon gives the atom the same electron configuration as neon, a noble gas. Carbon wants to have the same configuration as neon because when it has eight valence electrons carbon is at its most stable, lowest energy state.



This forms a total of three bonds to each carbon atom, giving them an sp^2 hybridization. Since the carbon atom is forming three sigma bonds instead of the four that it can, it only needs to hybridize three of its outer orbitals, instead of four. It does this by using the $2s$ electron and two of the $2p$ electrons, leaving the other unchanged. This new orbital is called an sp^2 hybrid because it is made from one s orbital and two p orbitals.



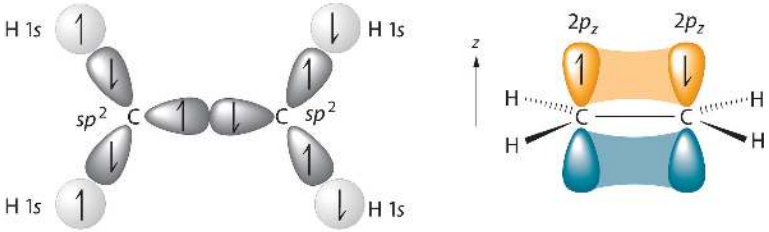
When atoms use sp^2 hybrids they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



The H-C-H bond angle is 117°, which is very close to the ideal 120° of a carbon with sp^2 hybridization. The other two angles (H-C=C) are both 121.5°.

RIGIDITY IN ETHENE

There is rigidity in the ethene molecule due to the double-bonded carbons. A double bond consists of one sigma bond formed by overlap of sp^2 hybrid orbitals and one pi bond formed by overlap of parallel 2 p orbitals. In ethene there is no free rotation about the carbon-carbon sigma bond because these two carbons also share a π bond. A π bond is only formed when there is adequate overlap between both top and bottom p-orbitals. Rotation of the p-orbitals causes them to be 90° from each other breaking the π bond because there would be no overlap. There is a much larger energy barrier to rotation than there is about a carbon-carbon sigma bond.



(a) C_2H_4 σ-bonded framework **(b) C_2H_4 π bonding**

(a) The σ-bonded framework is formed by the overlap of two sets of singly occupied carbon sp^2 hybrid orbitals and four singly occupied hydrogen 1s orbitals to form electron-pair bonds. This uses 10 of the 12 valence electrons to form a total of five σ bonds (four C–H bonds and one C–C bond).

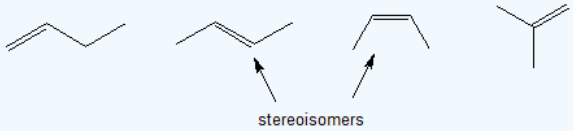
(b) One singly occupied unhybridized $2p_z$ orbital remains on each carbon atom to form a carbon–carbon π bond. (Note: by convention, in planar molecules the axis perpendicular to the molecular plane is the z-axis.)

EXERCISE

1. Although there is only one alkene with the formula C_2H_4 (ethene) and only one with the formula C_3H_6 (propene), there are several alkenes with the formula C_4H_8. Draw all of the possible bond line structures for alkenes with the formula C_4H_8 including all possible structural and stereoisomers.

Answer

1. There are three possible structural isomers. 2-butene can exist as two different stereoisomers.



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7.2: INDUSTRIAL PREPARATION AND USE OF ALKENES

OBJECTIVES

After completing this section, you should be able to

1. discuss the industrial importance of ethylene (ethene) and propylene (propene).
2. describe, briefly, the industrial process known as thermal cracking.

STUDY NOTES

Among the most important and most abundant organic chemicals produced worldwide are the two simple alkenes, ethylene and propylene. They are used as the starting materials to synthesize numerous valuable compounds.

Produced from ethylene (ethene)

Chemical	Uses
ethanol	solvent; constituent of cleaning preparations; in synthesis of esters
acetaldehyde	slug killer, in the form of methaldehyde $(CH_3CHO)_4$
acetic acid	manufacture of vinyl acetate polymers, ethyl acetate solvent and cellulose acetate polymers
ethylene oxide	"cellosolves" (industrial solvents)
ethylene glycol	anti-freeze; production of DacronOR
ethylene dichloride	solvent; production of vinyl chloride
vinyl chloride	manufacture of poly (vinyl chloride)—PVC
vinyl acetate	manufacture of poly (vinyl acetate) used in paint emulsions, plywood adhesives and textiles
polyethylene	"plastic" bags; toys; packaging

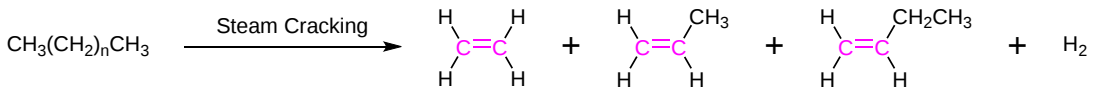
Produced from propylene (propene)

Chemical	Uses
isopropyl alcohol	rubbing alcohol; cosmetics; synthesis of acetone
propylene oxide	manufacture of polyurethanes; polyesters
cumene	industrial preparation of phenol and acetone
polypropylene	molded articles (e.g., kitchenware); fibres for indoor-outdoor carpeting

INDUSTRIAL PREPARATION OF ETHYLENE AND PROPYLENE

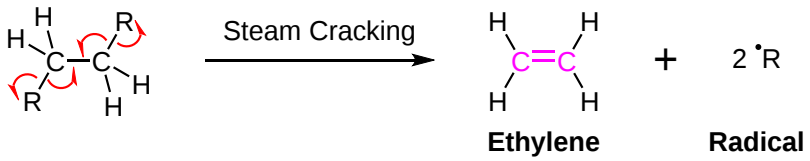
Ethene (CH_2CH_2) and propene (CH_3CHCH_2), are most often called by their common names—ethylene and propylene. Ethylene is a major commercial chemical. The US chemical industry produces about 25 billion kilograms of ethylene annually, more than any other synthetic organic chemical. More than half of this ethylene goes into the manufacture of polyethylene, one of the most familiar plastics. Propylene is also an important industrial chemical. It is converted to plastics, isopropyl alcohol, and a variety of other products. Both ethylene and propylene are the feedstock for the industrial synthesis of a wide variety of small organic molecules.

Ethylene, propylene, and butylene ($CH_3CH_2CHCH_2$) are typically industrially synthesized through the steam cracking of light alkanes (C < 8) obtained from fractional distillation of crude oil. Cracking is the name given to a number of petroleum refining processes which break up large hydrocarbon molecules into smaller fragment. Steam cracking is achieved without a catalyst by using high temperatures (~900 ^oC) and produces a mixtures of products containing high proportions of hydrocarbons with double bonds. There is not any single unique reaction happening during steam cracking. The hydrocarbon molecules are broken up in a fairly random way but the process can be generically represented by the reaction below.



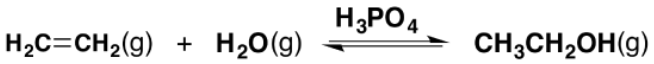
The mechanism of the steam cracking is complex and believed to involve the formation of free radicals. The high temperatures of steam cracking is enough to cause the homolytic cleavage of C-C and C-H bonds in the starting material. The cleavage of C-C bonds inherently

creates smaller hydrocarbons as represented below.



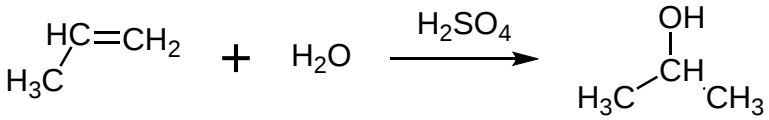
INDUSTRIAL PREPARATIONS OF ALCOHOLS FROM ETHYLENE AND PROPYLENE

Ethanol is manufactured by reacting ethylene with steam. The catalyst used is solid silicon dioxide coated with phosphoric acid. The reaction is reversible.

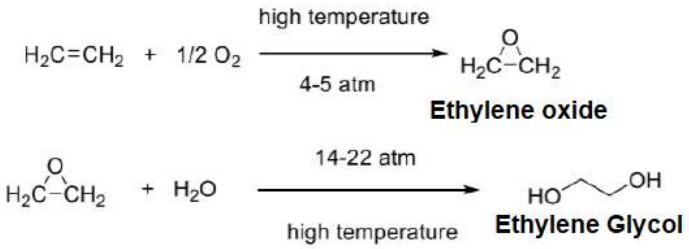


Only 5% of the ethylene is converted into ethanol at each pass through the reactor. By removing the ethanol from the equilibrium mixture and recycling the ethylene, it is possible to achieve an overall 95% conversion.

Isopropyl alcohol is synthesized on an industrial scale using a similar reaction with propylene.



Ethylene is also used in the industrial synthesis of ethylene glycol. Ethylene glycol is a major industrial compound with a wide range of applications. The traditional method to synthesize ethylene glycol is a two step process in which ethylene is directly oxidized to ethylene oxide. Next the three-membered ring of ethylene oxide is opened using water at high temperatures and pressures to form ethylene glycol.



INDUSTRIAL PREPARATIONS OF PLASTICS FROM ETHYLENE AND PROPYLENE

One of the primary uses of industrial synthesized ethylene is the production of the polymer **polyethylene (PE)**. Polyethylene is the most common plastic. As of 2017, over 100 million tons of polyethylene resins are produced annually, accounting for 34% of the total plastics market. Its primary use is in packaging (plastic bags, plastic films, geomembranes, containers including bottles, etc.). Many kinds of polyethylene are known, with most having the chemical formula $(C_2H_4)_n$.

It is the simplest polymer, consisting of random-length (but generally very long) chains made up of two-carbon units. During the polymerization process many ethylene molecules are linked together to form the carbon backbone of polyethylene. In the polyethylene structures are represented below. The squiggly lines at the ends of the long structure indicate that the same pattern extends indefinitely. The more compact notation on the right shows the minimal repeating unit enclosed in brackets; this means the same thing and is the preferred way of depicting polymer structures.

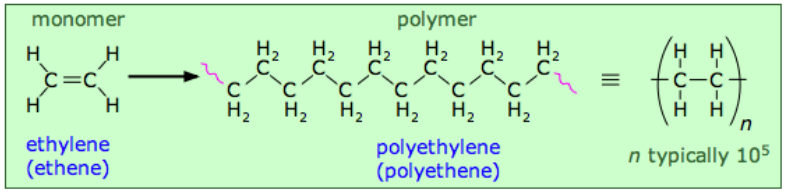


Figure **7.2.1** Polyethylene.

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7.3: CALCULATING DEGREE OF UNSATURATION

OBJECTIVES

After completing this section, you should be able to

- determine the degree of unsaturation of an organic compound, given its molecular formula, and hence determine the number of double bonds, triple bonds and rings present in the compound.
- draw all the possible isomers that correspond to a given molecular formula containing only carbon (up to a maximum of six atoms) and hydrogen.
- draw a specified number of isomers that correspond to a given molecular formula containing carbon, hydrogen, and possibly other elements, such as oxygen, nitrogen and the halogens.

KEY TERMS

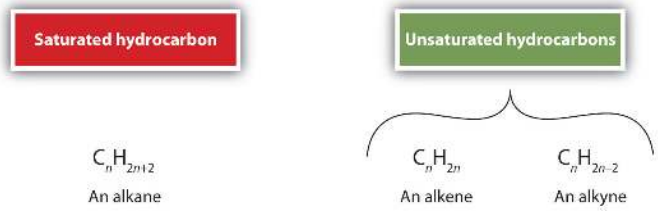
Make certain that you can define, and use in context, the key terms below.

- degree of unsaturation
- saturated
- unsaturated

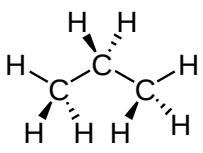
There are many ways one can go about determining the structure of an unknown organic molecule. Although, nuclear magnetic resonance (NMR) and infrared radiation (IR) are the primary ways of determining molecular structures, calculating the degrees of unsaturation is useful information because it easily provides information about molecular structure.

SATURATED AND UNSATURATED MOLECULES

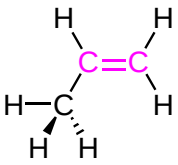
Because alkanes have the maximum number of H atoms possible according to the rules of covalent bonds, alkanes are also referred to as **saturated hydrocarbons**. The presence of a double bond causes alkenes to have less hydrogens than an alkane with the same number of carbons. Likewise, compounds containing a carbon-to-carbon triple bonds (R–C≡C–R) called alkynes (**Discussed in Chapter 9**), also have fewer hydrogens than the corresponding alkane. Collectively, compounds which have fewer hydrogen atoms than an alkane with the same number of carbon atoms are called **unsaturated hydrocarbons**. The relationship between the number of carbons (n) and hydrogens in the molecular formula for alkanes, alkenes, and alkynes are listed below.



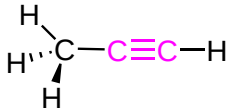
For example, the three carbon alkane, propane has the molecular formula of C_3H_8. While the unsaturated compounds propene (C_3H_6) and propyne (C_3H_4) both have fewer hydrogens. Also, it is important to note that cycloalkanes with one ring have a general molecular formula of C_nH_{2n} just like alkenes. Because they also have fewer than maximum number of hydrogens possible, cyclic compounds are also considered unsaturated.



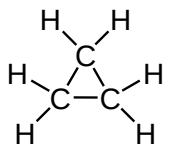
Propane (C_3H_8) Saturated



Propene (C_3H_6) Unaturated



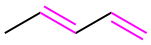
Propyne (C_3H_4) Unaturated



Cyclopropane (C_3H_6) Unaturated

IDENTIFYING DEGREES OF UNSATURATION

Every ring or pi bond in a compound is said to represent one degree of unsaturation. Being able to determine the degrees of unsaturation in a given compound is an important skill. Each of the following compounds are isomers of C_5H_7 and contain two degrees of unsaturation.



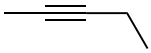
1,3-Pentadiene (Two double bonds)



Cyclopentene (One double bond and one ring)



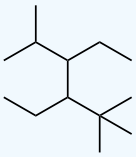
Bycyclo[2.1.0]pentane (Two rings)



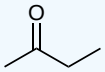
2-Pentyne (One triple bond)

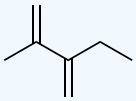
? EXERCISE 7.3.1

How many degrees of unsaturation do the following compounds have?

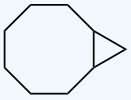
a) 

b) $CH_3CH_2CH{=}CHCF_3$

c) 

d) 

e) 3-chloro-5-octyne

f) 

Answer

a) 0

b) 1

c) 1

d) 2

e) 2

f) 2

CALCULATING THE DEGREE OF UNSATURATION (DOU)

As noted above, every degree of unsaturation causes the loss of two hydrogens from a compound's molecular formula when compared to an alkane with the same number of carbons. Understanding this relationship allows for the degrees of unsaturation of a compound to be calculated from its molecular formula. First, the maximum number of hydrogens possible for a given compound **(2C + 2)** is calculated and then the actual number of hydrogens present in the compound **(H)** is subtracted**.** If this difference is then divided by 2 the answer will be equal to the degrees of unsaturation for the compound.

For a compound which only contains carbon and hydrogen:

$$\text{DoU} = (2C + 2) - H / 2$$

As an example, for the molecular formula C_3H_4 the number of actual hydrogens needed for the compound to be saturated is 8 **[2C+2= (2x3)+2=8]**. Because the compound only has 4 hydrogens in its molecular formula, it would have to gain 4 more hydrogens in order to be fully saturated **(8-4 = 4)**. Degrees of unsaturation is equal to half the number of hydrogens the molecule needs to be fully saturated. This compound has 2 degrees of unsaturation **(4/2 = 2)**.

The DoU of compounds containing elements other than carbon and hydrogen can also be calculated in a similar fashion. However, different elements can affect the formula used to calculate DoU.

For a compound which contains elements other than carbon and hydrogen:

$$DoU = \frac{2C + 2 + N - X - H}{2} \tag{7.2.1}$$

- C is the number of carbons

- N is the number of nitrogens
- X is the number of halogens (F, Cl, Br, I)
- H is the number of hydrogens

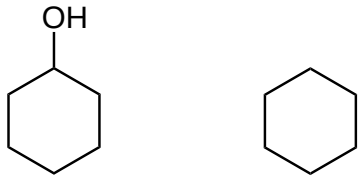
A halogen (X) replaces a hydrogen in a compound because both form one single bond. Therefore the DoU formula subtracts the number of halogens (X) present in a compound. For instance, 1,1-dichloroethene ($C_2H_2Cl_2$) has two fewer hydrogens than ethene (C_2H_4) yet they both have one degree of unsaturation.



1,1-Dichloroethene ($C_2H_2Cl_2$) **Ethene (C_2H_4)**

One Degree of Unsaturation

Oxygen and sulfur are not included in the DoU formula because saturation is unaffected by these elements. The inclusion of an alcohol or sulfur in a compound does not change the number of hydrogens to obtain saturation. As seen in alcohols, the number of hydrogens in cyclohexanol ($C_6H_{12}O$) matches the number of hydrogens in cyclohexane (C_6H_{12}) and they both have one degree of unsaturation.



Cyclohexanol ($C_6H_{12}O$) **Cyclohexane (C_6H_{12})**

One Degree of Unsaturation

When a nitrogen is present in a compound one more hydrogen is required to reach saturation. Therefore, we add the number of nitrogens (N). Propyl amine (C_3H_9N) has one more hydrogen compared to propane (C_3H_8) both of which are saturated compounds with 0 DoU.



Propyl Amine (C_3H_9N) **Propane (C_3H_8)**

Zero Degrees of Unsaturation

With the degrees of unsaturation comes information about the possible number of rings and multiple bonds in a given compound. Remember, the degrees of unsaturation only gives the sum of pi bonds and/or rings.

- One degree of unsaturation is equivalent to 1 ring or 1 double bond (1 π bond).
- Two degrees of unsaturation is equivalent to 2 double bonds, 1 ring and 1 double bond, 2 rings, or 1 triple bond (2 π bonds).

EXAMPLE 7.3.1: BENZENE

What is the Degree of Unsaturation for Benzene?

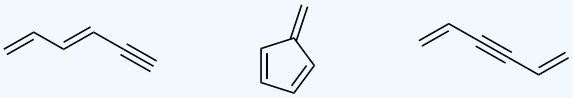
Solution

The molecular formula for benzene is C_6H_6. Thus,

DoU= 4, where C=6, N=0,X=0, and H=6. 1 DoB can equal 1 ring or 1 double bond. This corresponds to benzene containing 1 ring and 3 double bonds.

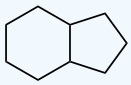


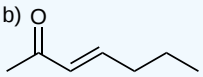
However, when given the molecular formula C_6H_6, benzene is only one of many possible structures (isomers). The following structures all have DoB of 4 and have the same molecular formula as benzene.

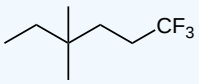


EXERCISE 7.3.2

Determine whether the following molecules are saturated or unsaturated.

a) 

b) 

c) 

d) $C_{10}H_6N_4$ e) $C_5H_{10}O$ f) $C_6H_{12}F_2$

Answer

a) **unsaturated** (*Even though the rings only contain single bonds, rings are considered unsaturated.)*

b) **unsaturated**

c) **saturated**

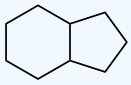
d) **unsaturated**

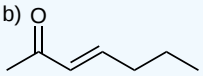
e) **unsaturated**

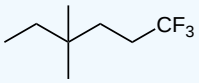
f) **saturated**

EXERCISE 7.3.3

Determine the degrees of unsaturation for each of the following compounds.

a) 

b) 

c) 

d) $C_{10}H_6N_4$ e) $C_5H_{10}O$ f) $C_6H_{12}F_2$

Answer

If the molecular structure is given, the easiest way to solve is to count the number of double bonds, triple bonds and/or rings. However, you can also determine the molecular formula and solve for the degrees of unsaturation by using the formula.

a) **2** (2 rings)

b) **2** *(one double bond and the double bond from the carbonyl)*

c) **0** (no double bonds or rings)

d) **10 (2(10) + 2 + 4 - 0 - 6)/2 = 10**

e) **1 (2(5) + 2 + 0 - 0 - 10)/2 = 1**

f) **0 (2(6) + 2 + 0 - 2 - 12)/2 = 0**

EXERCISE 7.3.4

Calculate the degrees of unsaturation for the following molecular formulas:

a) C_9H_{20} b) C_7H_8 c) C_5H_7Cl d) $C_9H_9NO_4$

Answer

Use the formula to solve (O not involved in the formula)

(a.) **0 (2(9) + 2 - 20)/2 = 0**

(b.) **4 (2(7) + 2 - 8)/2 = 4**

(c.) **2 (2(5) + 2 - 1 -7)/2 = 2**

(d.) **6 (2(9) + 1 - 7)/2 = 6**

REFERENCES

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5thEd.). New York: W. H. Freeman. (473-474)
2. Shore, N. (2007). *Study Guide and Solutions Manual for Organic Chemistry* (5th Ed.). New York: W.H. Freeman. (201)

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7.4: NAMING ALKENES

OBJECTIVES

After completing this section, you should be able to

- provide the correct IUPAC name for an acyclic or cyclic alkene, given its Kekulé, condensed or shorthand structure.
- draw the Kekulé, condensed or shorthand structure of an alkene (cyclic or acyclic), given its IUPAC name.
- give the IUPAC equivalent of the following trivial names: ethylene, propylene, isobutylene and isoprene.
- draw the structure of a vinyl (ethenyl) and allyl (2-propenyl) group, and use these names in alkene nomenclature.

STUDY NOTES

This course uses IUPAC nomenclature; therefore, you need not usually memorize a large number of trivial names. However, you will encounter some trivial names so frequently in books and articles that they soon become familiar.

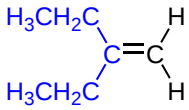
An alkene that can exhibit geometric isomerism has not been properly named unless its name specifies whether the double bond (or bonds) is (or are) cis or trans. The most effective way of giving this information is discussed, and more details of cis and trans follow in Section 7.4.

Alkenes contain carbon-carbon double bonds and are unsaturated hydrocarbons with the molecular formula is C_nH_{2n}; this is also the same molecular formula as cycloalkanes. The parent chain of an alkene is the longest chain containing both carbon atoms of the double bond. Alkenes are named by dropping the **-ane** ending of the parent and adding **-ene**. Also, the position of double bond in the parent chain of the alkene is indicated with a number.

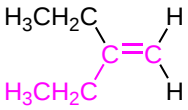
THE BASIC RULES FOR NAMING ALKENES

For straight chain alkenes, it is the same basic rules as nomenclature of alkanes apply except the **-ane** suffix is changed to **-ene**.

1) Find the longest carbon chain that contains both carbons of the double bond.

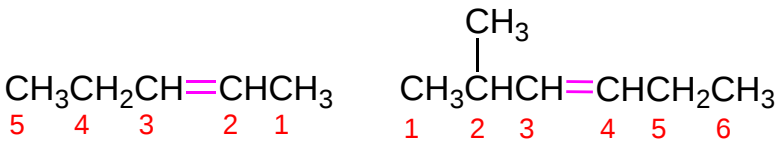


This compound is NOT named as an pentene



This compound is named as a butene because the double bond is contained in the four carbon chain

2) Start numbering from the end of the parent chain which gives the lowest possible number to the double bond. If the double bond is equidistant from both ends of the parent chain, number from the end which gives the substituents the lowest possible number. The double bond in cycloalkenes do not need to number because it is understood that they are in the one position.

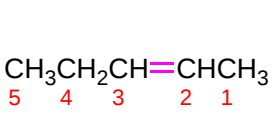


3) Place the location number of the double bond directly before the parent name. The location number indicates the position of the first carbon of the double bond. Add substituents and their position to the alkene as prefixes. Remember substituents are written in alphabetical order.

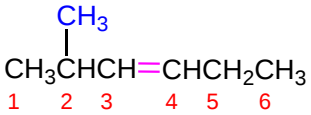
The presence of multiple double bonds is indicated by using the appropriate suffix such as **-diene**, **-triene**, ect. Each of the multiple bonds receives a location number. Also, only **-ne** is removed from the parent alkane chain name leaving an "a" in the name.

Overall, the name of an alkene should look like:

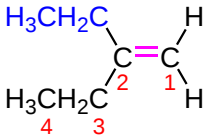
(Location number of substituent)-(Name of substituent)-(Location number of double bond)-(Name of parent chain) + ene



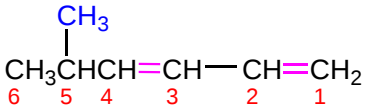
2-Pentene



2-Methyl-3-hexene



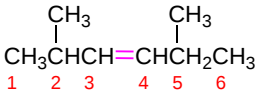
3-Ethyl-1-butene

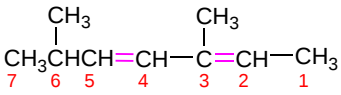


5-Methyl-1,3-hexadiene

NEWER IUPAC NOMENCLATURE

In 1993 IUPAC updated their naming recommendation to place the location number of the double bond before the -ene suffix of alkene names. The provides names such as hex-2-ene rather than 2-hexene. The newer system is slowly being accepted so it may occasionally be encountered.

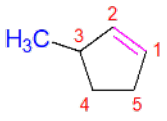




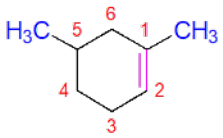
Older Numbering System:	**2,5-Dimethyl-3-hexene**	**5-Methyl-1,3-hexadiene**
Newer Numbering System:	**2,5-Dimethylhex-3-ene**	**5-Methylhexa-1,3-diene**

NAMING CYCLOALKENES

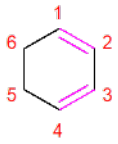
Because there are no chain ends in cycloalkenes, the double bond is assumed to numbered C1 and C2 and its location number is not required in the name. The direction of the numbering is determined by which will give the substituent closest to the double bond the lowest number. If multiple double bonds are present, it may be necessary to include their location numbers in the name. One of the double bonds will be number C1 and C2 and the numbering direction is determined by which gives the remaining double bonds the lowest possible number.



3-Methylcyclopent-1-ene



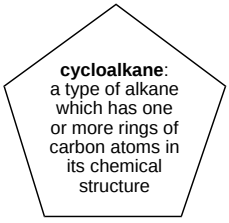
1,5-Dimethylcyclohexene



1,3-Cyclohexadiene
(New:Cyclohexa-1,3-diene)

ENDOCYCLIC VS. EXOCYCLIC ALKENES

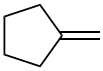
Endocyclic double bonds have both carbons in the ring and exocyclic double bonds have only one carbon as part of the ring.



Cyclopentene is an example of an endocyclic double bond.



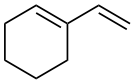
Methylenecylopentane is an example of an exocyclic double bond.



Name the following compounds...



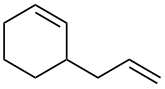
1-methylcyclobutene. The methyl group places the double bond. It is correct to also name this compound as 1-methylcyclobut-1-ene.



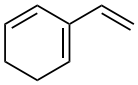
1-ethenylcyclohexene, the methyl group places the double bond. It is correct to also name this compound as 1-ethenylcyclohex-1-ene. A common name would be 1-vinylcyclohexene.

Try to draw structures for the following compounds...

- 3-allylcyclohex-1-ene

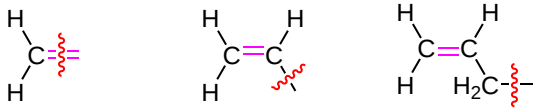


- 2-vinyl-1,3-cyclohexadiene



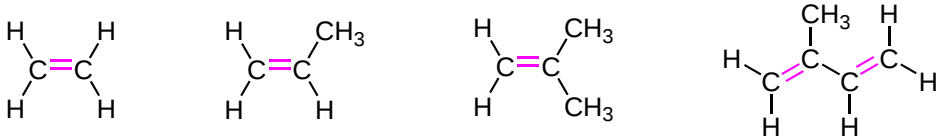
COMMON NAMES OF ALKENE FRAGMENTS

Some alkene containing fragments have common names which should be recognized. These common names can be used to simplify naming much the alkyl fragments discussed in **Section: 3.3**. Some of these fragments are the methylene group (H_2C=), the vinyl group (H_2C=CH-), and the allyl group (H_2C=CH-CH_2-).



Methylene Group **Vinyl Group** **Allyl Group**

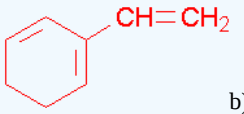
In addition, the common name some small alkene compounds are still accepted by IUPAC. It is important to be able to identify them.

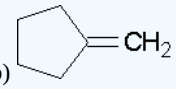


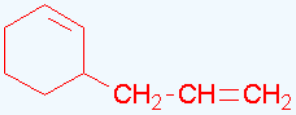
Common Name:	**Ethylene**	**Propylene**	**Isobutylene**	**Isoprene**
IUPAC Name:	**Ethene**	**Propene**	**2-Methylpropene**	**2-Methyl-1,3-butadiene**

? EXERCISE 7.4.1

Name the following compounds using common fragment names.

a) 

b) 

C) 

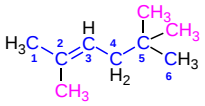
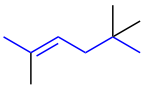
Answer

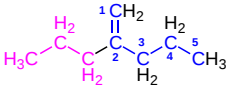
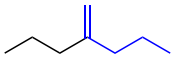
a) 2-Vinyl-cyclohexa-1,3-diene

b) Methylenecylopentane

c) 3-Allylcyclohex-1-ene

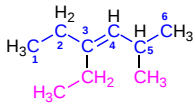
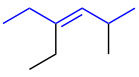
EXAMPLES

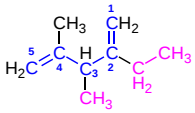
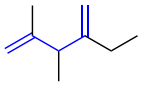
(1)  ≡  ≡ $(CH_3)_2C{=}CHCH_2C(CH_3)_3$
2,5,5-trimethyl-2-hexene

(2)  ≡  ≡ $(CH_3CH_2CH_2)_2C{=}CH_2$
2-propyl-1-pentene

Both these compounds have double bonds, making them alkenes. In example (1) the longest chain consists of six carbons, so the root name of this compound will be hexene. Three methyl substituents (colored red) are present. Numbering the six-carbon chain begins at the end nearest the double bond (the left end), so the methyl groups are located on carbons 2 & 5. The IUPAC name is therefore: 2,5,5-trimethyl-2-hexene.

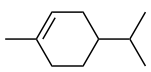
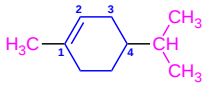
In example (2) the longest chain incorporating both carbon atoms of the double bond has a length of five. There is a seven-carbon chain, but it contains only one of the double bond carbon atoms. Consequently, the root name of this compound will be pentene. There is a propyl substituent on the inside double bond carbon atom (#2), so the IUPAC name is: 2-propyl-1-pentene.

(3)  ≡  ≡ $(CH_3CH_2)_2C{=}CHCH(CH_3)_2$
4-ethyl-2-methyl-3-hexene

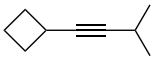
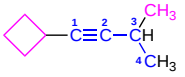
(4)  ≡  ≡ $CH_2{=}C(CH_3)CH(CH_3)C(C_2H_5){=}CH_2$
2-ethyl-3,4-dimethyl-1,4-pentadiene

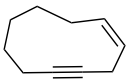
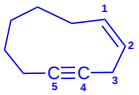
The double bond in example (3) is located in the center of a six-carbon chain. The double bond would therefore have a locator number of 3 regardless of the end chosen to begin numbering. The right hand end is selected because it gives the lowest first-substituent number (2 for the methyl as compared with 3 for the ethyl if numbering were started from the left). The IUPAC name is assigned as shown.

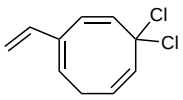
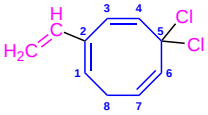
Example (4) is a diene (two double bonds). Both double bonds must be contained in the longest chain, which is therefore five- rather than six-carbons in length. The second and fourth carbons of this 1,4-pentadiene are both substituted, so the numbering begins at the end nearest the alphabetically first-cited substituent (the ethyl group).

(5)  ≡  ≡ 4-isopropyl-1-methylcyclohexene

4-isopropyl-1-methylcyclohex-1-ene

(6)  ≡  ≡ 1-cyclobutyl-3-methyl-1-butyne

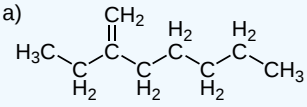
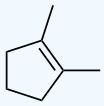
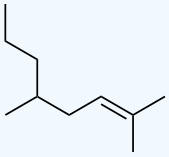
(7)  ≡  ≡ 1-cyclodecen-4-yne

(8)  ≡  ≡ 5,5-dichloro-2-vinyl-1,3,6-cyclooctatriene

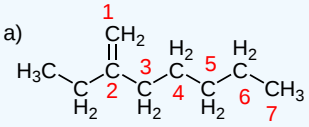
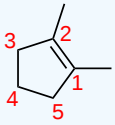
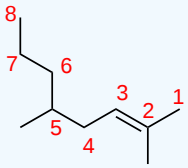
These examples include rings of carbon atoms as well as some carbon-carbon triple bonds. Example (6) is best named as an alkyne bearing a cyclobutyl substituent. Example (7) is simply a ten-membered ring containing both a double and a triple bond. The double bond is cited first in the IUPAC name, so numbering begins with those two carbons in the direction that gives the triple bond carbons the lowest locator numbers. Because of the linear geometry of a triple bond, a-ten membered ring is the smallest ring in which this functional group is easily accommodated. Example (8) is a cyclooctatriene (three double bonds in an eight-membered ring). The numbering must begin with one of the end carbons of the conjugated diene moiety (adjacent double bonds), because in this way the double bond carbon atoms are assigned the smallest possible locator numbers (1, 2, 3, 4, 6 & 7). Of the two ways in which this can be done, we choose the one that gives the vinyl substituent the lower number.

EXERCISE 7.4.2

Name the following alkenes.

a)  b)  c) 

Answer

a)  b)  c) 

a) 2-ethylhept-1-ene or 2-ethyl-1-heptene

b) 1,2-dimethylcyclohept-1-ene

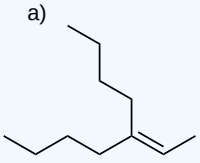
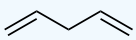
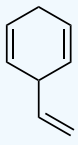
c) 2,5-dimethyloct-2-ene or 2,5-dimethyl-1-octene

EXERCISE 7.4.3

Draw structures for the following compounds from the given names.

a. 3-butylhept-2-ene (3-butyl-2-heptene)
b. 1,4-pentadiene (penta-1,4-diene)
c. 3-vinyl-1,4-cyclohexadiene (cyclohexa-1,4-diene)

Answer

a)  b)  c) 

REFERENCES

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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7.5: CIS-TRANS ISOMERISM IN ALKENES

OBJECTIVES

After completing this section, you should be able to

- discuss the formation of carbon-carbon double bonds using the concept of sp^2 hybridization.
- describe the geometry of compounds containing carbon-carbon double bonds.
- compare the molecular parameters (bond lengths, strengths and angles) of a typical alkene with those of a typical alkane.
- explain why free rotation is not possible about a carbon-carbon double bond.
- explain why the lack of free rotation about a carbon-carbon double bond results in the occurrence of cis-trans isomerism in certain alkenes.
- decide whether or not cis-trans isomerism is possible for a given alkene, and where such isomerism is possible, draw the Kekulé structure of each isomer.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- cis-trans stereoisomers

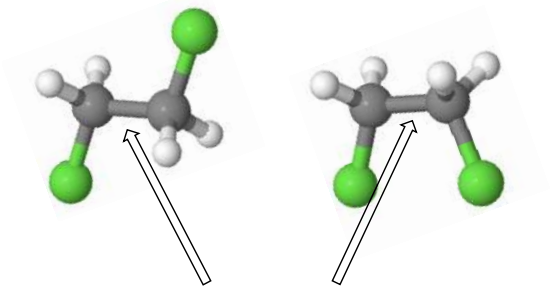
STUDY NOTES

Your previous studies in chemistry may have prepared you to discuss the nature of a carbon-carbon double bond. If not, you should review Section 1.8 of this course before beginning the present section. It is particularly important that you make molecular models of some simple alkenes to gain insight into the geometry of these compounds.

Geometric isomerism (also known as cis-trans isomerism or E-Z isomerism) is a form of stereoisomerism. Isomers are molecules that have the same molecular formula, but have a different arrangement of the atoms in space. That excludes any different arrangements which are simply due to the molecule rotating as a whole, or rotating about particular bonds. Where the atoms making up the various isomers are joined up in a different order, this is known as structural isomerism. Structural isomerism is **not** a form of stereoisomerism, and is dealt with in a separate Module.

GEOMETRIC (CIS / TRANS) ISOMERISM

These isomers occur where you have restricted rotation somewhere in a molecule. At an introductory level in organic chemistry, examples usually just involve the carbon-carbon double bond - and that's what this page will concentrate on. Think about what happens in molecules where there is **un**restricted rotation about carbon bonds - in other words where the carbon-carbon bonds are all single. The next diagram shows two possible configurations of 1,2-dichloroethane.

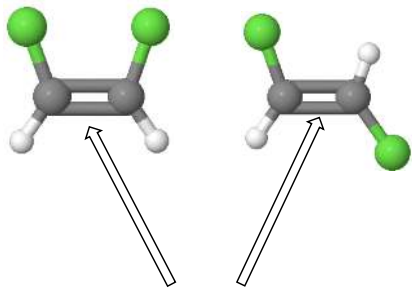


free rotation about carbon-carbon single bond

These two models represent exactly the same molecule. You can get from one to the other just by twisting around the carbon-carbon single bond. These molecules are *not* isomers. If you draw a structural formula instead of using models, you have to bear in mind the possibility of this free rotation about single bonds. You must accept that these two structures represent the same molecule:



But what happens if you have a carbon-carbon double bond - as in 1,2-dichloroethene?

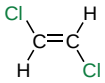


no free rotation about carbon-carbon double bond

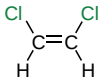
These two molecules are not the same. The carbon-carbon double bond won't rotate and so you would have to take the models to pieces in order to convert one structure into the other one. That is a simple test for isomers. If you have to take a model to pieces to convert it into another one, then you've got isomers. If you merely have to twist it a bit, then you haven't!

Drawing structural formulae for the last pair of models gives two possible isomers:

1. In one, the two chlorine atoms are locked on opposite sides of the double bond. This is known as the ***trans*** isomer. (*trans* : from latin meaning "across" - as in transatlantic).
2. In the other, the two chlorine atoms are locked on the same side of the double bond. This is know as the ***cis*** isomer. (*cis* : from latin meaning "on this side")

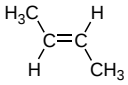


trans-1,2-dichloroethene

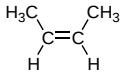


cis-1,2-dichloroethene

The most likely example of geometric isomerism you will meet at an introductory level is but-2-ene. In one case, the CH_3 groups are on opposite sides of the double bond, and in the other case they are on the same side.



trans-but-2-ene



cis-but-2-ene

THE IMPORTANCE OF DRAWING GEOMETRIC ISOMERS PROPERLY

It's very easy to miss geometric isomers in exams if you take short-cuts in drawing the structural formulae. For example, it is very tempting to draw but-2-ene as

$$CH_3CH=CHCH_3$$

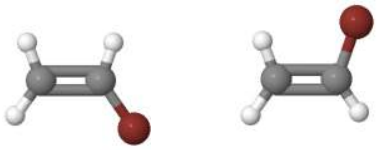
If you write it like this, you will almost certainly miss the fact that there are geometric isomers. If there is even the slightest hint in a question that isomers might be involved, always draw compounds containing carbon-carbon double bonds showing the correct bond angles (120°) around the carbon atoms at the ends of the bond. In other words, use the format shown in the last diagrams above.

HOW TO RECOGNIZE THE POSSIBILITY OF GEOMETRIC ISOMERISM

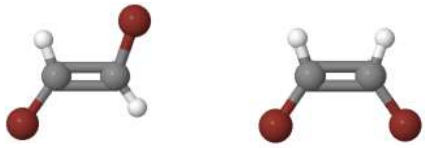
You obviously need to have restricted rotation somewhere in the molecule. Compounds containing a carbon-carbon double bond have this restricted rotation. (Other sorts of compounds may have restricted rotation as well, but we are concentrating on the case you are most likely to meet when you first come across geometric isomers.) If you have a carbon-carbon double bond, you need to think carefully about the possibility of geometric isomers.

What needs to be attached to the carbon-carbon double bond?

Think about this case:



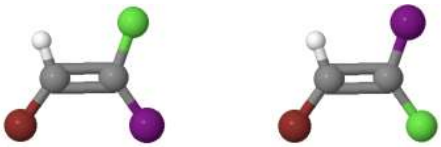
Although we've swapped the right-hand groups around, these are still the same molecule. To get from one to the other, all you would have to do is to turn the whole model over. You won't have geometric isomers if there are two groups the same on one end of the bond - in this case, the two pink groups on the left-hand end. So there must be two different groups on the left-hand carbon and two different groups on the right-hand one. The cases we've been exploring earlier are like this:



But you could make things even more different and still have geometric isomers:

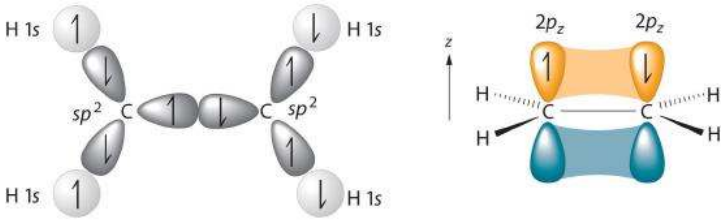


Here, the blue and green groups are either on the same side of the bond or the opposite side. Or you could go the whole hog and make everything different. You still get geometric isomers, but by now the words *cis* and *trans* are meaningless. This is where the more sophisticated *E*-*Z* notation comes in.



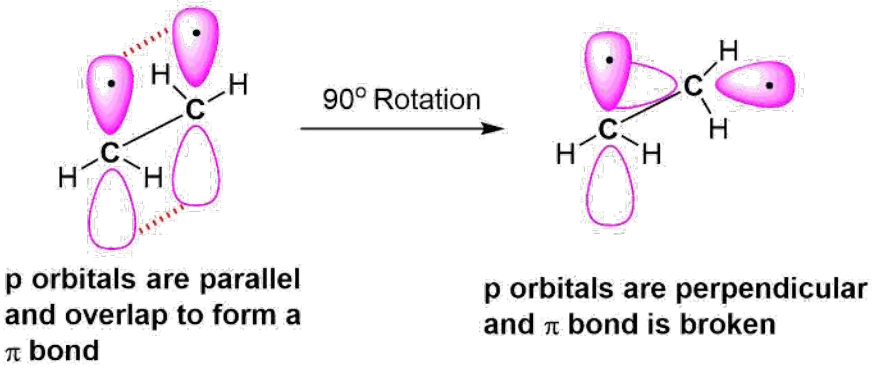
RIGIDITY OF C=C BONDS

As discussed in Section 1.8 the double bond in the molecule ethene ($H_2C=CH_2$) is created by the overlap of two different sets of orbitals. The C-C σ bond is formed when an sp^2 orbital from each carbon atom overlaps end to end. Also, the C-C pi bond is created by the side-to-side overlap of a p_z orbital from each carbon atom.

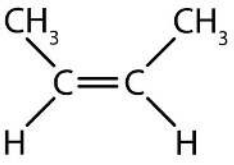


(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

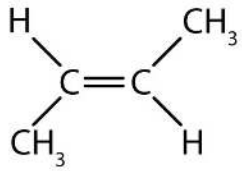
Because they are the result of side-by-side overlap (rather then end-to-end overlap like a sigma bond), *pi bonds are not free to rotate.* If rotation about this bond were to occur, it would involve disrupting the side-by-side overlap between the two $2p_z$ orbitals that make up the pi bond. If free rotation were to occur the p-orbitals would have to go through a phase where they are 90° from each other, which would break the pi bond because there would be no overlap. Since the pi bond is essential to the structure of ethene it must not break, so there can be no free rotation about the carbon-carbon sigma bond. The presence of the pi bond thus 'locks' the six atoms of ethene into the same plane.



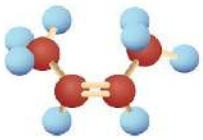
Restricted rotation about the double bond means that the relative positions of substituent groups above or below the double bond become significant. This leads to a special kind of isomerism in double bonds. Consider the alkene with the condensed structural formula $CH_3CH{=}CHCH_3$. We could name it 2-butene, but there are actually two such compounds due to this isomerism. The isomer in which the two methyl (CH_3) groups lie on the same side of the molecule is called the cis isomer (Latin *cis*, meaning "on this side") and is named cis-2-butene. The isomer with the two (CH_3) groups on opposite sides of the molecule is the trans isomer (Latin *trans*, meaning "across") and is named *trans*-2-butene. These two compounds are *cis-trans* isomers (or geometric isomers), compounds that have different configurations (groups permanently in different places in space) because of the presence of a rigid structure in their molecule. In general these isomers have different physical, chemical, and physiological properties.

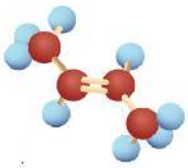


cis-2-butene

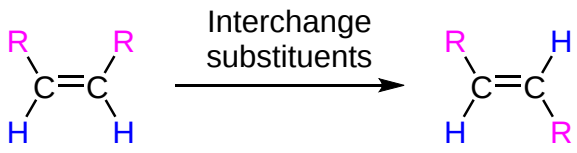


trans-2-butene



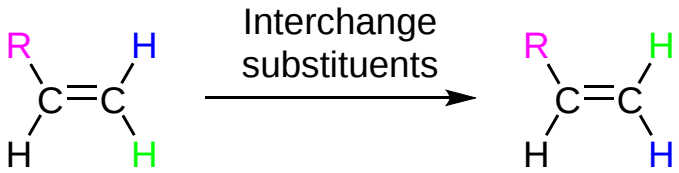


It is important to note that the presence of a double bond does **not** necessarily lead to *cis-trans* isomerism. Being able to tell if a double bond has the possibility of isomerism is a very important skill. *Cis-trans* can occur whenever both double-bond carbons are directly attached to a carbon and a hydrogen. In this case, interchanging the substituents on one of the double-bond carbons creates a different isomer.



***cis*-Isomer** ***trans*-isomer**

If one of the double-bond carbons of an alkene is attached to two identical groups, *cis-trans* isomerism is not possible. Here, interchanging the substituents on one of the double-bond carbons forms an identical molecule.



These two molecules are identical

? WORKED EXAMPLE 7.5.1

Are the following molecules *cis-trans* isomers?



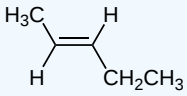
Answer

Although the two molecules *are seemingly* different propenes, these two structures are not really different from each other. Because the one of the double-bond carbons is attached to two identical groups (hydrogens) it is incapable of forming *cis-trans* isomers. The interchange of two substituents seen here does not create a new isomer. If either molecule were flipped over top to bottom, the two would you would look identical.

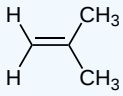
? EXERCISE 7.5.1

Classify each compound as a *cis* isomer, a *trans* isomer, or neither.

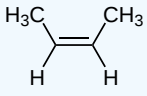
a)



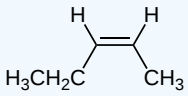
b)



c)



d)



Answer

a) trans isomer

b) neither

c) cis isomer

d) cis isomer

? EXERCISE 7.5.2

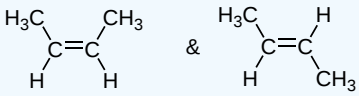
Which of the following compounds could exist as cis/trans isomers? Draw (& label) both of the isomers for the ones that can.

a. $CH_3CH{=}CHCH_3$
b. $(CH_3)_2C{=}CHCH_3$
c. $H_2C{=}CHCH_3$
d. $CH_3CH_2CH{=}CHBr$

Answer

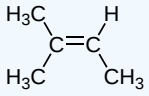
https://chem.libretexts.org/@go/page/31454

a)



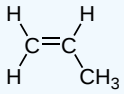
cis isomer & trans isomer

b)



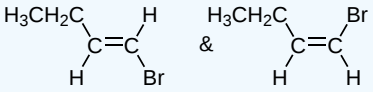
no cis/trans isomers

c)



no cis/trans isomers

d)



trans isomer & cis isomer

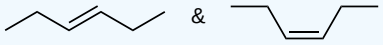
EXERCISE 7.5.3

Draw (& label) the cis and trans isomer for each of the following compound names. If no cis/trans isomerism is possible, write none.

a. 3-hexene
b. 1-hexene
c. 4-methylpent-2-ene (4-methyl-2-pentene)
d. 1,1-dibromobut-2-ene (1,1-dibromo-2-butene)

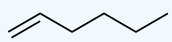
Answer

a)



trans isomer & cis isomer

b)



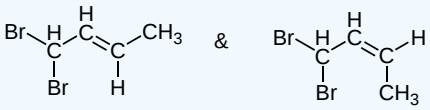
no cis/trans isomers

c)



trans isomer & cis isomer

d)

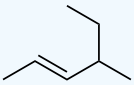


trans isomer & cis isomer

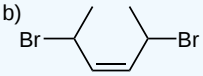
EXERCISE 7.5.4

Name the following compounds using cis/trans nomenclature

a)



b)



Answer

a) *trans*-4-methylhex-2-ene (*trans*-4-methyl-2-hexene)

b) *cis*-2,5-dibromohex-3-ene (*cis*-2,5-dibromo-3-hexene)

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7.6: SEQUENCE RULES - THE E,Z DESIGNATION

OBJECTIVES

After completing this section, you should be able to

- illustrate, by means of a suitable example, the limitations of the terms *cis* and *trans* in naming isomeric alkenes.
- use the *E*/*Z* designation to describe the geometry of a given alkene structure.
- incorporate the *E*/*Z* designation into the IUPAC name of a given alkene.
- draw the correct Kekulé, condensed or shorthand structure of an alkene, given its *E*/*Z* designation plus other necessary information (e.g., molecular formula, IUPAC name).

KEY TERMS

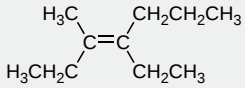
Make certain that you can define, and use in context, the key term below.

- sequence rules (Cahn-Ingold-Prelog rules)

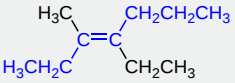
STUDY NOTES

The limitations of the *cis/trans* system are illustrated in the examples given below.

1. From your study of the IUPAC system, you should be able to identify this compound as 4-ethyl-3-methyl-3-heptene, but is it *cis* or *trans*?

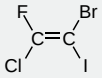


At first you might say *cis*, because it appears that two ethyl groups appear on the same side of the double bond. However, the correct answer is *trans*. The rule is that the designation *cis* or *trans* must correspond to the configuration of the *longest* carbon chain. Tracing out the seven-carbon chain in the compound shown above, you change sides as you pass through the double bond:

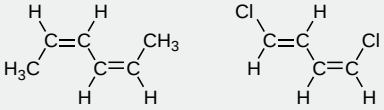


So, the full name for this compound is *trans*-4-ethyl-3methyl-3-heptene.

2. The *cis*/*trans* system breaks down completely in a compound such as that shown below. The *E*/*Z* system, which is the subject of this section, is designed to accommodate such situations.



In cases where two or more double bonds are present, you must be prepared to assign an *E* or *Z* designation to each of the double bonds. For example:

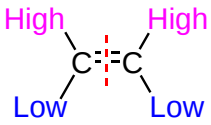


Another use for these sequence rules will be part of the discussion of optical isomerism in Section 9.5.

E/Z NOMENCLATURE

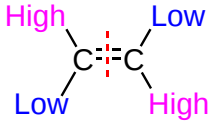
When each carbon in a double bond is attached to a hydrogen and and a non-hydrogen substituent, the geometric isomers can be identified by using the *cis-trans* nomenclature discussed in the previous section. However, when a double bond is attached to three or four non-hydrogen substituents there are some examples where *cis-trans* nomenclature is ineffective in describing the substituents orientation in geometric isomers. In these situations the rigorous IUPAC system for naming alkene isomers, called the E/Z system, is used. The E/Z system analyzes the two substituents attached to each carbon in the double bond and assigns each either a high or low priority. If the higher priority group on both carbons in the double bond the **same** side the alkene is said to have a **Z isomer** (from German zusammen = together).

You could think of Z as Zame Zide to help memorize it. If the higher priority group on **opposite** sides the alkene has an **E isomer** (from German entgegen = opposite).



Z Configuration

High priority substituents are on the same side of the double bond



E Configuration

High priority substituents are on opposide sides of the double bond

Note, if both substituents an a double bond carbon are exactly the same there is no E/Z isomerizem is possible. Also, if E/Z isomerism is possible, interchanging the substituents attached on double-bond carbon converts one isomer to the other.

Substituent priority for the E,Z system is assigned using the Cahn–Ingold–Prelog (CIP) sequence rules. These are the same rules used to assign R/S configurations to chiral centers in **Section 5.5**. A brief overview of using CIP rules to determine alkene configuration is given here but CIP rules are discussed in greater detail in **Section 5.5**.

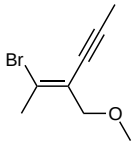
NOTE

The priority rules are often called the Cahn-Ingold-Prelog (CIP) rules, after the chemists who developed the system

RULE 1: THE "FIRST POINT OF DIFFERENCE" RULE

First, determine the two substituents on each double-bond carbon separately. Rank these substituents based on **the atom** which directly attached to the double-bond carbon. The substituent whose atom has a higher atomic number takes precedence over the substituent whose atom has a lower atomic number.

Which is higher priority, by the CIP rules: a C with an O and 2 H attached to it or a C with three C? The first C has one atom of high priority but also two atoms of low priority. How do these "balance out"? Answering this requires a clear understanding of how the ranking is done. The simple answer is that the first point of difference is what matters; the O wins.



To illustrate this, consider the molecule at the left. Is the double bond here *E* or *Z*? At the left end of the double bond, Br > C. But the right end of the double bond requires a careful analysis.

At the right hand end, the first atom attached to the double bond is a C at each position. A tie, so we look at what is attached to this first C. For the upper C, it is CCC (since the triple bond counts three times). For the lower C, it is OHH -- listed in order from high priority atom to low. OHH is higher priority than CCC, because of the first atom in the list. That is, the O of the lower group beats the C of the upper group. In other words, the O is the highest priority atom of any in this comparison; thus the O "wins".

Therefore, the high priority groups are "up" on the left end (the -Br) and "down" on the right end (the $-CH_2-O-CH_3$). This means that the isomer shown is opposite = entgegen = *E*. And what is the name? The "name" is (E)-2-Bromo-3-(methoxymethyl)hex-2-en-4-yne.

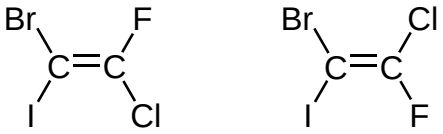
RULE 2

If the first atom on both substituents are the identical, then proceed along both substituent chains until the first point of difference is determined.

RULE 3

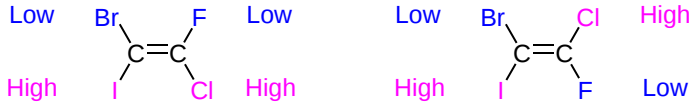
Remember that atoms involved in multiple bonds are considered with a specific set of rules. These atoms are treated as if they have the same number of single-bond atoms as they have attached to multiply bonded atoms.

An easy example which shows the necessity of the E/Z system is the alkene, 1-bromo-2-chloro-2-fluoro-1-iodoethene, which has four different substituents attached to the double bond. The figure below shows that there are two distinctly different geometric isomers for this molecule neither of which can be named using the *cis-trans* system.



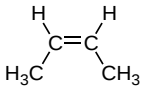
Consider the left hand structure. On the double bond carbon on the left, the two atoms attached to the double bond are Br and I. By the CIP priority rules, I is higher priority than Br (higher atomic number). Now look at carbon on the right. The attached atoms are Cl and F, with Cl having the higher atomic number and the higher priority.

When considering the relative positions of the higher priority groups, the higher priority group is "down" on the left double bond carbon and "down" at right double bond carbon. Since the two higher priority groups are both on the **same** side of the double bond ("down", in this case), they are zusammen = together. Therefore, this is the (Z) isomer. Similarly, the right hand structure is (E).

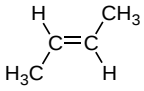


Z Configuration **E Configuration**

EXAMPLE 7..61: BUTENE



cis-2-butene
(*Z*)-2-butene



trans-2-butene
(*E*)-2-butene

The Figure above shows the two isomers of 2-butene. You should recognize them as *cis* and *trans*. Let's analyze them to see whether they are *E* or *Z*. Start with the left hand structure (the cis isomer). On C2 (the left end of the double bond), the two atoms attached to the double bond are C and H. By the CIP priority rules, C is higher priority than H (higher atomic number). Now look at C3 (the right end of the double bond). Similarly, the atoms are C and H, with C being higher priority. We see that the higher priority group is "down" at C2 and "down" at C3. Since the two priority groups are both on the **same** side of the double bond ("down", in this case), they are zusammen = together. Therefore, this is (*Z*)-2-butene.

Now look at the right hand structure (the *trans* isomer). In this case, the priority group is "down" on the left end of the double bond and "up" on the right end of the double bond. Since the two priority groups are on **opposite** sides of the double bond, they are entgegen = opposite. Therefore, this is (*E*)-2-butene.

E/*Z* WILL WORK – EVEN WHEN *CIS*/*TRANS* FAILS

In simple cases, such as 2-butene, *Z* corresponds to *cis* and *E* to *trans*. However, that is **not** a rule. This section and the following one illustrate some idiosyncrasies that happen when you try to compare the two systems. The real advantage of the *E*/*Z* system is that it will always work. In contrast, the *cis*/*trans* system breaks down with many ambiguous cases.

EXAMPLE 7.6.2

The following figure shows two isomers of an alkene with four different groups on the double bond, 1-bromo-2-chloro-2-fluoro-1-iodoethene.



(*Z*)-1-bromo-2-chloro-2-fluoro-1-iodoethene



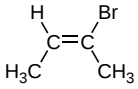
(*E*)-1-bromo-2-chloro-2-fluoro-1-iodoethene

It should be apparent that the two structures shown are distinct chemicals. However, it is impossible to name them as *cis* or *trans*. On the other hand, the *E*/*Z* system works fine... Consider the left hand structure. On C1 (the left end of the double bond), the two atoms

attached to the double bond are Br and I. By the CIP priority rules, I is higher priority than Br (higher atomic number). Now look at C2. The atoms are Cl and F, with Cl being higher priority. We see that the higher priority group is "down" at C1 and "down" at C2. Since the two priority groups are both on the **same** side of the double bond ("down", in this case), they are zusammen = together. Therefore, this is the (*Z*) isomer. Similarly, the right hand structure is (*E*).

E/*Z* WILL WORK, BUT MAY NOT AGREE WITH *CIS*/*TRANS*

Consider the molecule shown below. This is 2-bromo-2-butene -- ignoring the geometric isomerism for now. *Cis* or *trans*? This molecule is clearly *cis*. The two methyl groups are on the same side. More rigorously, the "parent chain" is *cis*.



E or *Z*? There is a methyl at each end of the double bond. On the left, the methyl is the high priority group -- because the other group is -H. On the right, the methyl is the low priority group -- because the other group is -Br. That is, the high priority groups are -CH_3 (left) and -Br (right). Thus the two priority groups are on opposite sides = entgegen = *E*.

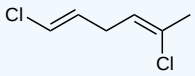
NOTE

This example should convince you that *cis* and *Z* are not synonyms. *Cis*/*trans* and *E*/*Z* are determined by distinct criteria. There may seem to be a simple correspondence, but it is not a rule. Be sure to determine *cis*/*trans* or *E*/*Z* separately, as needed.

MULTIPLE DOUBLE BONDS

If the compound contains more than one double bond, then each one is analyzed and declared to be *E* or *Z*.

EXAMPLE 7.6.3

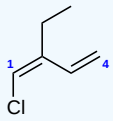


The configuration at the left hand double bond is *E*; at the right hand double bond it is *Z*. Thus this compound is (1*E*,4*Z*)-1,5-dichloro-1,4-hexadiene.

THE DOUBLE-BOND RULE IN DETERMINING PRIORITIES

EXAMPLE 7.6.4

Consider the compound below

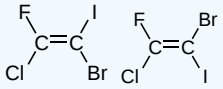


This is 1-chloro-2-ethyl-1,3-butadiene -- ignoring, for the moment, the geometric isomerism. There is no geometric isomerism at the second double bond, at 3-4, because it has 2 H at its far end.

What about the first double bond, at 1-2? On the left hand end, there is H and Cl; Cl is higher priority (by atomic number). On the right hand end, there is -CH_2-CH_3 (an ethyl group) and -CH=CH_2 (a vinyl or ethenyl group). Both of these groups have C as the first atom, so we have a tie so far and must look further. What is attached to this first C? For the ethyl group, the first C is attached to C, H, and H. For the ethenyl group, the first C is attached to a C twice, so we count it twice; therefore that C is attached to C, C, H. CCH is higher than CHH; therefore, the ethenyl group is higher priority. Since the priority groups, Cl and ethenyl, are on the same side of the double bond, this is the *Z*-isomer; the compound is (*Z*)-1-chloro-2-ethyl-1,3-butadiene.

EXAMPLE 7.6.5

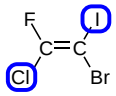
The configuration about double bonds is undoubtedly best specified by the *cis*/*trans* notation when there is no ambiguity involved. Unfortunately, many compounds cannot be described adequately by the *cis*/*trans* system. Consider, for example, configurational isomers of 1-fluoro-1-chloro-2-bromo-2-iodo-ethene, 9 and 10. There is no obvious way in which the *cis*/*trans* system can be used:



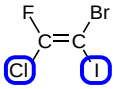
9 **10**

A system that is easy to use and which is based on the sequence rules already described for the *R*,*S* system works as follows:

1. An order of precedence is established for the two atoms or groups attached to each end of the double bond according to the sequence rules of Section 19-6. When these rules are applied to 1-fluoro- 1-chloro-2-bromo-2- iodoethene, the priority sequence is:
   - at carbon atom 1, C1 > F
   - at carbon atom 2, I > Br
2. Examination of the two configurations shows that the two priority groups- one on each end- are either on the same side of the double bond or on opposite sides:

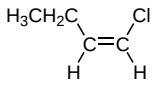


priority groups on opposite sides
(*E*) configuration

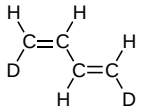


priority groups on same side
(*Z*) configuration

The *Z* isomer is designated as the isomer in which the top priority groups are on the same side (*Z* is taken from the German word zusammen- together). The *E* isomer has these groups on opposite sides (*E*, German for entgegen across). Two further examples show how the nomenclature is used:



(*Z*)-1-chloro-1-butene



(1*Z*,3*E*)-1,3-butadiene-1,4-*d*2

EXERCISES

EXERCISE 7.6.1

Which of the following sets has a higher ranking?

a. $-CH_3$ or $-CH_2Br$
b. -Br or -Cl
c. $-CH{=}CH_2$ or -CH=O

Answer

a) $-CH_2Br$

b) -Br

c) -CH=O

EXERCISE 7.6.2

Place the following sets of substituents in each group in order of lowest priority (1st) to highest priority (4th)

a. $-CH(CH_3)_2$, $-CH_2CH_3$, $-C(CH_3)_3$, $-CH_3$
b. $-NH_2$, -F, -Br, $-CH_3$
c. -SH, $-NH_2$, -F, -H

Answer

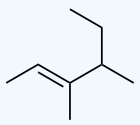
a) (lowest priority) $-CH_3 < -CH_2CH_3 < -CH(CH_3)_2 < -C(CH_3)_3$ (highest priority)

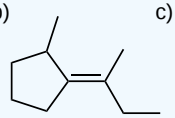
b) (lowest priority) $-CH_3 < -NH_2 <$ -F < -Br (highest priority)

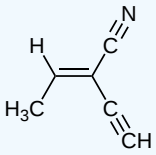
c) (lowest priority) -H < -NH_2 < -F < -SH (highest priority)

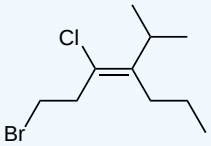
EXERCISE 7.6.3

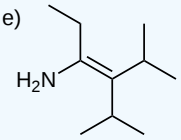
Label the following alkenes as E, Z, or neither.

a) 

b) 

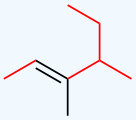
c) 

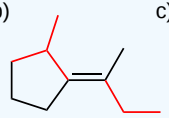
d) 

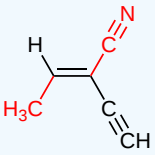
e) 

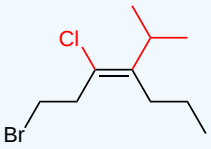
Answer

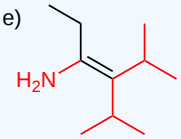
The higher priority group is highlighted in red.

a) 

b) 

c) 

d) 

e) 

a) E

b) E

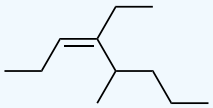
c) E

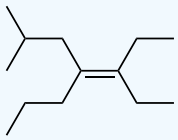
d) Z

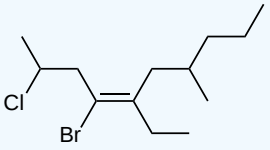
e) neither (both isopropyls on the right have the same priority)

EXERCISE 7.6.4

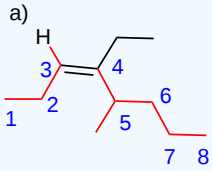
Name the following alkenes.

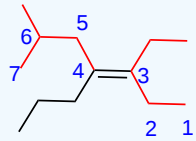
a) 

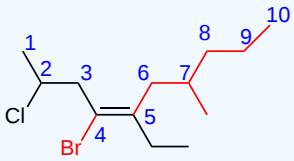
b) 

c) 

Answer

a) 

b) 

c) 

The higher priority group is highlighted in red.

a. (Z)-4-ethyl-5-methyloct-3-ene or (Z)-4-ethyl-5-methyl-3-octene

b. 3-ethyl-6-methyl-4-propylhept-3-ene or 3-ethyl-6-methyl-4-propyl-3-heptene

c. (E)-4-bromo-2-chloro-5-ethyl-7-methyldec-4-ene or (E)-4-bromo-2-chloro-5-ethyl-7-methyl-4-decene

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7.7: STABILITY OF ALKENES

OBJECTIVES

After completing this section, you should be able to

- explain why *cis* alkenes are generally less stable than their *trans* isomers.
- explain that catalytic reduction of a *cis* alkene produces the same alkane as the catalytic reduction of the *trans* isomer.
- explain how heats of hydrogenation ($\Delta H°_{hydrog}$) can be used to show that *cis* alkenes are less stable than their *trans* isomers, and discuss, briefly, the limitations of this approach.
- arrange a series of alkenes in order of increasing or decreasing stability.
- describe, briefly, two of the hypotheses proposed to explain why alkene stability increases with increased substitution. [**Note:** This problem is a typical example of those instances in science where there is probably no single "correct" explanation for an observed phenomenon.]

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- catalytic hydrogenation
- heat of hydrogenation ($\Delta H°_{hydrog}$)
- hyperconjugation

STUDY NOTES

The two alkenes, *cis*-$CH_3CH{=}CHCH_3$ and $(CH_3)_2C{=}CH_2$ have similar heats of hydrogenation (−120 kJ/mol and −119 kJ/mol, respectively), and are therefore of similar stability. However, they are both less stable than *trans*-$CH_3CH{=}CHCH_3$ (−116 kJ/mol).

You may wonder why an sp^2 -sp^3 bond is stronger than an sp^3-sp^3 bond. Bond strength depends on the efficiency with which orbitals can overlap. In general, *s* orbitals overlap more efficiently than do *p* orbitals; therefore, the *s*-*s* bond in the hydrogen molecule is stronger than the *p*-*p* bond in fluorine. In hybrid orbitals, the greater the *s* character of the orbital, the more efficiently it can overlap: an sp^2 orbital, which has a 33% *s* character, can overlap more effectively than an sp^3 orbital, with only 25% *s* character.

HYDROGENATION

Alkene hydrogenation is the addition of hydrogen gas (H_2) to an alkene which saturates the bond and forms an alkane. Alkene hydrogenation reactions require a transition metal catalyst, such as Pt or Pd, to speed up the reaction. The hydrogenation reaction is used in this section to investigate the stability of alkenes, however, it will be discussed in greater detail in **Section 8.7**. Hydrogenation reactions are exothermic and the enthalpy change in this reaction is called the heat of hydrogenation ($\Delta H°_{hydrog}$). Since the double bond is breaking in this reaction, the energy released during hydrogenation is proportional to the energy in the double bond of the molecule. By comparing the heat of hydrogenations from a series of alkenes that produce the same alkane, a quantitative measure of relative alkene stabilities can be produced. These experiments will lead to an general understanding of structural features which tend to stabilize or destabilize alkenes.

THE CATALYST

A catalyst increases the reaction rate by lowering the activation energy of the reaction. Although the catalyst is not consumed in the reaction, it is required to accelerate the reaction sufficiently to be observed in a reasonable amount of time. Catalysts commonly used in alkene hydrogenation are: platinum, palladium, and nickel. The metal catalyst acts as a surface on which the reaction takes place. This increases the rate by putting the reactants in close proximity to each other, facilitating interactions between them. With this catalyst present, the sigma bond of H_2 breaks, and the two hydrogen atoms instead bind to the metal (see #2 in the figure below). The π bond of the alkene weakens as it also interacts with the metal (see #3 below).

Since both the reactants are bound to the metal catalyst, the hydrogen atoms can easily add, one at a time, to the previously double-bonded carbons (see #4 and #5 below). The position of both of the reactants bound to the catalyst makes it so the hydrogen atoms are only exposed to one side of the alkene. This explains why the hydrogen atoms add to same side of the molecule, called syn-addition.

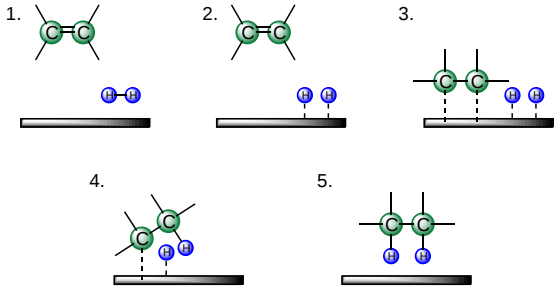


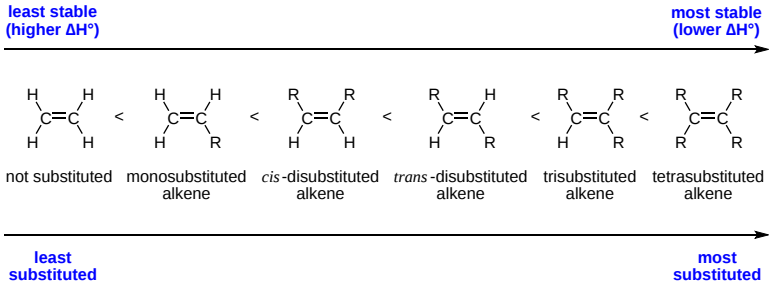
Figure **7.7.1***: Hydrogenation takes place in the presence of a metal catalyst.*

NOTE

The catalyst remains intact and unchanged throughout the reaction.

HEATS OF HYDROGENATION

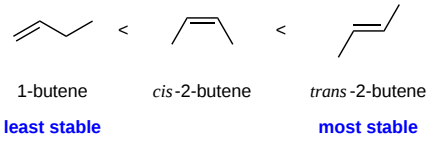
The stability of alkene can be determined by measuring the amount of energy associated with the hydrogenation of the molecule. Since the double bond is breaking in this reaction, the energy released in hydrogenation is proportional to the energy in the double bond of the molecule. This is a useful tool because heats of hydrogenation can be measured very accurately. The $\Delta H°$ is usually around -30 kcal/mol for alkenes. Stability is simply a measure of energy. Lower energy molecules are more stable than higher energy molecules. More substituted alkenes are more stable than less substituted ones due to hyperconjugation. They have a lower heat of hydrogenation. The following illustrates stability of alkenes with various substituents:



CIS/TRANS ISOMERS

Between cis and trans isomers of an alkene, the cis isomer tends to be less stable due to the molecular crowding created nonbonding interaction between two alky groups on the same side of the double bond. The crowding creates steric strain which distorts bond angles creating less effective bond orbital overlap and desabilizing the molecule. Steric strain has previously been seen in gauche interactions in Newman projections (**Section 3.7**) and 1,3-diaxial interactions in substituted cyclohexanes (**Section 4.7**). Steric strain is directly related to the size of the species being crowded. The difference in energy between *cis* and *trans* 2-butene is 5 kJ/mol, however, this difference would be greater if larger group were being held in the *cis* position. Two *cis*-*tert*-butyl group can create over 40 kJ/mol of steric strain.

See the following isomers of butene:



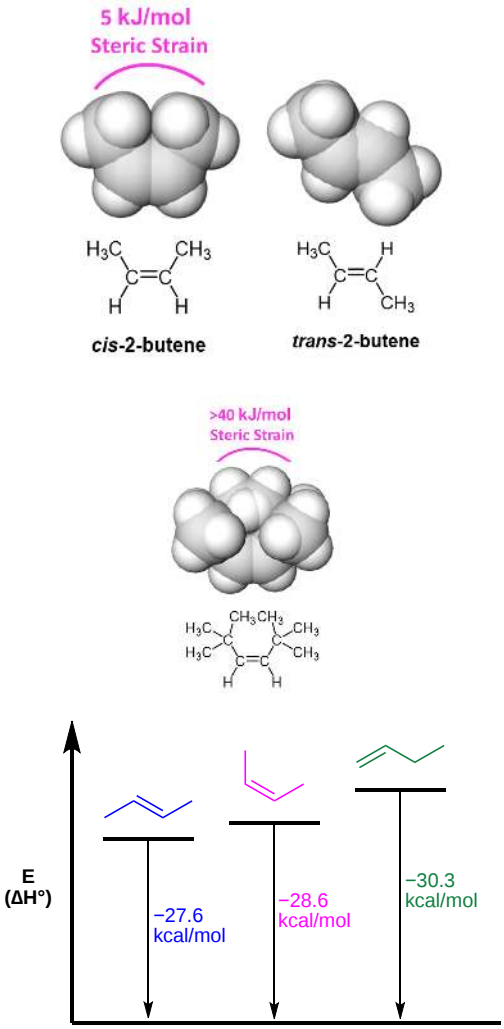


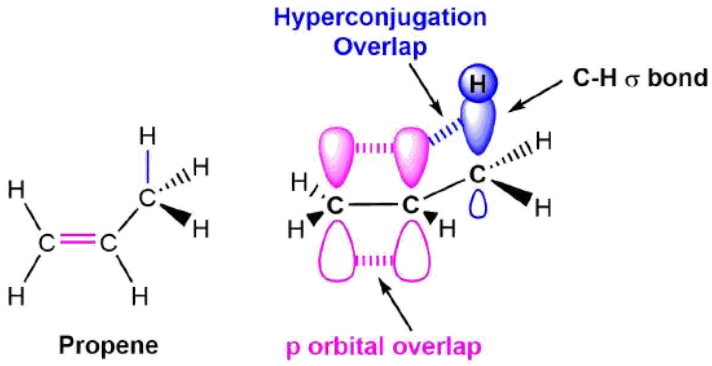
Figure 7.7.2: *Trans-2-butene is the most stable because it has the lowest heat of hydrogenation.*

ALKENE STABILIZATION BY ALKYL SUBSTITUENTS

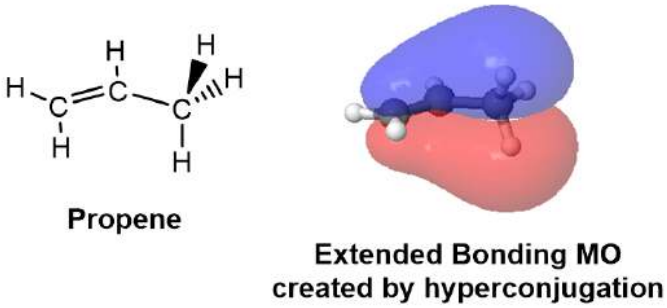
In general, the stability of an alkene increases with the number of alkyl substituents. This effect is due by the combination of two factors:

HYPERCONJUGATION

In classical valence-bond theory, electron delocalization can only occur by the parallel overlap of adjacent p orbitals. According to hyperconjugation theory, electron delocalization could also occur by the parallel overlap of p orbitals with adjacent hybridized orbitals participating in sigma bonds. This electron delocalization serves to stabilize the alkene. As the number of alkyl substituents increases, the number of sigma bonds available for hyperconjugation increases, and the alkene tends to become more stabilized. In the example of propene shown below, a p orbital from a sp^2 hybridized carbon involved in the double bond interacts with a sp^3 hybridized orbital participating in an adjacent C-H sigma bond.

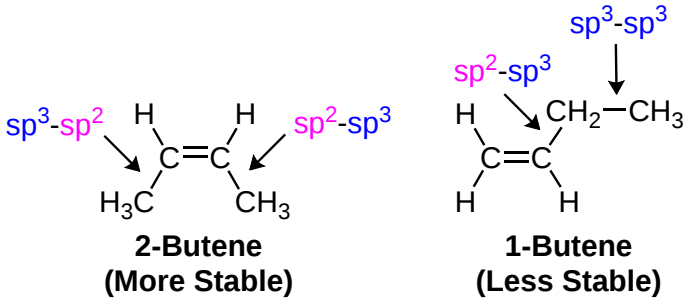


In a molecular orbital description of hyperconjugation, the electrons in sigma molecular orbitals (C-H or C-C) of alkyl substituens, interact with adjacent unpopulated non-bonding or antibonding molecular orbitals from the double bond. The interaction creates a bonding molecular orbital which extends over the four atom chain (C=C-C-H) involved in hyperconjugation. The expanded molecular orbital helps to stabilize the double bond.



BOND STABILITY

Bond strengths play an important part in determining the overall stability of a molecule. A C-C bond between a sp^3 carbon and a sp^2 carbon is slightly stronger than a C-C bond between two sp^3 carbons. Increasing the number alkyl substituents of a double bond also increases the number of sp^3-sp^2 C-C bonds making the alkene more stable. This is idea can be clearly seen when comparing the isomers 1-butene and 2-butene. The molecule 1-butene is monosubstituted and contains a sp^3-sp^3 C-C and a sp^3-sp^2 C-C bond. The disubstituted, 2-butene, contains 2 sp^3-sp^2 C-C bonds which contributes to its greater stability.



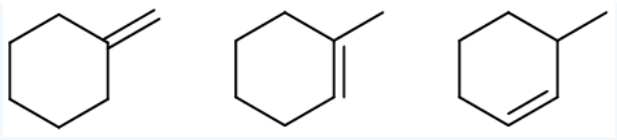
NOTE

In cycloalkenes smaller than cyclooctene, the cis isomers are more stable than the trans as a result of ring strain.

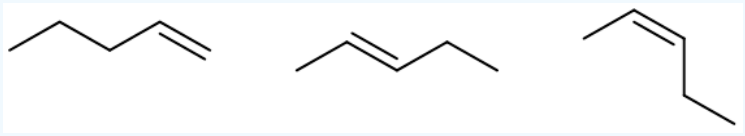
EXERCISE 7.7.1

Of the three following isomers which would be expected to be the most stable?

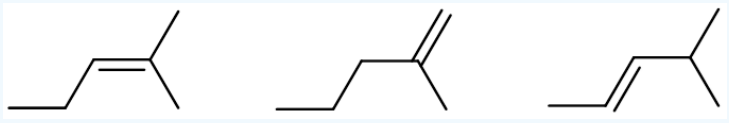
a)



b)



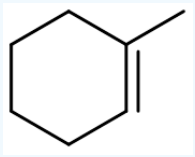
c)



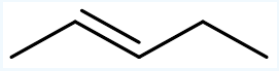
Answer

1)

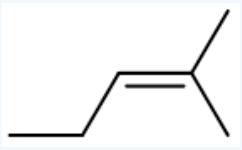
a)



b)

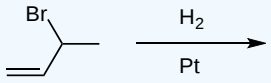


c)



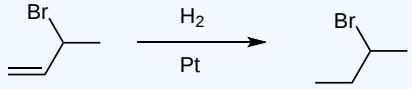
EXERCISE 7.7.2

3-Bromobut-1-ene reacts with hydrogen gas in the presence of a platinum catalyst. What is the name of the product?



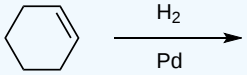
Answer

2-Bromobutane (numbering changes when alkene is no longer present)



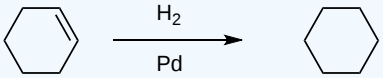
EXERCISE 7.7.3

Cyclohexene reacts with hydrogen gas in the presence of a palladium catalyst. What is the name of the product?



Answer

Cyclohexane



EXERCISE 7.7.4

What is the stereochemistry (syn or anti addition) of an alkene hydrogenation reaction?

Answer

Syn-addition

EXERCISE 7.7.5

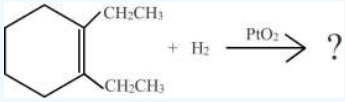
When looking at their heats of hydrogenation, is the cis or the trans isomer generally more stable?

Answer

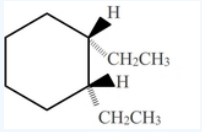
Trans

EXERCISE 7.7.6

Show the product for the following



Answer



REFERENCES

1. Fox, Marye Anne, and James K. Whitesell. Organic Chemistry. 3rd ed. Sudbury, MA: Janes and Bartlett Publishers, 2004.
2. Hanson, James R. Functional Group Chemistry. Bristol, UK: The Royal Society of Chemistry, 2001.
3. Streitwieser, Andrew Jr., and Clayton H. Heathcock. Introduction to Organic Chemistry. 2nd ed. New York, NY: Macmillan Publishing Co., Inc., 1981.
4. Vollhardt, Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York, NY: W.H. Freeman and Company, 2007.
5. Zlatkis, Albert, Eberhard Breitmaier, and Gunther Jung. A Concise Introduction to Organic Chemistry. New York: McGraw-Hill Book Company, 1973.

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7.8: ELECTROPHILIC ADDITION REACTIONS OF ALKENES

OBJECTIVES

After completing this section, you should be able to

- explain the term “electrophilic addition reaction,” using the reaction of a protic acid, HX, with an alkene as an example.
- write the mechanism for the reaction of a protic acid, HX, with an alkene.
- sketch a reaction energy diagram for the electrophilic addition of an acid, HX, to an alkene.

KEY TERMS

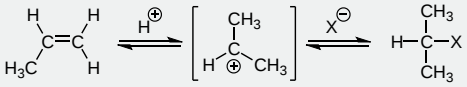
Make certain that you can define, and use in context, the key terms below.

- carbocation (carbonium ion)
- electrophilic addition reaction

STUDY NOTES

An *electrophilic addition reaction* is a reaction in which a substrate is initially attacked by an electrophile, and the overall result is the addition of one or more relatively simple molecules across a multiple bond.

The mechanism for the addition of hydrogen halide to propene shown in the reading is quite detailed. Normally, an organic chemist would write the reaction scheme as follows:



However, the more detailed mechanism shown in the reading does allow you to see the exact fate of all the electrons involved in the reaction.

In your previous chemistry course, you were probably taught the importance of balancing chemical equations. It may come as a surprise to you that organic chemists usually do not balance their equations, and often represent reactions using a format which is quite different from the carefully written, balanced equations encountered in general chemistry courses. In fact, organic chemists are rarely interested in the inorganic products of their reactions; furthermore, most organic reactions are non-quantitative in nature.

In many of the reactions in this course, the percentage yield is indicated beneath the products: you are not expected to memorize these figures. The question of yield is very important in organic chemistry, where two, five, ten or even twenty reactions may be needed to synthesize a desired product. For example, if a chemist wishes to prepare compound D by the following reaction sequence:

$$A \rightarrow B \rightarrow C \rightarrow D$$

and each of the individual steps gives only a 50% yield, one mole of A would give only

$$1 \text{ mol} \times \frac{50\%}{100\%} \times \frac{50\%}{100\%} \times \frac{50\%}{100\%} = 0.125 \text{ mol of D}$$

You will gain first-hand experience of such situations in the laboratory component of this course.

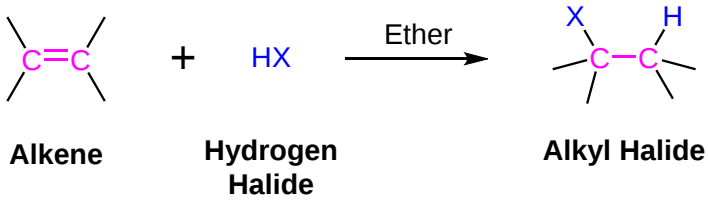
INTRODUCTION

One of the most important reactions for alkenes is called electrophilic addition. In this chapter several variations of the electrophilic addition reaction will be discussed. Each case will have aspects common among all electrophilic addition. In this section, the electrophilic addition reaction will be discussed in general to provide a better understanding of subsequent alkene reactions.

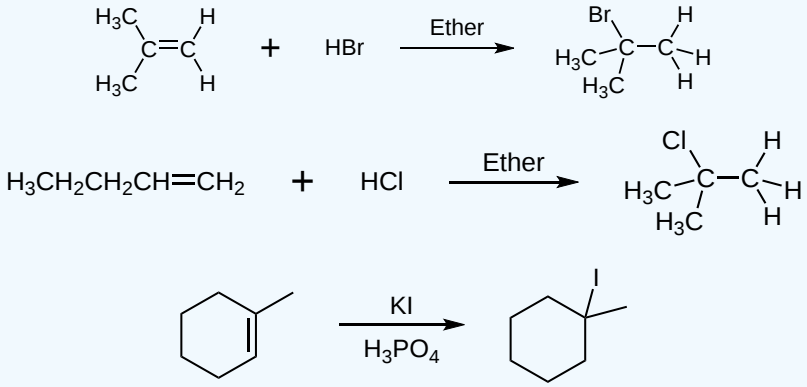
As discussed in Section 6-5, the double bond in alkenes is electron rich due to the prescience of 4 electrons instead of the two in a single bond. Also, the pi electrons are positioned above and below the double bond making them more accessibly for reactions. Overall, double bonds can easily donate lone pair electrons to act like a nucleophile (nucleus-loving, electron rich, a Lewis acid). During an electrophilic addition reactions double bonds donate lone pair electrons to an electrophile (Electron-loving, electron poor, a Lewis base). There are many types of electrophilic addition, but this section will focus on the addition of hydrogen halides (HX). Many of the basic ideas discussed will aplicable to subsequent electrophilic addition reactions.

GENERAL REACTION

Overall during this reaction the pi bond of the alkene is broken to form two single, sigma bonds. As shown in the reaction mechanism, one of these sigma bonds is connected to the H and the other to the X of the hydrogen halide. This reaction works well with HBr and HCl. HI can also but used but is is usually generated during the reaction by reacting potassium iodidie (KI) with phosphoric acid (H_3PO_4).



EXAMPLE 7.8.1



ADDITION TO SYMMETRICAL ALKENES

What happens?

All alkenes undergo addition reactions with the hydrogen halides. A hydrogen atom joins to one of the carbon atoms originally in the double bond, and a halogen atom to the other.

For example, with ethene and hydrogen chloride, you get chloroethane:



Figure **7.8.1** Electrophilic addition of HCl to ethene.

With but-2-ene you get 2-chlorobutane:

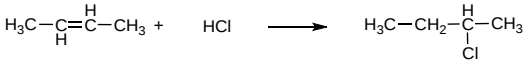


Figure **7.8.2** Electrophilic addition of HCl to but-2-ene.

What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in space. That would be different of the alkene was unsymmetrical - that's why we have to look at them separately.

MECHANISM

Step 1) Electrophilic Attack

During the first step of the mechanism, the 2 pi electrons from the double bond attack the H in the HBr electrophile which is shown by a curved arrow. The two pi electrons form a C-H sigma bond between the hydrogen from HBr and a carbon from the double bond. Simultaneously the electrons from the H-X bond move onto the halogen to form a halide anion. The removal of pi electrons form the double

bond makes one of the carbons become an electron deficient carbocation intermediate. This carbon is sp^2 hybridized and the positive charge is contained in an unhybridized p orbital.

Step 2) Nucleophilic attack by halide anion

The formed carbocation now can act as an electrophile and accept an electron pair from the nucleophilic halide anion. The electron pair becomes a X-C sigma bond to create the neutral alkyl halide product of electrophilic addition.

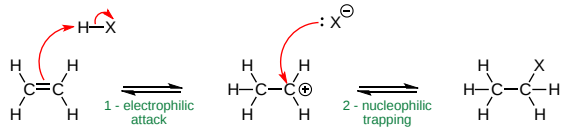


Figure **7.8.3***Mechanism of Electrophilic Addition of Hydrogen Halide to Ethene*

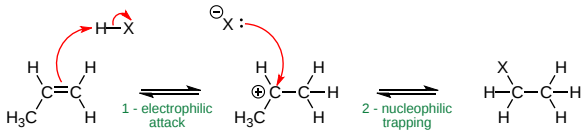
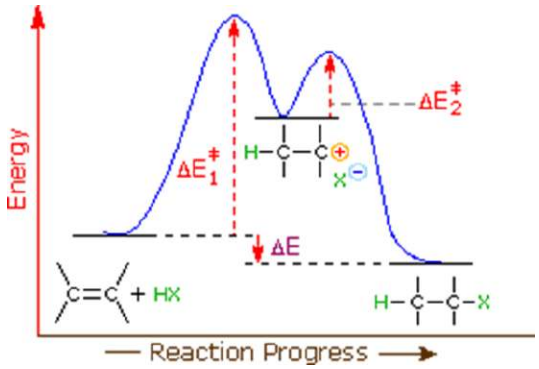


Figure **7.8.4** *Mechanism of Electrophilic Addition of Hydrogen Halide to Propene*

All of the halides (HBr, HCl, HI, HF) can participate in this reaction and add on in the same manner. Although different halides do have different rates of reaction, due to the H-X bond getting weaker as X gets larger (poor overlap of orbitals)s.

REACTION ENERGY DIAGRAM

An energy diagram for the two-step electrophilic addition mechanism is shown below. The energy diagram has two peaks which represent the transition state for each mechanistic step. The peaks are separated by a valley which represents the high energy carbocation reaction intermediate. Because the energy of activation for the first step of the mechanism ($\Delta E^{\ddagger}_1$) is much larger than the second ($\Delta E^{\ddagger}_1$), the first step of the mechanism is the rate-determining step. Both the alkene and the hydrogen halide are reactants in the first step of the mechanism, this electrophilic addition is a second order reaction and the rate law expression can be written rate = k[Alkene][HX]. Also, any structural feature which can stabilize the transition state between the reactants the carbocation intermediate will lower $\Delta E^{\ddagger}_1$ and thereby increase the reaction rate. Overall, the alkyl halide product of this reaction more stable than the reactants making the reaction exothermic.



REACTION RATES

Variation of rates when you change the halogen

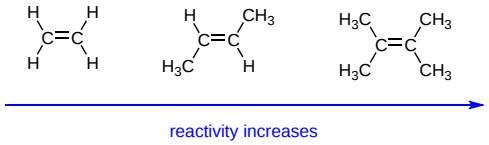
Reaction rates increase in the order HF - HCl - HBr - HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions.

When the hydrogen halides react with alkenes, the hydrogen-halogen bond has to be broken. The bond strength falls as you go from HF to HI, and the hydrogen-fluorine bond is particularly strong. Because it is difficult to break the bond between the hydrogen and the fluorine, the addition of HF is bound to be slow.

Variation of rates when you change the alkene

This applies to unsymmetrical alkenes as well as to symmetrical ones. For simplicity the examples given below are all symmetrical ones- but they don't have to be.

Reaction rates increase as the alkene gets more complicated - in the sense of the number of alkyl groups (such as methyl groups) attached to the carbon atoms at either end of the double bond. For example:

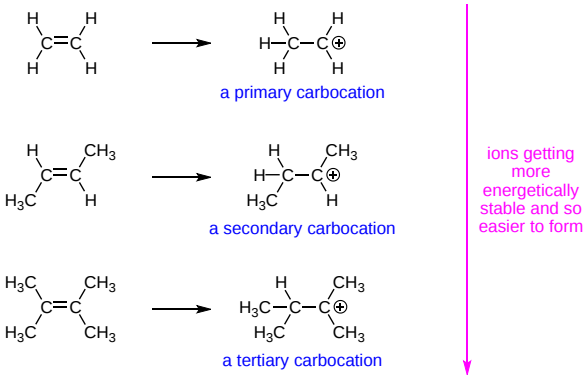


There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

Alkenes react because the electrons in the pi bond attract things with any degree of positive charge. Anything which increases the electron density around the double bond will help this.

Alkyl groups have a tendency to "push" electrons away from themselves towards the double bond. The more alkyl groups you have, the more negative the area around the double bonds becomes. The more negatively charged that region becomes, the more it will attract molecules like hydrogen chloride.

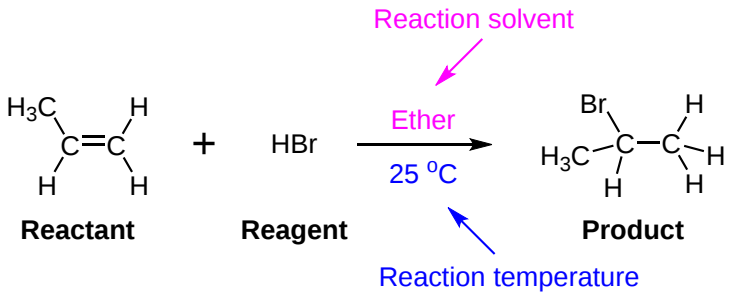
The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



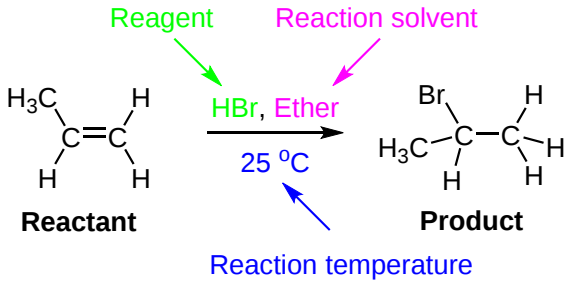
The stability of the intermediate ions governs the activation energy for the reaction. As you go towards the more complicated alkenes, the activation energy for the reaction falls. That means that the reactions become faster.

REPRESENTING ORGANIC REACTIONS

Organic reaction equations are often written in one of two ways. The reactant for the reaction is written to the left of the reaction arrow. The products are written to the right of the arrow. The reagent for the reaction is written above the arrow. Other reaction conditions such as the solvent or the temperature can be written above or below the reaction arrow.



Alternatively the reactant and reagent can both be written to the left of the reaction arrow. This is typically done to highlight the importance of the reactant. The solvent and reaction temperature are still written above or below the reaction arrow. The reaction products are still written to the right of the reaction arrow.



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7.9: ORIENTATION OF ELECTROPHILIC ADDITIONS - MARKOVNIKOV'S RULE

OBJECTIVES

After completing this section, you should be able to

- use Markovnikov's rule to predict the product formed when a protic acid, HX, reacts with an alkene.
- identify the protic acid, HX, and the alkene that must be reacted together to produce a given alkyl halide. [**Note:** Special conditions are needed if an alkyl iodide is to be produced.]
- distinguish among primary, secondary and tertiary carbocations.

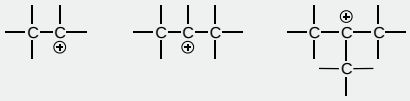
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Markovnikov's rule
- regioselective (regiospecific)

STUDY NOTES

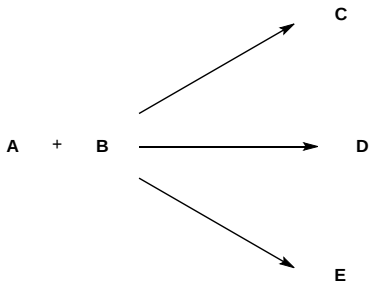
Recall the definitions of primary, secondary and tertiary hydrogen atoms given in Section 3.3. It follows that a "primary carbocation" is a carbocation in which the carbon atom carrying the positive charge is bonded to only one other carbon atom, a "secondary carbocation" is one in which the carbon atom carrying the positive charge is bonded to two other carbon atoms, and so on.



REGIOSELECTIVITY

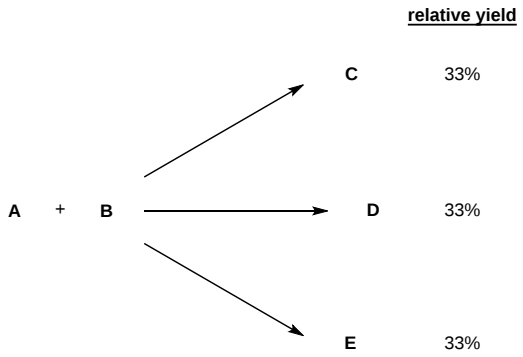
If more than one reaction could occur between a set of reactants under the same conditions giving products that are constitutional isomers and if one product forms in greater amounts than the others, the overall reaction is said to be regioselective.

Say three reactions could occur between the hypothetical reactants **A** and **B** under the same conditions giving the constitutionally isomeric products **C**, **D**, and **E**.



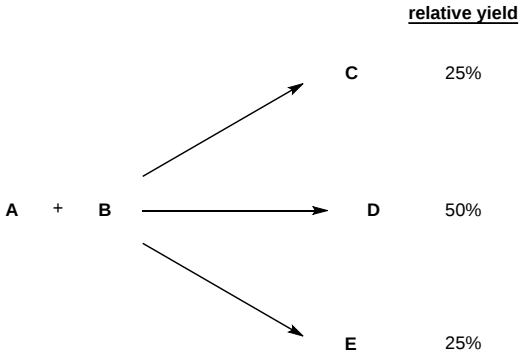
There are two possibilities:

1. The three products form in equal amounts, i.e., of the total product 33% is **C**, another 33% **D**, the remaining 33% **E**. (These percentages are called relative yields of the products.)



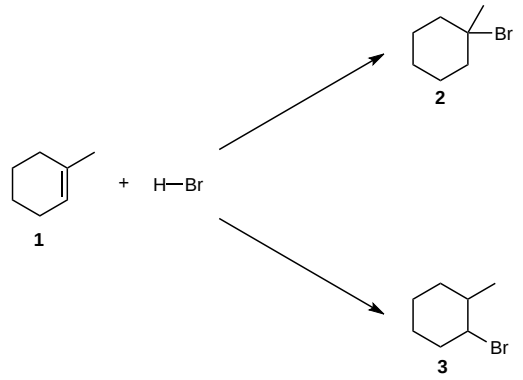
If this is what is observed, the overall reaction between **A** and **B** is not regioselective.

2. One product forms in greater amounts than the others. Say, for example, the relative yields of **C**, **D**, and **E** are 25%, 50%, and 25%, respectively.



If this is what is observed, the overall reaction between **A** and **B** is regioselective.

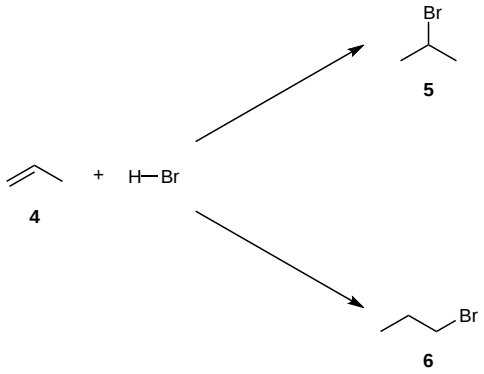
eg:



Experimentally, **2** is the major product; **3** is the minor product. Thus, the overall reaction between **1** and HBr is regioselective toward **2**.

If more than one reaction could occur between a set of reactants under the same conditions giving products that are constitutional isomers and if only one product is observed, the overall reaction is said to be 100% regioselective or regiospecific.

eg:

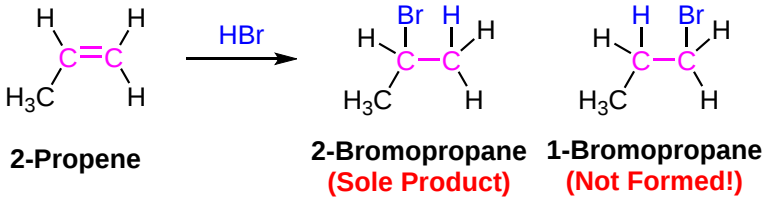


The only observed product is **5**. (Relative yields of **5** and **6** are 100% and 0%, respectively.) Thus the overall reaction between **4** and HBr is regiospecific toward **5**.

Regiospecificity is merely the limiting case of regioselectivity. All regiospecific reactions are regioselective, but not all regioselective reactions are regiospecific.

ADDITION TO UNSYMMETRICAL ALKENES

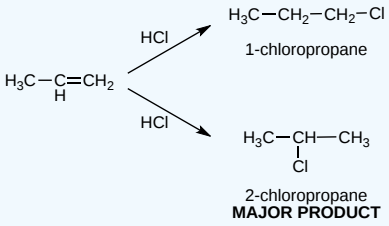
During the electrophilic addition of HX to an alkene, the halide (X) could attach to either carbon in the double bond producing two different isomers as products. But, when an unsymmertrically alkyl substituted alkene undergoes an electrophillic addition with HX a single isomer is typically produced. For example, if propene were reacted with HBr, two products could possibly form: 2-bromolpropane and 1-bromopropane. However, 2-bromopropane is produced as the reaction's only product. Reactions are called regiospecific when only one of multiple possible isomers is exclusively formed.



EXAMPLE 7.9.1

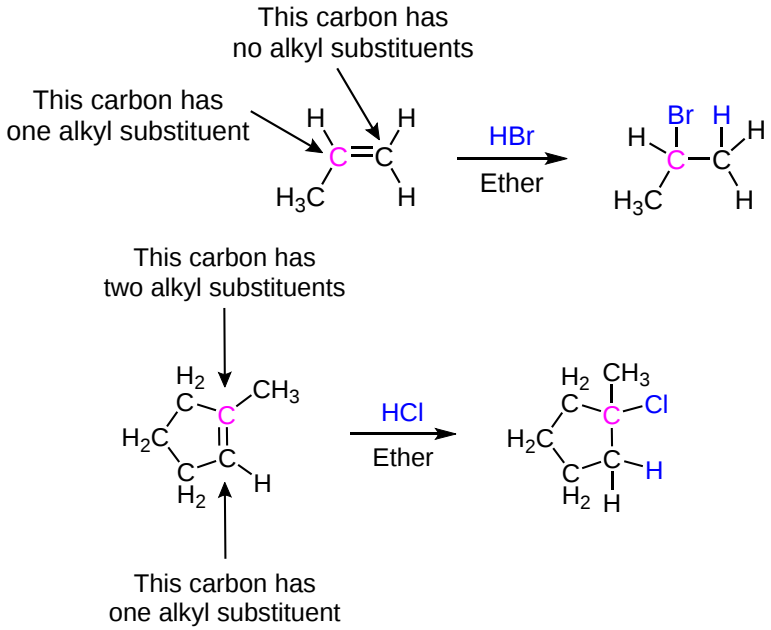
If HCl adds to an unsymmetrical alkene like propene what will the major product be?

Solution

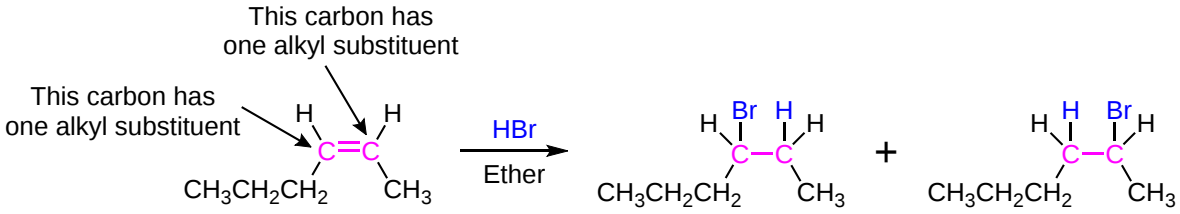


The regiospecificity of electrophilic additions to alkenes is commonly known as **Markovnikov's rule**, after the Russian chemist Vladimir Markovnikov who proposed it in 1869. The electrophilic addition of HX to an alkene is said to follow Markovnikov's rule.

Markovnikov's rule: During the electrophilic addition of HX to an alkene, the H adds to the carbon of the double bond with the fewest number of alkyl substitutent. The halide (X) adds to the double bond carbon with the most alkyl substituents. Although Markovnikov's rule has been specifically stated for the electrophilic addition of HX, later in this chapter many more reaction will be shown to also follow Markovnikov's rule.

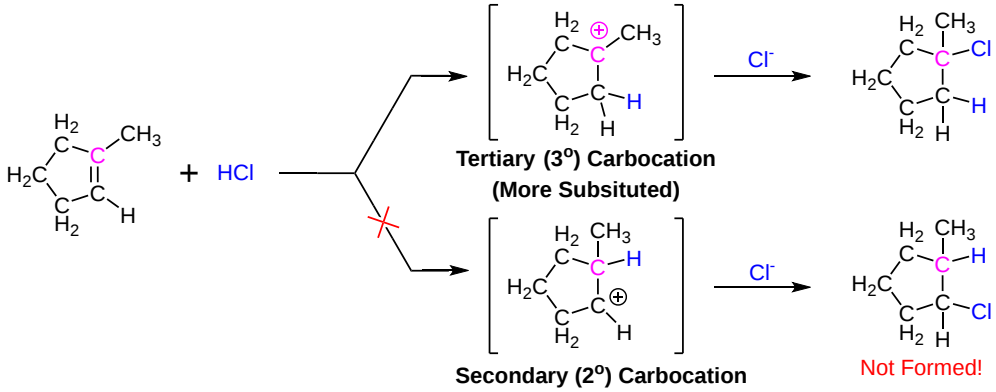


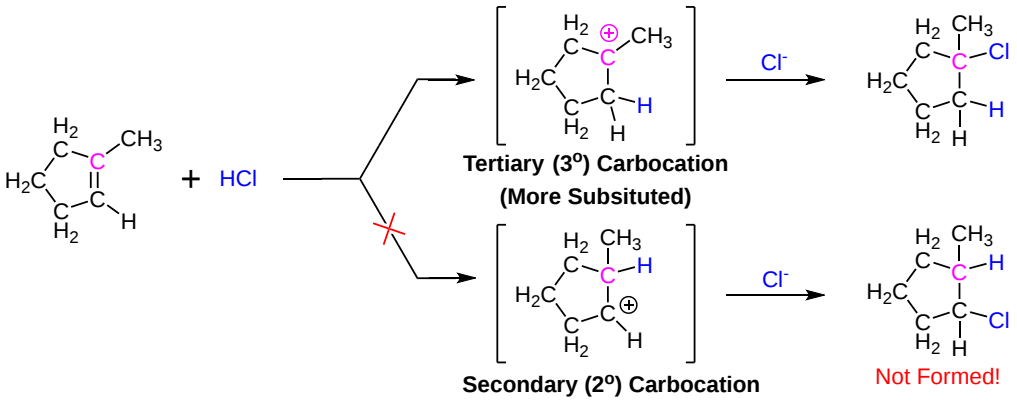
It is important to point out that Markovnikov's rule only truly applies when there is a difference between the number of alky groups attached to each carbon in the double bond. When both carbon of the double bond have the same degree of alkyl substitution, Markovnikovs's rule becomes void and a mixture of both possible isomers is produced.



To consider an explanation for why Markovnikov's rule holds true, the mechanism of the reaction needs to be considered. As seen in the previous section, the mechanism starts with the addition of H to a carbon in the double bond. This in turn caused the other double bond carbon to become a carbocation intermediate. In the second step of the mechanism the halide ion attacks the carbocation to form a C-X. Because Markovnikov's rule says that the halogen adds to the carbon in the double bond with the most alky substituents, it can be said the carbocation also prefers to form on the carbon with the most alkyl substituents. The reason for this holds the explaination for Markovnikov's rule. To simplify this idea, Markovnikov's rule can be restated in a different form.

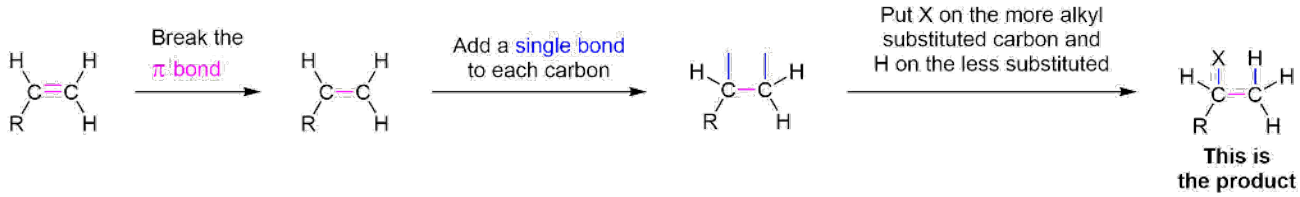
Markovnikov's rule: During the electrophilic addition of HX to an alkene, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents.





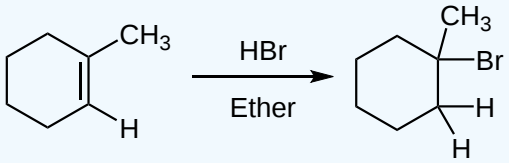
PREDICTING THE PRODUCT OF AN ELECTROPHILIC ADDITION WITH HX

Overall, during the electrophilic addition of HX to an alkene there are two major changes in the bonding. First, the pi bond of the alkene is broken. Second, a single bond is formed on each carbon that was originally in the double bond. The two single bonds will become attached to and H and an X. If the alkene is unsymmertrically alkyl substituted, Markovnikov's rule is followed and the X will be bonded to the more alky substituted carbon and the H to the less substiuted. If the alkene is symmertrically alkyl substituted a mixture of isomers will be produced in the product.



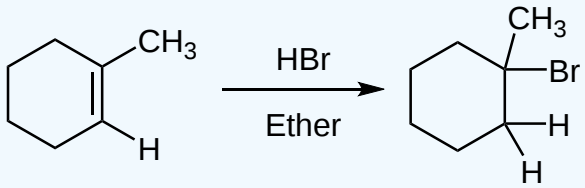
? WORKED EXAMPLE 7.9.1

Please draw the product of the following reaction:



Answer

In answering these types of questions it is always important to first determine which reaction is occurring. Because an alkene is the reactant and HBr is the product this reaction is an electrophilic addition. Overall, the double bond will be broken as H and Br are added. The next step is to determine if Markovnikov's rule needs to be applied. In the reactant's double bond the upper carbon has two alkyl substituents and the lower carbon has only two. Markovnikov's rule says that Br will attach to the upper carbon and H to the lower.

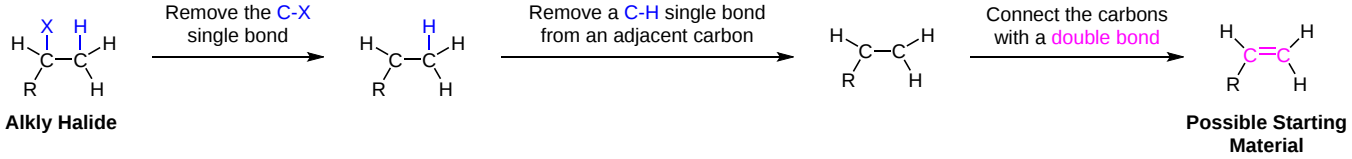


PLANNING THE SYNTHESIS OF AN ALKYL HALIDE USING ELECTROPHILIC ADDITION

Understanding the starting material and reaction required for the synthesis a specific target molecule is an important concept in organic chemistry. The preferred method for answering these types of questions is to work backwards from the target molecule. Often there will be

multiple variations of reactions and starting materials capable synthesizing the target molecule. Further analysis of these variations can draw out strengths and weaknesses and lead to the pathway with the best chance of success.

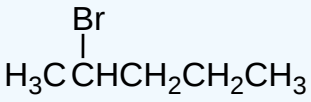
To create a possible starting material for a given alkyl halide simply reverse the bonding changes expected during an electrophilic addition. Remove the C-X single bond and a C-H bond from an adjacent carbon. Then connect these two carbons with a double bond.



Alkly Halide **Possible Starting Material**

? WORKED EXAMPLE 7.9.1

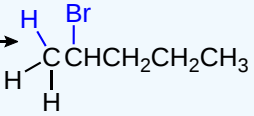
What alkene would be required to make the following 2-bromopentane using an electrophilic addition?



Answer

Analysis: Possible starting materials can be made by first removing the C-Br bond and an adjacent C-H bond. Then connecting the two carbons with a double bond. Because there are two different locations where an adjacent C-H bond can be removed there will be two possible starting material.

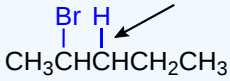
Adjacent C-H Bond

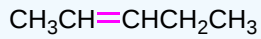




Possible Starting Material #1

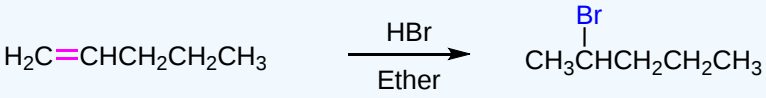
Adjacent C-H Bond



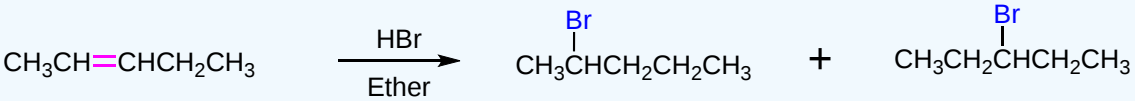


Possible Starting Material #2

Solution: When comparing the the possible starting materials, #1 will follow Markovnikov's rule and produce 2-bromopentane as the sole product. Starting material #2 is symmertrically alkyl substituted, so Markovnikov's rule does not apply. A mixture of 2-bromopentane and 3-bromopentane would be produced. Between the two possible starting material #1 would be preferred because only one product is produced.



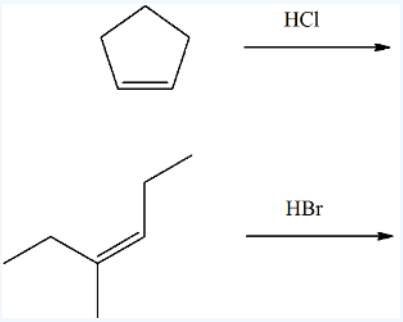
Possible Starting Material #1 **2-Bromopentane**



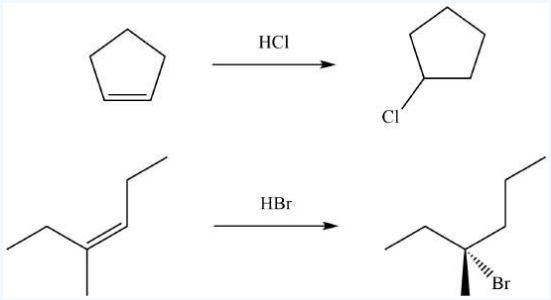
Possible Starting Material #2 **2-Bromopentane** **2-Bromopentane**

EXERCISE 7.9.1

Predict the product(s) for the following reactions:

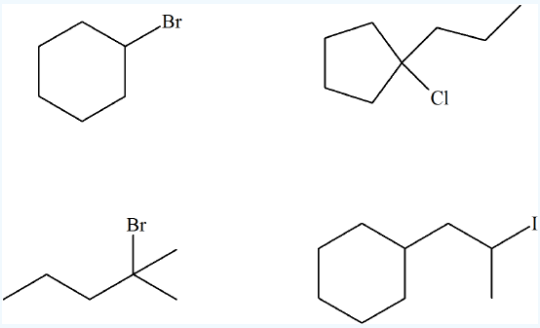


Answer

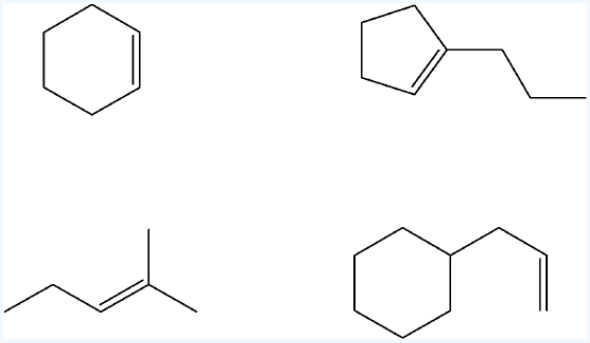


EXERCISE 7.9.2

In each case, suggest an alkene that would give the product shown.

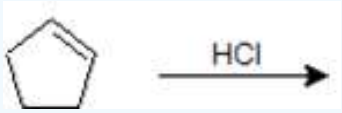


Answer

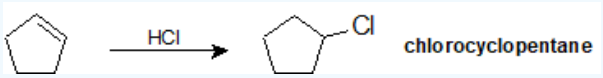


EXERCISE 7.9.3

Give the IUPAC name for the product of the following reaction.



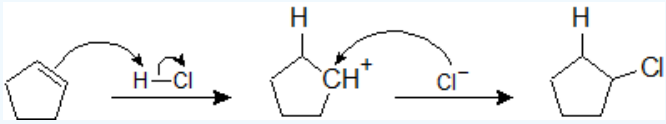
Answer



EXERCISE 7.9.4

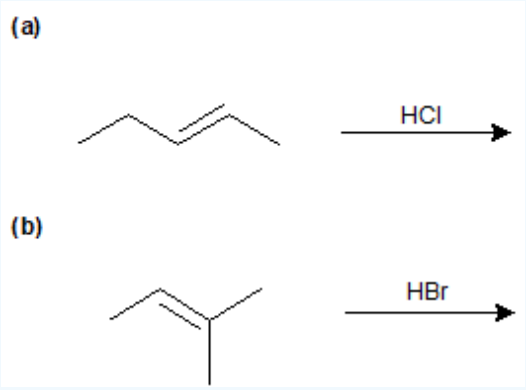
Draw the reaction mechanism of the previous problem

Answer

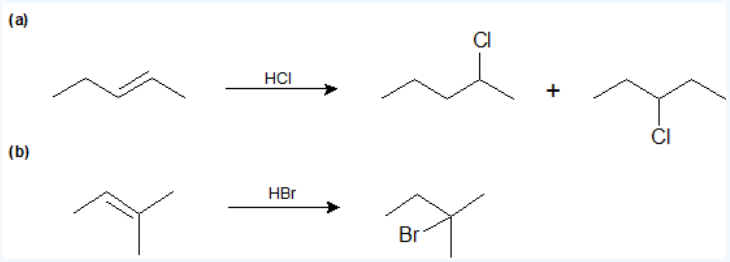


EXERCISE 7.9.5

Identify the products of the following reactions.



Answer



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7.10: CARBOCATION STRUCTURE AND STABILITY

OBJECTIVES

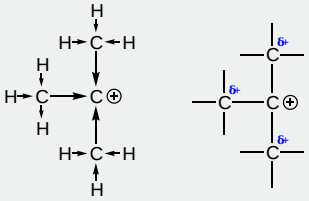
After completing this section, you should be able to

- describe the geometry of a given carbocation.
- arrange a given series of carbocations in order of increasing or decreasing stability.
- explain the relative stability of methyl, primary, secondary and tertiary carbocations in terms of hyperconjugation and inductive effects.

STUDY NOTES

Although hyperconjugation can be used to explain the relative stabilities of carbocations, this explanation is certainly not the only one, and is by no means universally accepted. A more common explanation, involving the concept of an inductive effect, is given below.

It is a general principle in chemistry that the more a charge is dispersed, the more stable is the species carrying the charge. Put simply, a species in which a positive charge is shared between two atoms would be more stable than a similar species in which the charge is borne wholly by a single atom. In a tertiary carbocation, the positively charged carbon atom attracts the bonding electrons in the three carbon-carbon sigma (σ) bonds, and thus creates slight positive charges on the carbon atoms of the three surrounding alkyl groups (and, indeed, on the hydrogen atoms attached to them). Chemists sometimes use an arrow to represent this inductive release:



Note: These diagrams do not reflect the geometry of the carbocation. The overall charge on the carbocation remains unchanged, but some of the charge is now carried by the alkyl groups attached to the central carbon atom; that is, the charge has been dispersed.

In the tertiary carbocation shown above, the three alkyl groups help to stabilize the positive charge. In a secondary carbocation, only two alkyl groups would be available for this purpose, while a primary carbocation has only one alkyl group available. Thus the observed order of stability for carbocations is as follows:

tertiary > secondary > primary > methyl.

STABILITY OF CARBOCATION INTERMEDIATES

The next step in understanding why Markovnikov's rule is often followed in electrophilic additions, involves understanding the structure and stability of the carboncation intermediate formed during the mechanism.

CARBOCATION STRUCTURE

Carbocations typically have three substituents which makes the carbon sp^2 hybridized and gives the overall molecule a trigonal planar geometry (Figure 7.10.1). The carbocation's substituents are all in the same plane and have a bond angle of 120º between them. The carbon atom in the carbocation is electron deficient; it only has six valence electrons which are used to form three sigma covalent bonds with the substituents. The carbocation carbon has an unoccupied p orbital which is perpendicular to the plane created by the substituents. The p orbital can easily accept electron pairs during reactions making carbocations excellent Lewis acids.

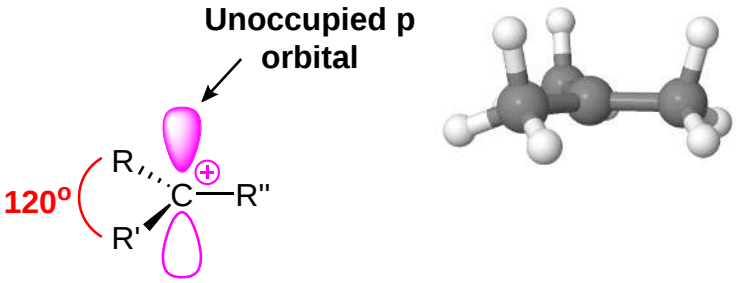
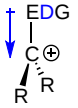


Figure **7.10.1**: (1) Hybridization of a generic carbocation and (2) the structure of the tert-butyl cation ($C_4H_9^+$).

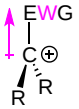
STABILITY OF CARBOCATION INTERMEDIATES

By being a reactive intermediate of the electrophilic addition mechanism, the stability of a carbocation has a direct effect on the reaction. The critical question now becomes, *what stabilizes a carbocation?*

A positively charged species such as a carbocation is very electron-poor, and thus anything which donates electron density will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.



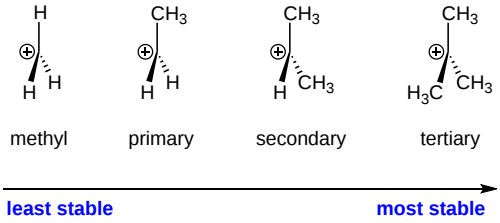
electron donating group *stabilizes* a carbocation



electron withdrawing group *destabilizes* a carbocation

Extensive experimental evidence has shown that a carbocation becomes more stable as the number of alkyl substituents increases. Carbocations can be given a designation based on the number of alkyl groups attached to the carbocation carbon. Three alkyl groups is called a tertiary (3°) carbocation, 2 alkyl groups is called secondary (2°), and 1 alkyl group is called primary (1°). No alkyl groups are attached (3 hydrogen substituents) is called a methyl carbocation.

The overall order of stability is as follows:

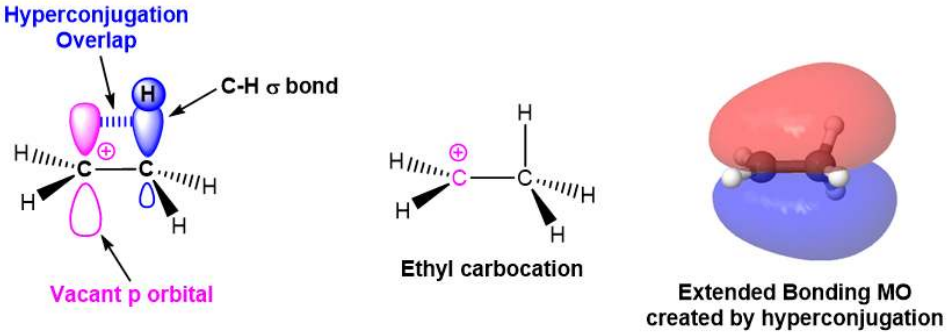


Alkyl groups stabilized carbocations for two reasons. The first is through inductive effects. As discussed in **Section 2-1**, inductive effects occur when the electrons in covalent bonds are shifted towards an nearby atom with a higher electronegativity. In this case, the positively charged carbocation draws in electron density from the surrounding substituents thereby gaining stabilization by slightly reducing its positive charge. Alkyl groups are more effective at inductively donating electron density than a hydrogen because they are larger, more polarizable, and contain more bonding electrons. As more alkyl groups are attached to the carbocation more inductive electron donation occurs and the carbocation becomes more stable.

The second reason alkyl groups stabilize carbocations is through hyperconjugation. As previously discussed in **Section 7.6**, hyperconjugation is an electron donation that occurs from the parallel overlap of p orbitals with adjacent hybridized orbitals participating in sigma bonds. This electron donation serves to stabilize the carbocation. As the number of alkyl substituents increases, the number of sigma bonds available for hyperconjugation increases, and the carbocation tends to become more stabilized.

In the example of ethyl carbocation shown below, the p orbital from a sp^2 hybridized carbocation carbon involved interacts with a sp^3 hybridized orbital participating in an adjacent C-H sigma bond. Electron density from the C-H sigma bond is donated into carbocation's p orbital providing stabilization.

The molecular orbital of the ethyl carbocation shows the interaction of electrons in methyl group's C-H sigma bonds with the adjacent empty p orbital from the carbocation. The interaction creates a bonding molecular orbital which extends over the three atom chain (C-C-H) involved in hyperconjugation. The expanded molecular orbital helps to stabilize the carbocation.



It is not accurate to say, however, that carbocations with higher substitution are *always* more stable than those with less substitution. Just as electron-donating groups can stabilize a carbocation, electron-withdrawing groups act to destabilize carbocations. Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the C=O double bond. It is possible to demonstrate in the laboratory that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.

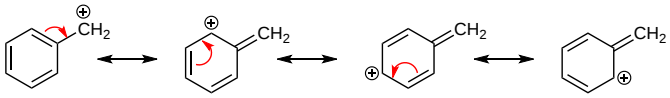


A: more stable **B**: less stable

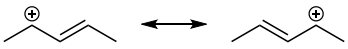
The difference in stability can be explained by considering the electron-withdrawing inductive effect of the ester carbonyl. Recall that inductive effects - whether electron-withdrawing or donating - are relayed through covalent bonds and that the strength of the effect decreases rapidly as the number of intermediary bonds increases. In other words, the effect decreases with distance. In species B the positive charge is closer to the carbonyl group, thus the destabilizing electron-withdrawing effect is stronger than it is in species A.

> In the next chapter we will see how the carbocation-destabilizing effect of electron-withdrawing fluorine substituents can be used in experiments designed to address the question of whether a biochemical nucleophilic substitution reaction is S_N1 or S_N2.

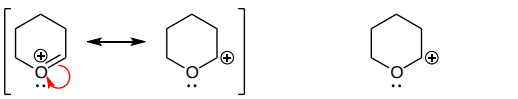
Stabilization of a carbocation can also occur through resonance effects, and as we have already discussed in the acid-base chapter, resonance effects as a rule are more powerful than inductive effects. Consider the simple case of a **benzylic** carbocation:



This carbocation is comparatively stable. In this case, electron donation is a resonance effect. Three additional resonance structures can be drawn for this carbocation in which the positive charge is located on one of three aromatic carbons. The positive charge is not isolated on the benzylic carbon, rather it is delocalized around the aromatic structure: this delocalization of charge results in significant stabilization. As a result, benzylic and **allylic** carbocations (where the positively charged carbon is conjugated to one or more non-aromatic double bonds) are significantly more stable than even tertiary alkyl carbocations.

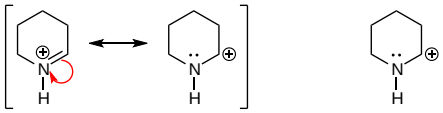


Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall effect is carbocation stabilization. This is due to the fact that although these heteroatoms are electron *withdrawing* groups by induction, they are electron *donating* groups by resonance, and it is this resonance effect which is more powerful. (We previously encountered this same idea when considering the relative acidity and basicity of phenols and aromatic amines in section 7.4). Consider the two pairs of carbocation species below:



more stable

less stable
(no resonance delocalization)

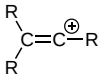


more stable

less stable
(no resonance delocalization)

In the more stable carbocations, the heteroatom acts as an electron donating group by resonance: in effect, the lone pair on the heteroatom is available to delocalize the positive charge. In the less stable carbocations the positively-charged carbon is more than one bond away from the heteroatom, and thus no resonance effects are possible. In fact, in these carbocation species the heteroatoms actually *destabilize* the positive charge, because they are electron withdrawing by induction.

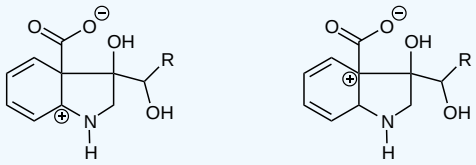
Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.



a vinylic carbocation (very unstable)

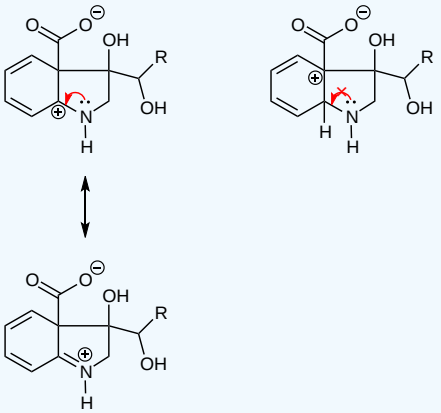
EXAMPLE 7.10.1

In which of the structures below is the carbocation expected to be more stable? Explain.



Answer

In the carbocation on the left, the positive charge is located in a position relative to the nitrogen such that the lone pair of electrons on the nitrogen can be donated to fill the empty orbital. This is not possible for the carbocation species on the right.

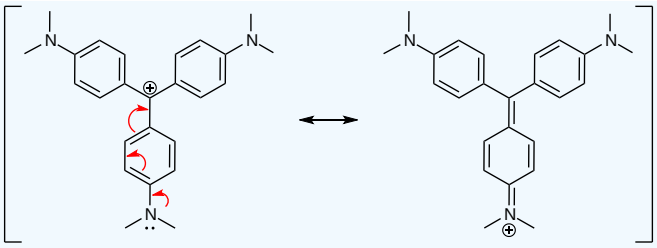


EXAMPLE 7.10.2

Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.

Answer

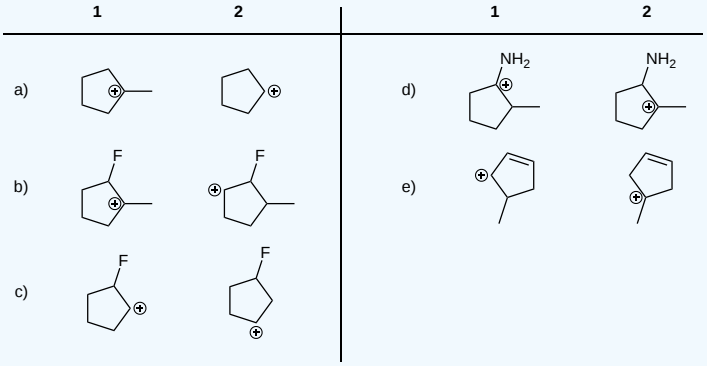
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When considering the possibility that a nucleophilic substitution reaction proceeds *via* an S_N1 pathway, it is critical to evaluate the stability of the hypothetical carbocation intermediate. If this intermediate is not sufficiently stable, an S_N1 mechanism must be considered unlikely, and the reaction probably proceeds by an S_N2 mechanism. In the next chapter we will see several examples of biologically important S_N1 reactions in which the positively charged intermediate is stabilized by inductive and resonance effects inherent in its own molecular structure.

EXAMPLE 7.10.3

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.



Answer

a. 1 (tertiary vs. secondary carbocation)
b. 1 (tertiary vs. secondary carbocation)
c. 2 (positive charge is further from electron-withdrawing fluorine)
d. 1 (lone pair on nitrogen can donate electrons by resonance)
e. 1 (allylic carbocation – positive charge can be delocalized to a second carbon)

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7.11: THE HAMMOND POSTULATE

OBJECTIVE

After completing this section, you should be able to use the Hammond postulate to explain the formation of the most stable carbocation during the addition of a protic acid, HX, to an alkene.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Hammond postulate

So far in this chapter the following points have been made about the electrophilic addition of HX to a double bond.

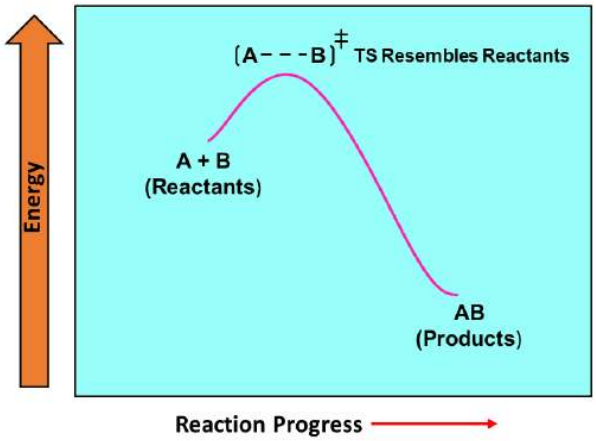
- The reaction takes place through a two step mechanism which forms a carbocation intermediate.
- During electrophilic addition the carbocation intermediate, and the subsequent H-X bond, forms on the double bond carbon with the most alkyl stubstituents *(***Markovnikov's rule)**
- Carbocations become more stable as the number of alkyl substituents increases.

It appears that the stability of the carbocation reactive intermediate has a direct effect on the products of a reaction. However, it is the activation energy required to reach the transition state of the reaction's rate determine step which determines which determines which product is produced. This implies that there is a relationship between the transition state and the carbocation reactive intermediate in the mechanism of electrophilic addition.

THE HAMMOND POSTULATE

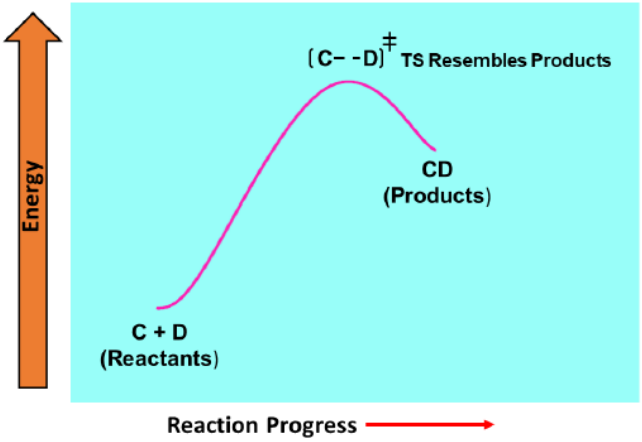
Chemists are often very interested in the structures of the transition states in a reaction's mechanism. In particular, the transition state for a mechanism's rate determining step directly determines the energy of activation barrier and thereby the rate for the overall reaction. Understanding the structure of a transition state allows chemists to consider structural features which might stabilize or destabilize the transition state causing a corresponding change in the rate of reaction. However, transition state structures cannot be directly observed because they are highly unstable activated complexes which instantly convert to a more stable species. In order to gain some insight into the structure of particular transition state, chemists often invoke the **Hammond postulate**, which states that *a transition state resembles the structure of the nearest stable species* (reactant, intermediate or product).

For an exergonic reaction, the transition state is closer in energy to the reactants. Therefore, the structure of the transition state can assumed to resemble the reactants more than the products. Shown below is a hypothetical exergonic reaction between reactant compounds A and B to form the product AB. The Hammond postulate would theorize that the distance between A and B in the transition state would be relatively large thus resembling the reactants where A and B are two isolated species.



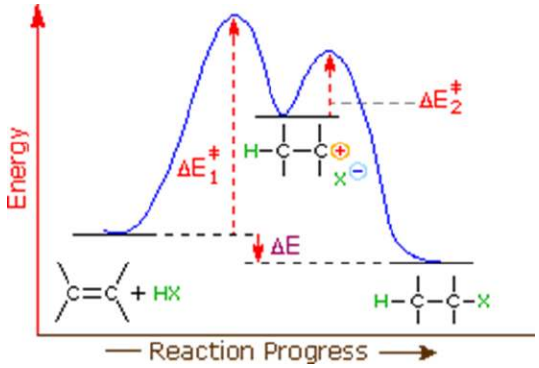
For an endergonic reaction, the transition state is closer in energy to the product. Therefore, the structure of the transition state can assumed to resemble the products more than the reactants. In the hypothetical endergonic reaction shown below, reactant compounds C and D react

to form the product CD. The Hammond postulate would predict that the distance between C and D in the transition state would be relatively small thus resembling the products where C and D are bonded together as a single product CD.

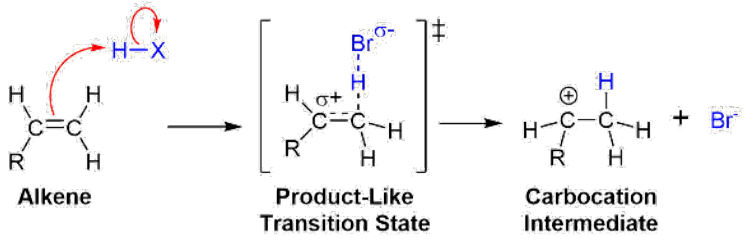


THE HAMMOND POSTULATE AND ELECTROPHILIC ADDITION

By applying the Hammond postulate and other ideas cultivated in this chapter the reason why electrophilic additions tend to follow Markovnikov's rule. When the energy diagram of an electrophilic addition was discussed in **Section 7.2**, it was noted the first step of the mechanism was the rate determining step. The first step of the mechanism also is endergonic and results in the formation of a carbocation intermediate.

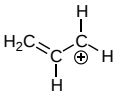
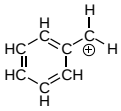
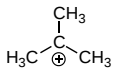


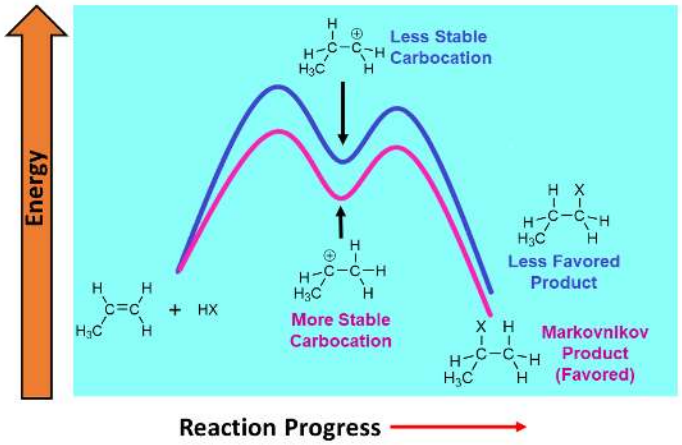
The Hammond postulate suggests that the transition state structure for the first step of the mechanism resembles that of the carbocation intermediate because they are the closest in energy. A transitions state, seen below, is typically drawn as a theoretical structure part way between the reactants and the product. For this transition state the pi bonds and the H-Br bond are in the process of being broken and are represented with a dashed line. The C-H bond is in the process of being formed so it also represented with a dashed line. The bromine is shown with a partial negative charge (sigma-) because it is becoming a bromide ion (Br^-) which has a full negative charge. Most importantly, the carbon is in the process of becoming a carbocation so it is shown to have a partial positive change (sigma+).



Because the Hammond postulate predicts this transitions state closely resembles the carbocation intermediate, the partial positive charge can said to closely resemble the full positive charge of the carbocation. Consequently, any structural feature that stabilized the carbocation intermediate will also stabilize the transition state. The partial positive charge of the transition state is stabilized by adjacent alkyl groups thorough inductive effects and hyperconjugation much like the carbocation intermediate. Adding more alkyl substituents to the partially positive charged carbon stabilizes the transition state, causing it to become lower in energy. This in turn, decreases the energy of activation

and increases the rate of the reaction. In short, during an electrophilic addition, the double bond carbon with the most alkyl substituents will for a carbocation intermediate and therefore its C-X bond faster than the double bond carbon with fewer alkyl substituents. These effects cause electrophillic additions to follow Markovnikov's rule and place the halogen (X) group on the more substituted carbon of asymmetrically alkyl substituted double bond.

Carbocation Stability		<<		<</td>		≈		<</td>		≈	

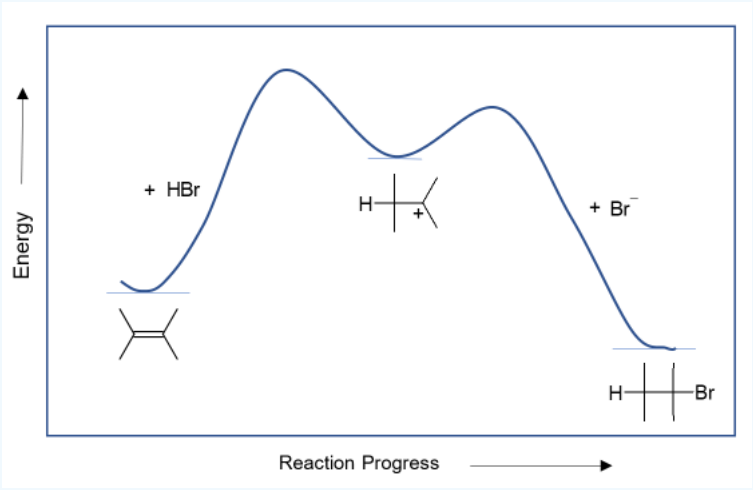


EXERCISE 7.11.1

Consider the second step in the electrophilic addition of HBr to an alkene. Is this step exergonic or endergonic and does the transition state represent the product or the reactant (cation)? Draw out an energy diagram of this step reaction.

Answer

Exergonic and the transition state (second step) represents the reactant (cation). As shown to go from intermediate cation to final product the step is exergonic.

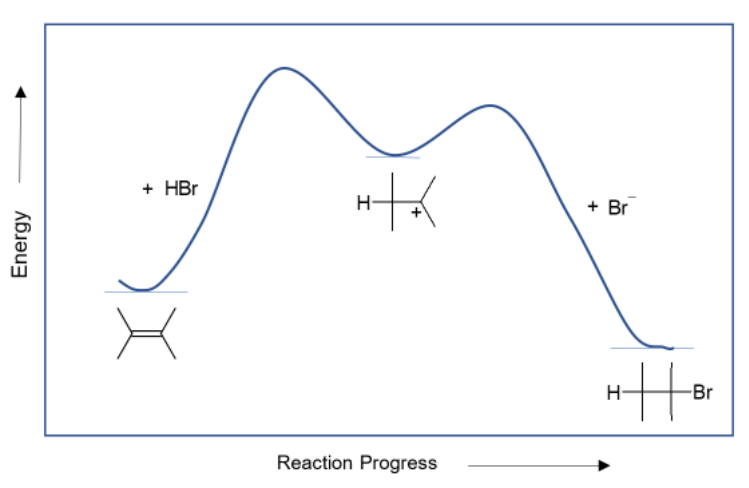


EXERCISE 7.11.2

Consider the second step in the electrophilic addition of HBr to an alkene. Is this step exergonic or endergonic and does the transition state represent the product or the reactant (cation)? Draw out an energy diagram of this step reaction.

Answer

Exergonic and the transition state (second step) represents the reactant (cation). As shown to go from intermediate cation to final product the step is exergonic.



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7.12: EVIDENCE FOR THE MECHANISM OF ELECTROPHILIC ADDITIONS - CARBOCATION REARRANGEMENTS

OBJECTIVE

After completing this section, you should be able to explain the “unusual” products formed in certain reactions in terms of the rearrangement of an intermediate carbocation.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alkyl shift
- hydride shift

STUDY NOTES

Whenever possible, carbocations will rearrange from a less stable isomer to a more stable isomer. This rearrangement can be achieved by either a hydride shift, where a hydrogen atom migrates from one carbon atom to the next, taking a pair of electrons with it; or an alkyl shift, in which an alkyl group undergoes a similar migration, again taking a bonding pair of electrons with it. These migrations usually occur between neighbouring carbon atoms, and hence are termed 1,2-hydride shifts or 1,2-alkyl shifts.

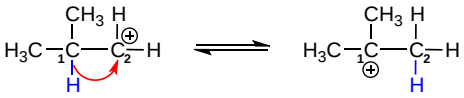
[A hydride ion consists of a proton and two electrons, that is, $[H:]^-$. Hydride ions exist in compounds such as sodium hydride, NaH, and calcium hydride, CaH_2.]

An electrophilic reaction such as HX with an alkene will often yield more than one product. This is strong evidence that the mechanism includes intermediate rearrangement steps of the cation.

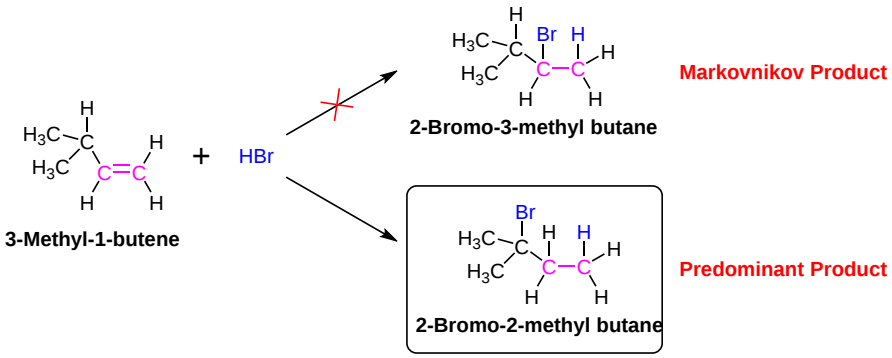
Throughout this textbook many reaction mechanisms will be presented. It is impossible to know with absolute certainty that a mechanism is correct. At best a proposed mechanism can be shown to be consistent with existing experimental data. Virtually all of the mechanisms in this textbook have been carefully studied by experiments designed to test their validity although the details are not usually discussed. An excellent example of experimental evidence which supports the carbocation based mechanism for electrophilic addition, is that structural rearrangements often occur during the reaction.

1,2-HYDRIDE SHIFT

A 1,2-hydride shift is a carbocation rearrangement in which a hydrogen atom in a carbocation migrates to the carbon atom bearing the formal charge of +1 (carbon 2 in the example below) from an adjacent carbon (carbon 1).

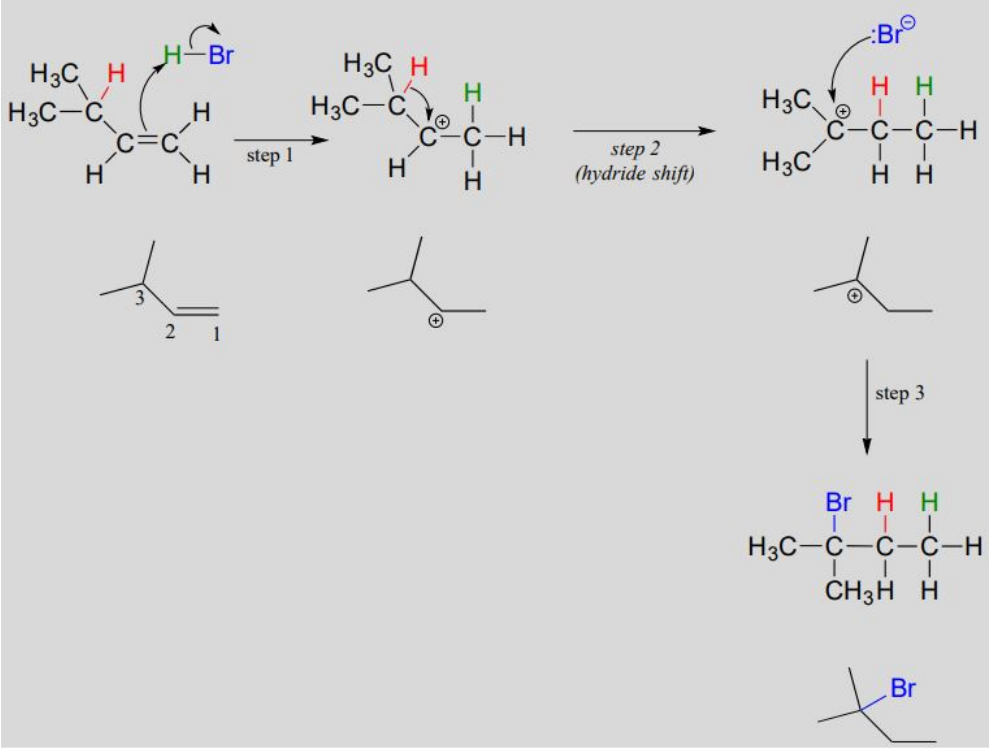


An example of this structural rearrangment occurs during the reaction of 3-methyl-1-butene with HBr. Markovnikov's rule predicts that the preferred product would be 2-bromo-3-methylbutane, however, very little of this product forms. The predominant product is actually 2-bromo-2-methylbutane.

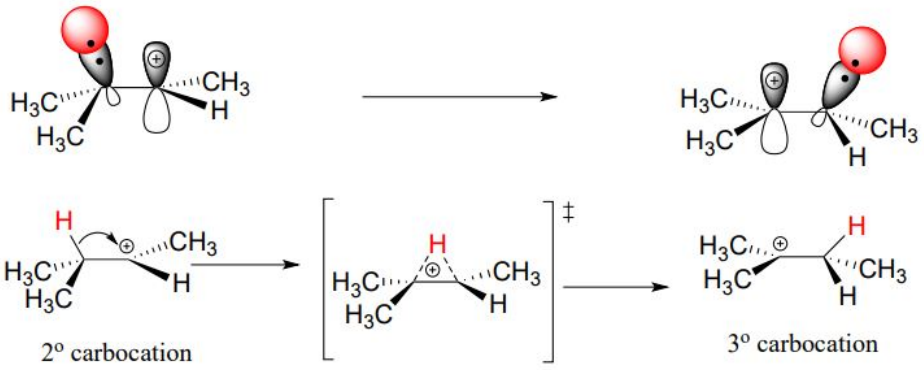


MECHANISM OF HYDRIDE SHIFT

This result comes from a **Hydride Shift** during the reaction mechanism. The mechanism begins with protonation of the alkene which places a positive charge on the more alkyl substituted double bond carbon resulting in a secondary carbocation. In step 2, The electrons in the C-H bond on carbon #3 are attracted by the positive charge on carbon #2, and they simply shift over to fill the carbocation's empty *p* orbital, pulling the proton over with them. The process called a carbocation rearrangement, and more specifically, a hydride shift. A hydride ion ($H:^-$) is a proton plus two electrons which not to be confused with H^+, which is just a proton without any electrons. Notice that the hydride, in shifting, is not acting as an actual leaving group - a hydride ion is a very strong base and a very poor leaving group.



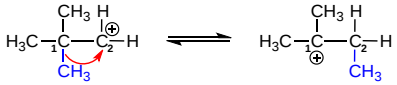
As the hydride shift proceeds, a new $C-H$ σ bond is formed at carbon #2, and carbon #3 is left with an empty p orbital and a positive charge.



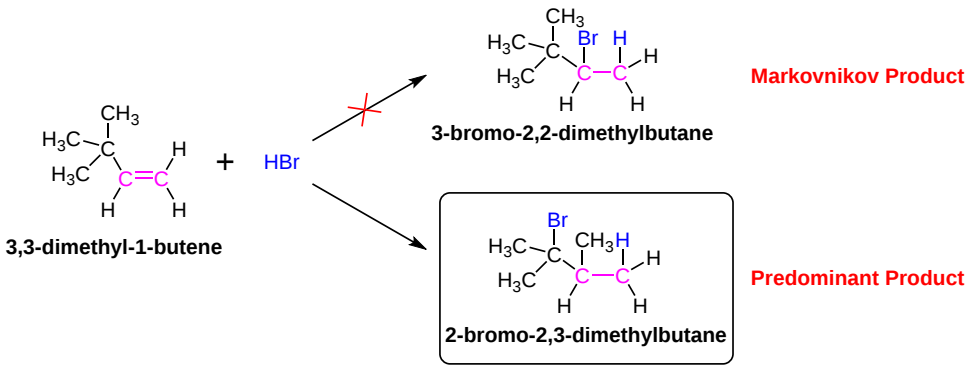
What is the thermodynamic driving force for this process? Notice that the hydride shift results in the conversion of a secondary carbocation (on carbon 2) to a (more stable) tertiary carbocation (on carbon 3) - a thermodynamically downhill step. As it turns out, the shift occurs so quickly that it is accomplished before the bromide nucleophile has time to attack at carbon #2. Rather, the bromide will attack after the hydride shift (step 3) at carbon #3 to complete the addition.

1,2-ALKYL SHIFT

A 1,2-alkyl shift is a carbocation rearrangement in which an alkyl group migrates to the carbon atom bearing the formal charge of +1 (carbon 2) from an adjacent carbon atom (carbon 1), e.g.



Consider another example. When HBr is added to 3,3-dimethyl-1-butene the preferred product is 2-bromo-2,3-dimethylbutane and not 3-bromo-2,2-dimethylbutane as predicted by Markovnikov's rule.



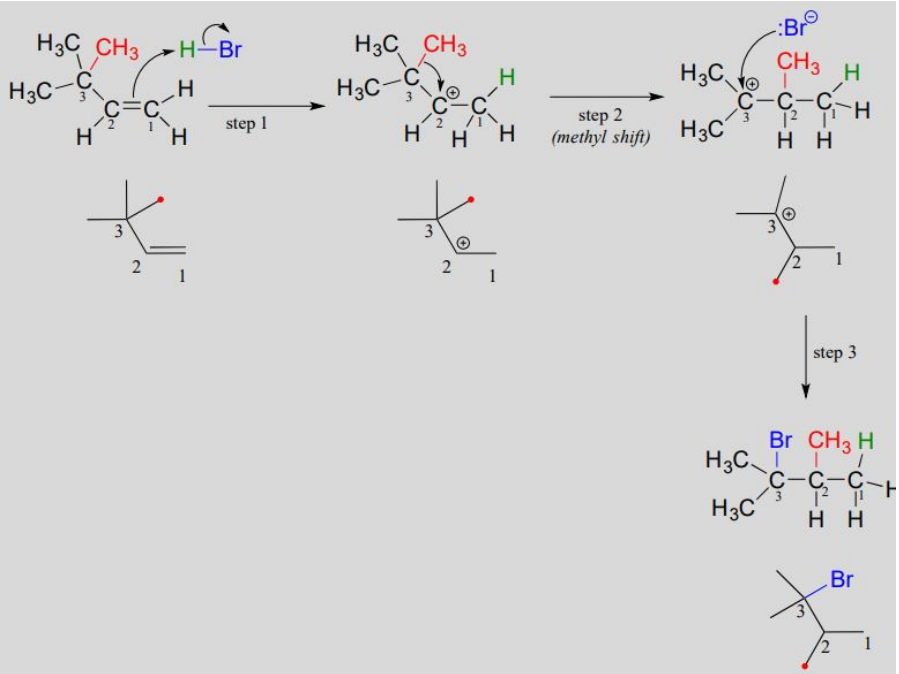
Notice that in the observed product, the carbon framework has been rearranged: a methyl carbon has been shifted. This is an example of another type of carbocation rearrangement, called an **alkyl shift** or more specifically a **methyl shift**.

MECHANISM OF ALKYL SHIFT

Below is the mechanism for the reaction. Once again a secondary carbocation intermediate is formed in step 1. In this case, there is no hydrogen on carbon #3 available to shift over create a more stable tertiary carbocation. Instead, it is a methyl group that does the shifting, as the electrons in the carbon-carbon ***σ*** bond shift over to fill the empty orbital on carbon #2 (step 2 below). The methyl shift results in the conversion of a secondary carbocation to a more stable tertiary carbocation. It is this tertiary carbocation which is attacked by the bromide nucleophile to make the rearranged end product. The end result is a rearrangement of the carbon framework of the molecule.

Electrophilic addition with methyl shift:

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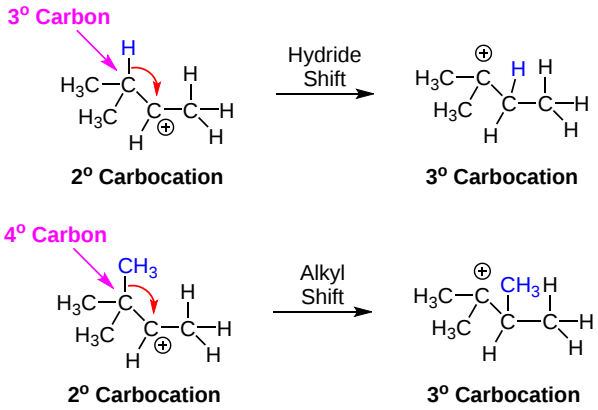
PREDICTING THE PRODUCT OF A CARBOCATION REARRANGEMENT

Carbocation shifts occur in many more reactions than just electrophilic additions as some of which will be discussed in subsequent chapters of this textbook. Whenever a carbocation is produced in a reaction's mechanism the possibility of rearrangements should be considered. As discussed in Section 7.9, there are multiple ways to stabilize a carbocation all of which could induce a rearrangement.

The most common situation for a rearrangement to occur during electrophilic addition is:

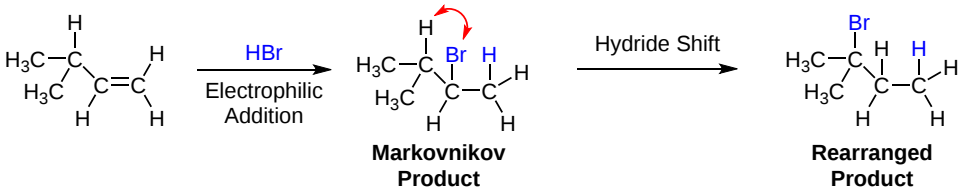
A 2^{O} CARBOCATION WITH A 3° OR 4° ALKYL SUBSTITUENT

When considering the possibility of a carbocation rearrangement the most important factors are the designation of the carbocation formed and the designation of the alkyl groups attached to the carbocation. When a 2º carbocation has a 3º alkyl substituent a hydride shift will occur to create a more stable 3º carbocation. When a 2º carbocation has a 4º alkyl substituent an alkyl shift will occur to create a more stable 3º carbocation.



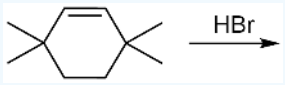
DRAWING THE REARRANGED PRODUCT

First, draw the unrearranged product. Add HX to the double bond following Markovnikov's rule if necessary. Then determine if a hydride or alkyl shift is occurring by observing the designation of the alkyl substituent. The switch X ⇔H for a hydride shift and X ⇔ CH_3 for an alkyl shift this will produce the rearranged product.

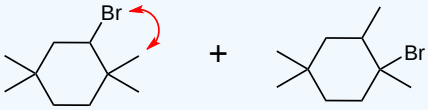


EXERCISE 7.12.1

Draw the expected products of the following reaction.

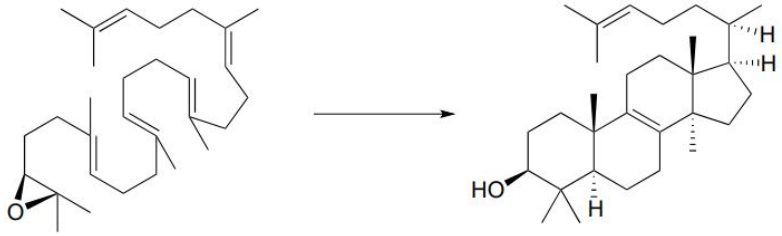


Answer



BIOLOGICAL CARBOCATION REARRANGEMENT

Carbocation rearrangements are involved in many known biochemical reactions. Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. For example, one of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol.

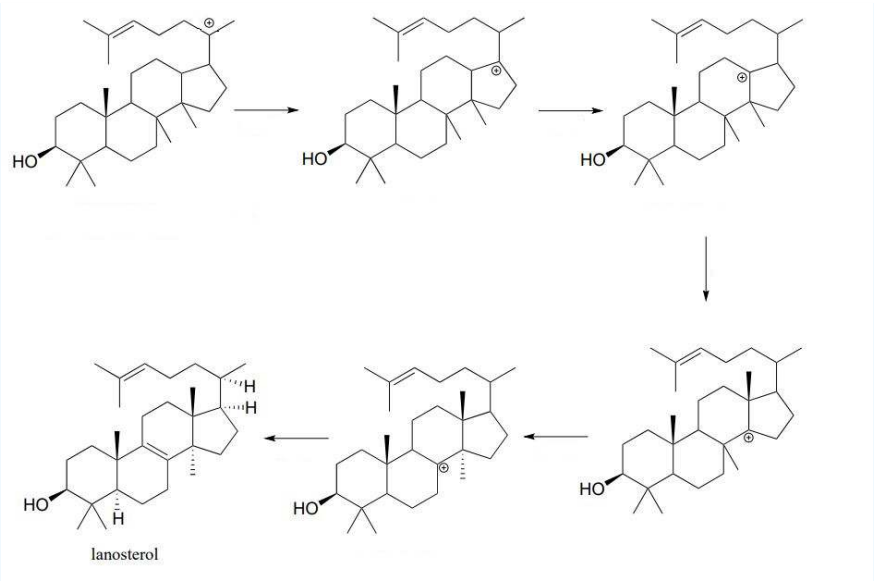


(3S)-2,3-oxidosqualene lanosterol

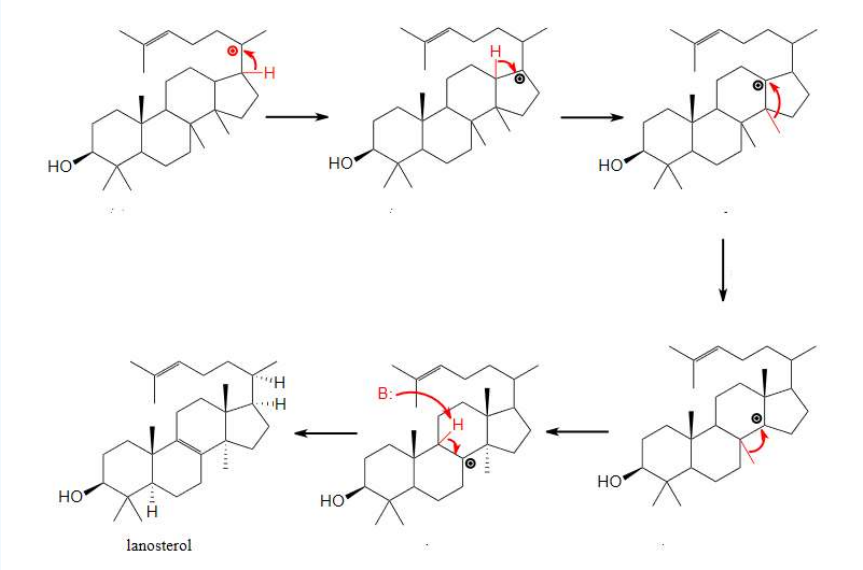
This complex but fascinating reaction has two phases. The first phase is where the actual cyclization takes place, with the formation of four new carbon-carbon bonds and a carbocation intermediate. The second phase involves a series of hydride and methyl shifts culminating in a deprotonation. In the exercise below, you will have the opportunity to work through the second phase of the cyclase reaction mechanism.

EXERCISE 7.12.1

The second phase of the cyclase reaction mechanism involves multiple rearrangement steps and a deprotonation. Please supply the missing mechanistic arrows.

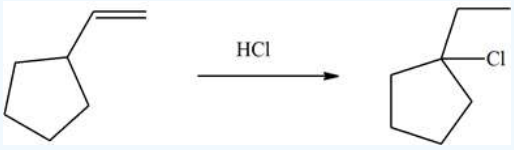


Answer

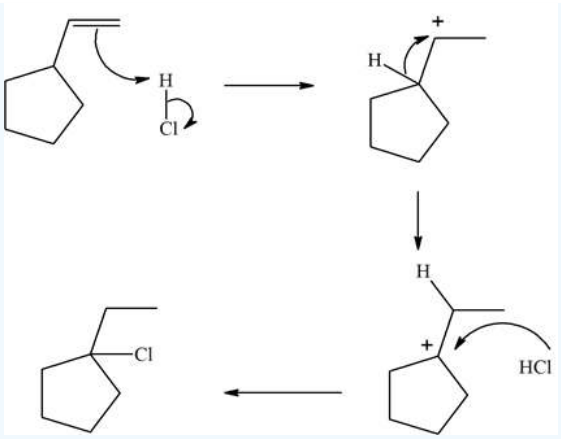


EXERCISE 7.12.2

The following reaction shows a rearrangement within the mechanism. Propose a mechanism that shows this.

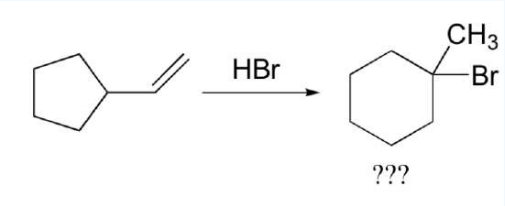


Answer



EXERCISE 7.12.1

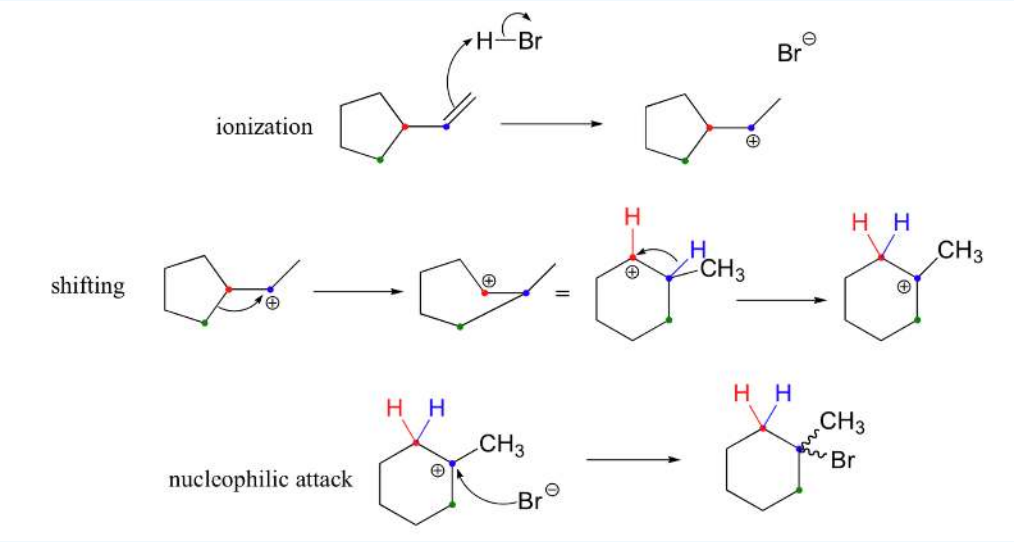
Propose a mechanism for the following reaction. It involves an electrophilic addition and the shift of a C-C and a C-H bond.



Answer

In most examples of carbocation rearrangements that you are likely to encounter, the shifting species is a hydride or methyl group. However, pretty much any alkyl group is capable of shifting. Sometimes, the entire side of a ring will shift over in a ring-expanding rearrangement.

The first 1,2-alkyl shift is driven by the expansion of a five-membered ring to a six-membered ring, which has slightly less ring strain. A hydride shift then converts a secondary carbocation to a tertiary carbocation, which is the electrophile ultimately attacked by the bromide nucleophile.



Once again, the driving force for this process is an increase in stability of the carbocation. Initially, there is a primary carbocation at C2, and this becomes a tertiary carbocation at C1 as a result of the (1,2)-methyl shift.

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7.S: ALKENES- STRUCTURE AND REACTIVITY (SUMMARY)

CONCEPTS & VOCABULARY

7.1 Industrial Preparation and Use of Alkenes

- Breaking up of large hydrocarbon molecules into smaller, useful molecules is called cracking.

7.2 Calculating Degree of Unsaturation

- Saturated molecules contain only single bonds and no rings.
- Saturated hydrocarbons have the formula C_nH_{2n+2}, where n can be any integer.
- Degrees of unsaturation account for the total number of rings and pi bonds in a molecule.
- Each degree of unsaturation reduces the number of hydrogens in the molecule by 2.

7.3 Naming Alkenes

- When the two largest groups are on the same side of the double bond (top or bottom) they are called cis or *Z*.
- When the two largest groups are on opposite sides of the double bond (top or bottom) they are called trans or *E*.
- Endocyclic double bonds occur when there is a pi bond within a ring.

7.4 Cis-Trans Isomerism in Alkenes

7.5 Alkene Stereochemistry and the E, Z Designation

- *E* and *Z* are less limited than cis and trans in naming.
- *E* and *Z* configurations use the same priority rules as R and S (CIP rules).

7.6 Stability of Alkenes

- Relative stability of alkenes can be measured by using heats of hydrogenation upon reduction to the related alkane.
- More substituted alkenes are more stable than less substituted.
- Alkenes with the largest groups trans are more stable than cis.

7.7 Electrophilic Addition Reactions of Alkenes

- In electrophilic addition reactions, the pi bond of the alkene acts as the nucleophile.
- Electrophilic addition reactions occur faster with larger hydrogen halides as well as more substituted alkenes.

7.8 Orientation of Electrophilic Additions: Markovnikov's Rule

- The more substituted carbocation intermediate forms during electrophilic addition reactions, since more substituted carbocations are more stable. This is known as Markovnikov's rule.

7.9 Carbocation Structure and Stability

- Molecules or ions that can disperse (delocalize) charge are more stable than structures with charge localized on a single atom.
- Due to inductive stabilization, carbocation stability follows the order:

tertiary > secondary > primary > methyl

- Electron donating groups stabilize carbocations.
- Electron withdrawing groups destabilize carbocations.
- Resonance effects can stabilize a carbocation (some examples include benzylic and allylic carbocations).
- Vinylic carbocations are unstable and are unlikely to form.

7.10 The Hammond Postulate

- The Hammond Postulate states that transition state structure most resembles the nearest stable species.
- Based on the Hammond Postulate, transition states for exothermic reaction steps resemble reactants, while endergonic step transition states resemble products.

7.11 Evidence for the Mechanism of ELectrophilic Additions: Carbocation Rearrangements

- Carbocations will rearrange from less stable to more stable isomers through hydride shifts or alkyl shifts.

SKILLS TO MASTER

- Skill 7.1 Calculate degree of unsaturation for organic molecular formulae.

- Skill 7.2 Draw isomers from a molecular formula.
- Skill 7.3 Name alkenes following IUPAC rules, including configuration (*E*, *Z*).
- Skill 7.4 Draw structures from IUPAC name.
- Skill 7.5 Describe bonding in alkenes including bond length, strength, angle and restricted rotation.
- Skill 7.6 Explain stability of alkenes.
- Skill 7.7 Rank alkenes in order of stability.
- Skill 7.8 Draw mechanism for electrophilic addition of HX to alkenes, including regiochemistry.
- Skill 7.9 Explain stability of carbocations.
- Skill 7.10 Explain transition states related to the Hammond Postulate.
- Skill 7.11 Explain products formed by carbocation rearrangements.

MEMORIZATION TASKS

MT 7.1 Memorize formula for saturated hydrocarbons C_nH_{2n+2}.

MT 7.2 Memorize basic IUPAC naming rules.

MT 7.3 Memorize relative stability of alkenes.

MT 7.4 Memorize relative stability of carbocations.

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CHAPTER OVERVIEW

8: ALKENES - REACTIONS AND SYNTHESIS

As you have seen, addition reactions dominate the chemistry of alkenes. This chapter shows how a variety of reagents can add to alkenes; how hydrogen bromide can be made to add to alkenes in a non-Markovnikov manner; and how alkene molecules can be cleaved into easily identifiable parts. First, you will examine the preparation of alkenes by elimination reactions.

8.0: Chapter Objectives

8.1: Preparation of Alkenes - A Preview of Elimination Reactions

8.2: Halogenation of Alkenes - Addition of X_2

8.3: Halohydrins from Alkenes - Addition of HOX

8.4: Hydration of Alkenes - Addition of H_2O by Oxymercuration

8.5: Hydration of Alkenes - Addition of H_2O by Hydroboration

8.6: Reduction of Alkenes - Hydrogenation

8.7: Oxidation of Alkenes - Epoxidation and Hydroxylation

8.8: Oxidation of Alkenes - Cleavage to Carbonyl Compounds

8.9: Addition of Carbenes to Alkenes - Cyclopropane Synthesis

8.10: Radical Additions to Alkenes - Chain-Growth Polymers

8.11: Biological Additions of Radicals to Alkenes

8.12: Stereochemistry of Reactions - Addition of H_2O to an Achiral Alkene

8.13: Stereochemistry of Reactions - Addition of H_2O to a Chiral Alkene

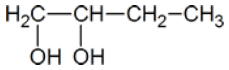
8.S: Alkenes - Reactions and Synthesis (Summary)

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8.0: CHAPTER OBJECTIVES

After you have completed Chapter 8, you should be able to

1. fulfill all of the detailed objectives listed under each section.
2. design a relatively simple, multistep synthesis using the reactions introduced in this chapter, given the structure, name, or both, of the starting material and product. For example, show how you would convert 1-bromobutane to



3. deduce the structures of a number of compounds involved in a certain reaction sequence, given sufficient information. In other words, solve so-called road-map problems.
4. define, and use in context, the key terms introduced in this chapter.

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8.1: PREPARATION OF ALKENES - A PREVIEW OF ELIMINATION REACTIONS

OBJECTIVES

After completing this section, you should be able to

- explain the relationship between an addition reaction and an elimination reaction.
- write an equation to describe the dehydrohalogenation of an alkyl halide.
- identify the reagents required to bring about dehydrohalogenation of an alkyl halide.
- write an equation to represent the dehydration of an alcohol.
- identify the reagents required to dehydrate a given alcohol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- dehydration
- dehydrohalogenation
- elimination reaction

STUDY NOTES

An *elimination reaction* is a reaction in which two or more atoms, one of which is usually hydrogen, are removed from adjacent atoms in the reactant, resulting in the formation of a multiple bond.

The relationship between addition reactions and elimination reactions is shown in Figure 8.1, below.

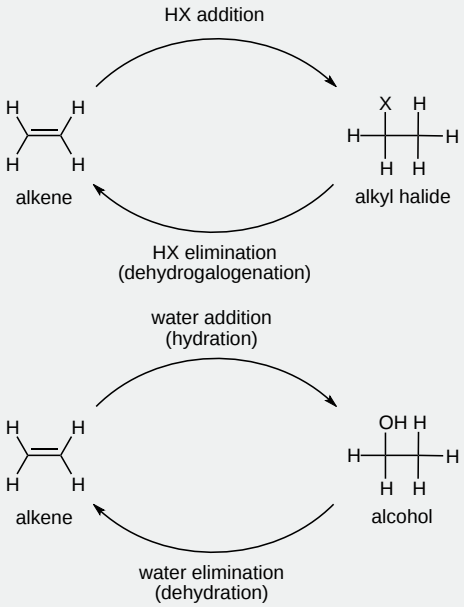
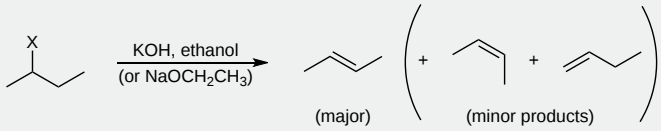
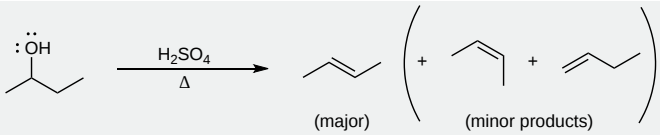


Figure 8.1: Relationship of addition and elimination reactions

Alkenes can be readily prepared from the alkylhalide (X = Cl, Br, I) or the alcohol.



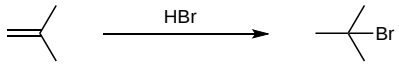


ELECTROPHILIC ADDITION

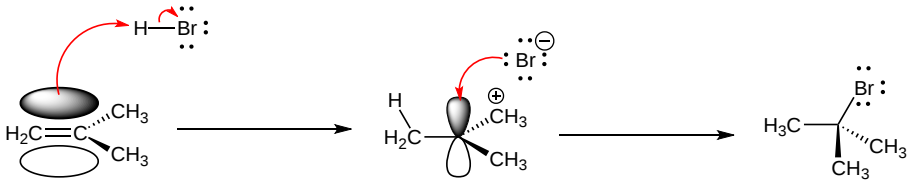
Alkenes are found throughout nature. They form the basis of many natural products, such as terpenes, which play a variety of roles in the lives of plants and insects. The C=C bonds of alkenes are very different from the C=O bonds that are also common in nature. The C=C bonds of alkenes are electron-rich and nucleophilic, in contrast to the electron-poor C=O bonds of carbohydrates, fatty acids and proteins. That difference plays a role in how terpenes form in nature.

Alkenes, or olefins, are also a major product of the petroleum industry. Reactions of alkenes form the basis for a significant portion of our manufacturing economy. Commonly used plastics such as polyethylene, polypropylene and polystyrene are all formed through the reactions of alkenes. These materials continue to find use in our society because of their valuable properties, such as high strength, flexibility and low weight.

Alkenes undergo addition reactions as you will see carbonyls do as well. Most commonly they add a proton to one end of the double bond and another group to the other end. These reactions happen in slightly different ways, however.



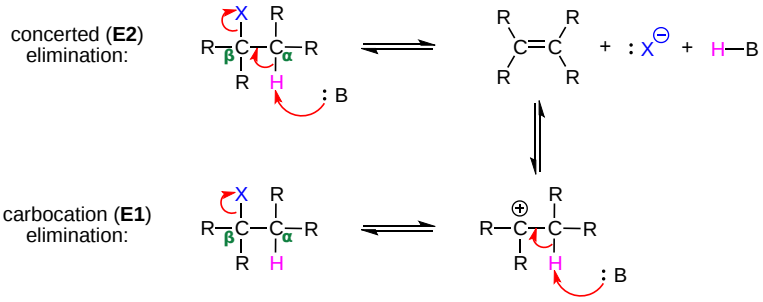
Alkenes are reactive because they have a high-lying pair of π-bonding electrons. These electrons are loosely held, being high in energy compared to σ-bonds. The fact that they are not located between the carbon nuclei, but are found above and below the plane of the double bond, also makes these electrons more accessible.



Alkenes can donate their electrons to strong electrophiles other than protons, too. Sometimes their reactivity pattern is a little different than the simple addition across the double bond, but that straightforward pattern is what we will focus on in this chapter.

ELIMINATION REACTIONS

Elimination reactions are possible by abstraction of a proton at positions that are next to a potential leaving group. This type of elimination can be described by two model mechanisms: it can occur in a single concerted step (proton abstraction at C_α occurring at the same time as C_β-X bond cleavage), or in two steps (C_β-X bond cleavage occurring first to form a carbocation intermediate, which is then 'quenched' by proton abstraction at the alpha-carbon).

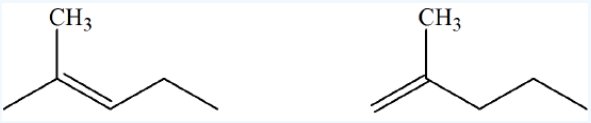


The most common elimination reactions are dehydrohalogenation and dehydration. In the mechanism above, X could be Cl, Br, or I for the dehydrohalogenation where there is a loss of HX from an alkyl halide. For dehydration, X would be an OH group in the above mechanism where the overall loss is water from an alcohol. These mechanisms, termed E2 and E1, respectively, are important in laboratory organic chemistry, but are less common in biological chemistry. As explained below, which mechanism actually occurs in a laboratory reaction will depend on the identity of the R groups (ie., whether the alkyl halide is primary, secondary, tertiary, etc.) as well as on the characteristics of the base.

EXERCISE 8.1.1

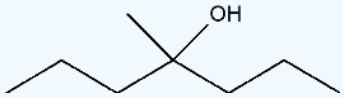
In elimination reactions there tends to have a mixture of products. What are the two possible alkene products for the reaction of 2-bromo-2-methylpentane with NaOH?

Answer

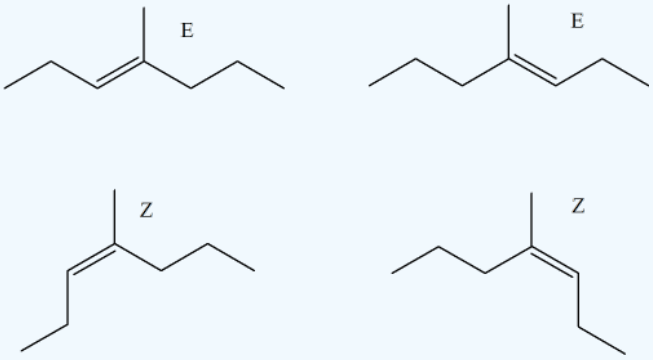


EXERCISE 8.1.2

Predict the *E*/*Z* isomers for the following molecule when reacted with H_2SO_4.



Answer



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8.2: HALOGENATION OF ALKENES - ADDITION OF X_2

OBJECTIVES

After completing this section, you should be able to

- write the equation for the reaction of chlorine or bromine with a given alkene.
- identify the conditions under which an addition reaction occurs between an alkene and chlorine or bromine.
- draw the structure of the product formed when a given alkene undergoes an addition reaction with chlorine or bromine.
- write the mechanism for the addition reaction that occurs between an alkene and chlorine or bromine, and account for the stereochemistry of the product.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- anti stereochemistry
- bromonium ion

STUDY NOTES

In the laboratory you will test a number of compounds for the presence of a carbon-carbon double bond. A common test is the decolourization of a reddish-brown bromine solution by an alkene.

The two-step mechanism shown in the LibreText pages gives you an idea of how the reaction between an alkene and a halogen occurs. Note the formation of the bridged bromonium ion intermediate and the anti stereochemistry of the final product because the two bromine atoms come from opposite faces of the double bond.

Additional evidence in support of the bromonium ion mechanism comes from the results obtained when an alkene (such as cyclopentene) reacts with bromine in the presence of sodium chloride (see Figure 8.2: Reaction of an alkene with bromine in the presence of sodium chloride, below).

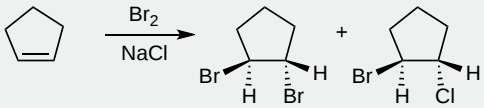


Figure 8.2: *Reaction of an alkene with bromine in the presence of sodium chloride*

Once formed, the bromonium ion is susceptible to attack by two nucleophiles—chloride ion and bromide ion—and, in fact, a mixture of two products (both produced by anti attack) is formed.

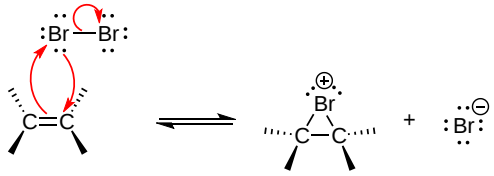
Halogens can act as electrophiles to which can be attacked by a pi bond from an alkene. Pi bonds represents a region of electron density and therefore function as a nucleophiles. How is it possible for a halogen to obtain positive charge to be an electrophile?

INTRODUCTION

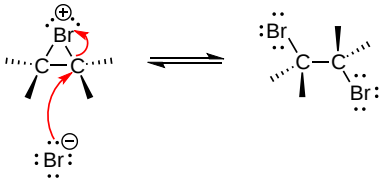
A halogen molecule, for example $Br_{2,}$ approaches a double bond of the alkene, electrons in the double bond repel electrons in the bromine molecule causing polarization of the halogen-halogen bond. This creates a dipole moment in the halogen-halogen bond. Heterolytic bond cleavage occurs and one of the halogens obtains a positive charge and reacts as an electrophile. The reaction of the addition is not regioselective but is stereoselective. Stereochemistry of this addition can be explained by the mechanism of the reaction. In the first step, the electrophilic halogen (with the positive charge) approaches the pi bond and 2p orbitals of the halogen bond with two carbon atoms creating a cyclic ion with a halogen as the intermediate. In the second step, the remaining halide ion (halogen with the negative charge) attacks either of the two carbons in the cyclic ion from the back side of the cycle as in the S_N2 reaction. Therefore stereochemistry of the product is anti addition of **vicinal dihalides**.

$$\mathbf{R_2C{=}CR_2 + X_2 \rightarrow R_2CX{-}CR_2X} \tag{8.2.1}$$

Step 1: In the first step of the addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a cyclic intermediate with the two carbons from the alkene.



Step 2: In the second step, bromide anion attacks either carbon of the bridged bromonium ion from the back side of the ring. The bromine atom in the bromonium ion acts as a shield in a way, forcing the bromonium anion to attack from the opposite side as it. The result of this is the ring opening up with the two halogens on opposite sides as each other. This is **anti** stereochemistry, which is defined as the two bromine atoms come from opposite faces of the double bond. The product is that the bromines add on trans to each other.



Halogens that are commonly used in this type of the reaction are: ***Br*** and ***Cl***. In thermodynamical terms ***I*** is too slow for this reaction because of the size of its atom, and ***F*** is too vigorous and explosive.

Because the halide ion can attack any carbon from the opposite side of the ring it creates a mixture of steric products. Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

ELECTROPHILIC ADDITION MECHANISM CONSISTS OF TWO STEPS.

Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene.

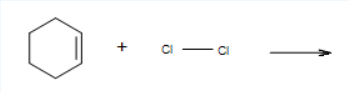
Nucleophile	**Double bond in alkene**
Electrophile	Br_2, Cl_2
Regiochemistry	not relevant
Stereochemistry	**ANTI**

SUMMARY

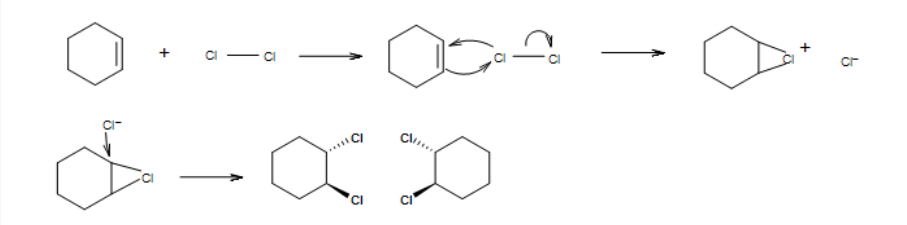
Halogens can act as electrophiles due to polarizability of their covalent bond. Addition of halogens is stereospecific and produces vicinal dihalides with anti addition.

? EXERCISE 8.2.1

What is the mechanism of adding Cl_2 to the cyclohexene?



Answer



EXERCISE 8.2.2

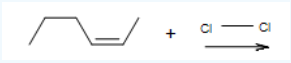
A reaction of Br_2 molecule in an inert solvent with alkene follows?

a. syn addition
b. anti addition
c. Morkovnikov rule

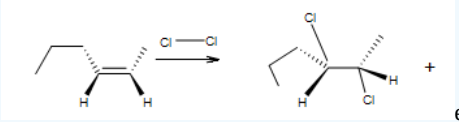
Answer

b

EXERCISE 8.2.3

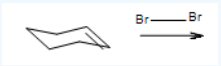


Answer

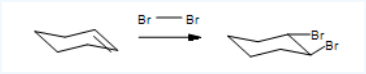


enantiomer

EXERCISE 8.2.4



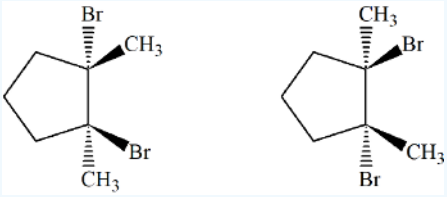
Answer



EXERCISE 8.2.5

Predict the products for 1,2-dimethylcyclopentene reacting with Br_2 with proper stereochemistry.

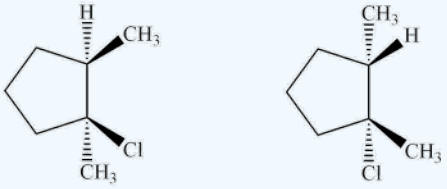
Answer



EXERCISE 8.2.6

Predict the products for 1,2-dimethylcyclpentene reacting with HCl, give the proper stereochemistry. What is the relationship between the two products?

Answer



These compounds are enantiomers.

REFERENCES

1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function. New York: W.H.Freeman and Company 2007
2. Chemistry-A European Journal 9 (2003) :1036-1044

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8.3: HALOHYDRINS FROM ALKENES - ADDITION OF HOX

OBJECTIVES

After completing this section, you should be able to

- write the equation for the formation of a halohydrin from an alkene.
- write the mechanism for the formation of a halohydrin from an alkene and a mixture of halogen and water.
- predict the mechanism of the addition reaction that occurs between a given reagent and an alkene, basing your prediction on mechanisms you have studied in this chapter.
- identify the alkene, the reagents, or both, that should be used to produce a given halohydrin by an addition reaction.
- identify N-bromosuccinimide in aqueous dimethyl sulphoxide as an alternative source of bromine for producing bromohydrins.

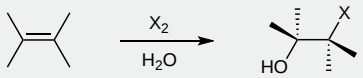
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bromohydrin
- halohydrin

STUDY NOTES

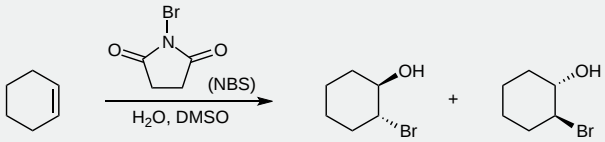
Bromohydrin and chlorohydrin are examples of halohydrins (where X = Br or Cl).



alkene halohydrin

Chemists often abbreviate the names of frequently used chemicals: DMSO for dimethyl sulfoxide, NBS for N-bromosuccinimide, etc. You should already be familiar with some similar examples from everyday life: DDT for dichlorodiphenyltrichloroethane, PCB for polychlorinated biphenyl, and ASA for acetylsalicylic acid (aspirin). You can see how someone with a limited knowledge of chemistry could misinterpret the abbreviation NBS—it is not a compound containing nitrogen, boron and sulfur!

NBS can serve as a less dangerous and easier to handle replacement for Br_2 in the formation of bromohydrins.



The proton is not the only electrophilic species that initiates addition reactions to the double bond of alkenes. Lewis acids like the halogens, boron hydrides and certain transition metal ions are able to bond to the alkene pi-electrons, and the resulting complexes rearrange or are attacked by nucleophiles to give addition products.The electrophilic character of the halogens is well known as discussed in the previous section. Chlorine (Cl_2) and bromine(Br_2) react selectively with the double bond of alkenes, and these reactions are what we will focus on. Fluorine adds uncontrollably with alkenes,and the addition of iodine is unfavorable, so these are not useful preparative methods.

The addition of chlorine and bromine to alkenes, as shown below, proceeds by an initial electrophilic attack on the pi-electrons of the double bond (Section 8.2). Dihalo-compounds in which the halogens are bound to adjacent carbons are called vicinal, from the Latin *vicinalis*, meaning neighboring.

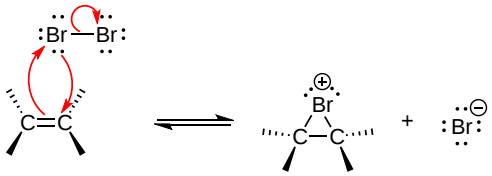
$$R_2C{=}CR_2 + X_2 \longrightarrow R_2CX\text{-}CR_2X$$

Another electrophilic addition to an alkene is the reaction of an alkene with the other halogen-containing reagents like hypohalous acids, HOX, to form halohydrins. However, halohydrins are not formed by directly adding a hypohalous acid, instead the alkene is reacted with Br_2 or Cl_2 in the presence of water. These reagents are unsymmetrical (unlike Br_2 or Cl_2), so their addition to unsymmetrical double bonds may in principle take place in two ways. In practice, these addition reactions are regioselective, with one of the two possible constitutionally isomeric products being favored. The electrophilic moiety in both of these reagents is the halogen.

$(CH_3)_2C{=}CH_2 + HOBr \longrightarrow (CH_3)_2COH\text{-}CH_2Br$

The regioselectivity of the above reactions may be explained by the same mechanism we used to rationalize the Markovnikov rule. Thus, bonding of an electrophilic species to the double bond of an alkene should result in preferential formation of the more stable (more highly substituted) carbocation, and this intermediate should then combine rapidly with a nucleophilic species to produce the addition product.

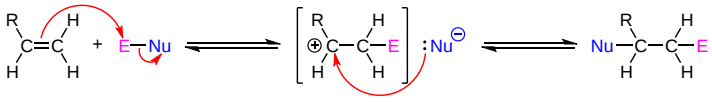
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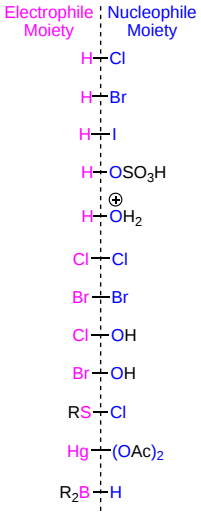
Step one is the same as halogenation of alkenes. The halogen, in this case bromine, reacts with the alkene to form a cyclic bromonium ion.

Step two does not have the bromine ion attack, but instead water acts as the nucleophile. Water is available at a higher concentration than the bromine ion, so is more likely to be available in the correct orientation for the nucleophilic attack. Water is also a better nucleophile than the bromine ion. The better a nucleophile, the more likely it is to attack. You may notice that as oxygen makes a bond it gets a positive formal charge at the completion of this step.

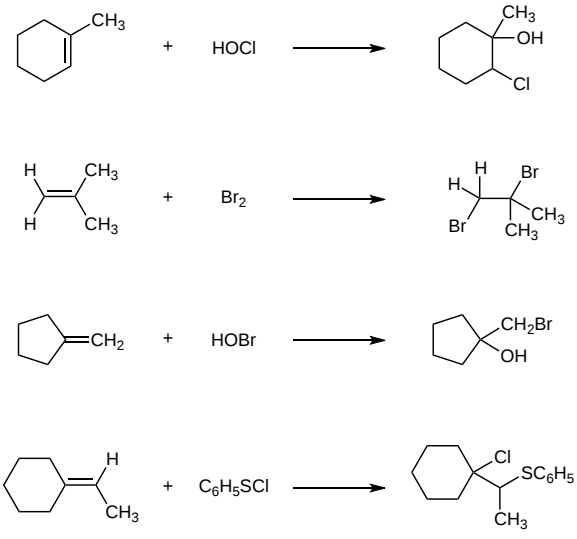
Step 3 is a final acid-base step, where there is a loss of a proton from the oxygen to the solvent (water) to form the neutral halohydrin. In this case, a bromohydrin is the product of the addition reaction.



To apply this mechanism we need to determine the electrophilic moiety in each of the reagents. By using electronegativity differences we can dissect common addition reagents into electrophilic and nucleophilic moieties, **as shown on the right**. In the case of hypochlorous and hypobromous acids (HOX), these weak Brønsted acids (pKa's ~ 8) do not react as proton donors; and since oxygen is more electronegative than chlorine or bromine, the electrophile will be a halide cation. The nucleophilic species that bonds to the intermediate carbocation is then hydroxide ion, or more likely water (the usual solvent for these reagents), and the products are called halohydrins. Sulfenyl chlorides add in the opposite manner because the electrophile is a sulfur cation, RS(+), whereas the nucleophilic moiety is chloride anion (chlorine is more electronegative than sulfur).

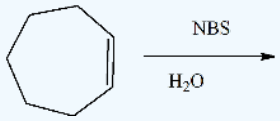


Below are some examples illustrating the addition of various electrophilic halogen reagents to alkene groups. Notice the specific regiochemistry of the products, as explained above.

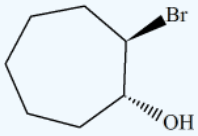


EXERCISE 8.3.1

Predict the product of the following reaction:



Answer



EXERCISE 8.3.2

When butene is treated with NBS in the presence of water, the product shows that the bromine is on the least substituted carbon, is this Markovnikov or anti-Markovnikov?

Answer

Since the bromine is the first addition to the alkene, this addition would be an anti-Markovnikov addition.

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8.4: HYDRATION OF ALKENES - ADDITION OF H_2O BY OXYMERCURATION

OBJECTIVES

After completing this section, you should be able to

- write an equation for the hydration of an alkene with sulfuric acid.
- write an equation for the formation of an alcohol from an alkene by the oxymercuration-demercuration process.
- identify the alkene, the reagents, or both, that should be used to produce a given alcohol by the oxymercuration-demercuration process.
- write the mechanism for the reaction of an alkene with mercury(II) acetate in aqueous tetrahydrofuran (THF).

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

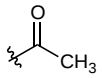
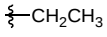
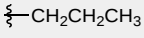
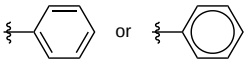
- hydration
- oxymercuration

STUDY NOTES

Oxymercuration is the reaction of an alkene with mercury(II) acetate in aqueous THF, followed by reduction with sodium borohydride. The final product is an alcohol.

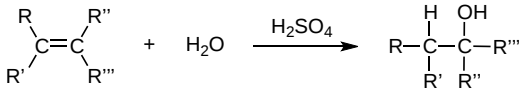
It is important that you recognize the similarity between the mechanisms of bromination and oxymercuration. Recognizing these similarities helps you to reduce the amount of factual material that you need to remember.

Mercuric acetate, or mercury(II) acetate, to give it the preferred IUPAC name, is written as $Hg(OAc)_2$; by comparing this formula with the formula $Hg(O_2CCH_3)_2$, you can equate Ac with -$COCH_3$. In fact, Ac is an abbreviation used for the acetyl group with the structure shown below as are other similar abbreviations that you will encounter.

Ac (acetyl)	
Me (methyl)	
Et (ethyl)	
Pr^n (*n*-propyl)	
Pr^i (isopropyl)	
Bu^t (*tert*-butyl)	
Ph (phenyl)	

WHAT IS ELECTROPHILIC HYDRATION?

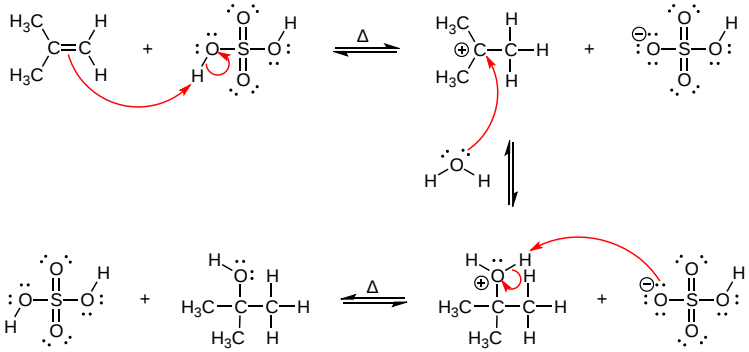
Electrophilic hydration is the act of adding an electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1º, 2º, or 3º alcohol on the alkane. Electrophilic hydration is the reverse dehydration of alcohols and has practical applications in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



An electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electron. An electrophilic hydrogen is commonly used to help break double bonds or restore catalysts (see S_N2 for more details).

MECHANISM FOR THE FORMATION OF A 3º ALCOHOL (1º AND 2º MECHANISMS ARE SIMILAR)

Hydration is the process where water is added to an alkene to yield an alcohol. Acid-catalyzed hydration is when a strong acid is used as a catalyst to begin the reaction, but let's look at the mechanism below and break down the steps.



Step 1: A hydrogen atom from the acid is attacked by the nucleophilic Pi-electrons in the double bond. This is similar to the other alkene reactions we have seen so far. In this process, a new C-H bond is formed at the location which creates the more stable carbocation.

Step 2: A nucleophilic water attacks or donates a lone pair to the carbocation intermediate created in the first step. A new C-O bond is formed with the O having a formal charge of +1. The product is a protonated alcohol.

Step 3: To obtain the neutral alcohol product, the final step is to deprotonate the oxygen atom with the +1 formal charge using the conjugate base of the acid catalyst. This final step regenerates the acid catalyst and yields the neutral alcohol product.

> Heat is used to catalyze electrophilic hydration; because the reaction is in equilibrium with the dehydration of an alcohol, which requires higher temperatures to form an alkene, lower temperatures are required to form an alcohol. *The exact temperatures used are highly variable and depend on the product being formed.*

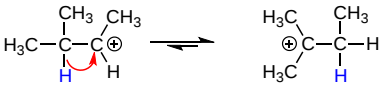
WHAT IS REGIOCHEMISTRY AND HOW DOES IT APPLY?

Regiochemistry deals with where the substituent bonds on the product is formed. **Zaitsev's** and **Markovnikov**'s rules address regiochemistry, but Zaitsev's rule applies when synthesizing an alkene while Markovnikov's rule describes where the substituent bond form in the product of an electrophilic additon. In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies. See the following for an in-depth explanation of regiochemistry: Markovnikov explanation: Radical Additions--Anti-Markovnikov Product Formation

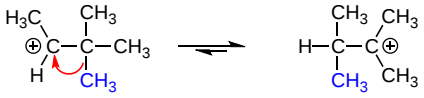
In the mechanism for the formation of a 3º alcohol shown above, the H is added to the least-substituted carbon in the nucleophilic double bond (it has less carbons attached to it). This means that the carbocation forms on the 3º carbon, causing it to be more stabilized by *hyperconjugation*—electrons in nearby sigma (single) bonds help fill the empty p-orbital of the carbocation, which lessens the positive charge. More substitution on a carbon means more sigma bonds are available to "help out" (by using overlap) with the positive charge, which creates greater *carbocation stability*. In other words, **carbocations form on the most substituted carbon** in the double bond.

If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

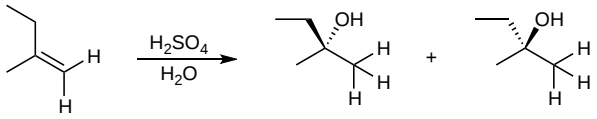


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3º alcohol shown above, water is the nucleophile. After one H atom is removed from the water molecule, the alcohol is attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

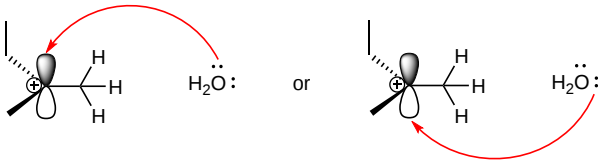
WHAT IS STEREOCHEMISTRY AND HOW DOES IT APPLY?

Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally likely to be found going into the plane of the board as it is out of the plane of the board. This indicates that **the product is a racemic mixture**.

Electrophilic hydration adopts a stereochemistry wherein the substituent is equally likely to bond pointing into the plane of the board as it is pointing out of the plane of the board. The 3º alcohol product of the following reaction could look like either of the following products:



There is no stereochemical control in acid-catalyzed hydration reactions. This is due to the trigonal planar, sp^2 nature of the carbocation intermediate. Water can act as a nucleophile to form a bond to either face of the carbocation, resulting in a mixture of stereochemical outcomes.



Note: Whenever a straight line is used along with dashes and wedges on the same molecule, it could be denoting that the straight line bond is in the same plane as the board. Practice with a molecular model kit and attempting the practice problems at the end can help eliminate any ambiguity.

IS THIS A REVERSIBLE SYNTHESIS?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To sway the equilibrium one way or another, the temperature or the concentration of the non-nucleophilic strong acid can be changed. For example:

- Less sulfuric or phosphoric acid and an excess of water help synthesize more alcohol product.
- Lower temperatures help synthesize more alcohol product.

IS THERE A BETTER WAY TO ADD WATER TO SYNTHESIZE AN ALCOHOL FROM AN ALKENE?

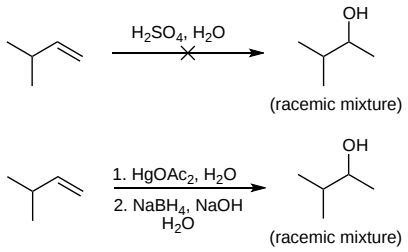
A more efficient pathway does exist: **Oxymercuration - Demercuration**, a special type of electrophilic addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (*R*)-enantiomer and an (*S*)-enantiomer)
- Using sulfuric or phosphoric acid

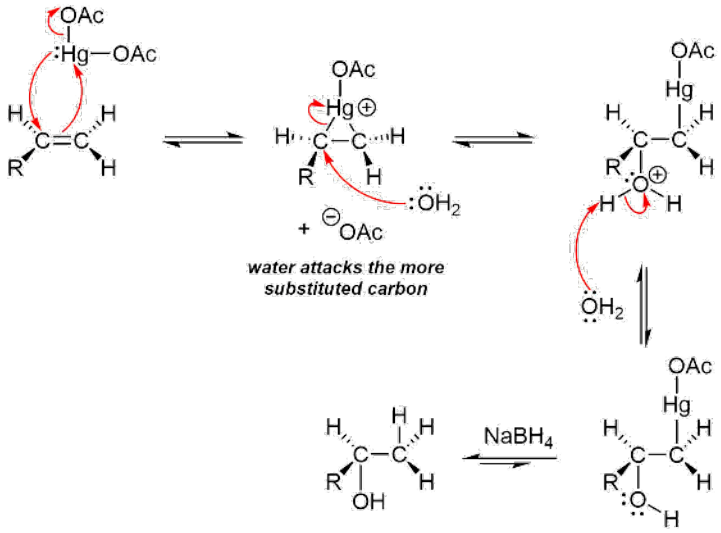
Oxymercuration is a special electrophilic addition. It is anti-stereospecific and regioselective. Regioselectivity is a process in which the substituents choses one direction it prefers to be attached to over all the other possible directions. The good thing about this reaction is that there are no carbocation rearrangement due to stabilization of the reactive intermediate. Similar stabilization is also seen in bromination addition to alkenes.

One of the major advantages to oxymercuration is that carbocation rearrangements cannot occur under these conditions ($Hg(OAc)_2$, H_2O). Carbocation rearrangement is a process in which the carbocation intermediate can undergo a methyl or alkyl shift to form a more stable ion.

Due to a possible carbocation rearrangement, the reaction below would not generate the product shown in high yields. In contrast, the oxymercuration reaction would proceed to form the desired product.



This reaction involves a mercury acting as a reagent attacking the alkene double bond to form a *Mercurinium Ion Bridge*. A water molecule will then attack the most substituted carbon to open the mercurium ion bridge, followed by proton transfer to solvent water molecule.



The organomercury intermediate is then reduced by sodium borohydride - the mechanism for this final step is beyond the scope of our discussion here. Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's regioselectivity with the OH group is attached to the most substituted carbon and the H is attach to the least substituted carbon. The reaction is useful, however, because strong acids are not required, and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

It is important to note that for the mechanism shown above, the enantiomer of the product shown is also formed. This is the result of formation of the mercurium ion below the alkene in the first step.

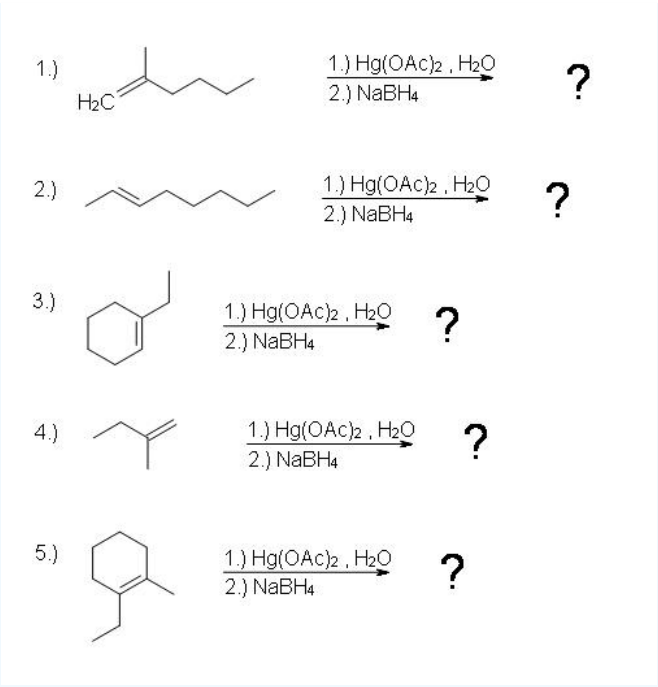
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1. Vollhardt, K. Peter C. Organic chemistry structure and function. New York: W.H. Freeman, 2007.
2. Smith, Michael B., and Jerry March. March's Advanced Organic Chemistry Reactions, Mechanisms, and Structure (March's Advanced Organic Chemistry). New York: Wiley-Interscience, 2007 2007.
3. Roderic P. Quirk , Robert E. Lea, Reductive demercuration of hex-5-enyl-1-mercuric bromide by metal hydrides. Rearrangement, isotope effects, and mechanism, *J. Am. Chem. Soc.*, 1976, 98 (19), pp 5973–5978.

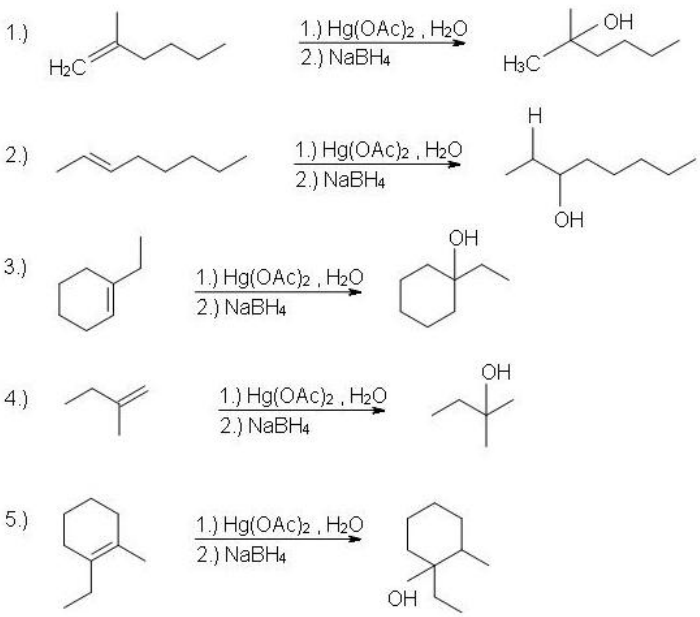
SOME PRACTICE PROBLEMS

? PRACTICE PROBLEMS

What are the end products of these reactants?



Answer

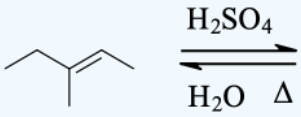


The end product to these practice problems are pretty much very similar. First, you locate where the double bond is on the reactant side. Then, you look at what substituents are attached to each side of the double bond and add the OH group to the more substituent side and the hydrogen on the less substituent side.

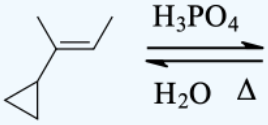
? MORE PROBLEMS

Predict the product of each reaction.

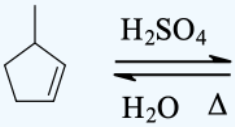
1)



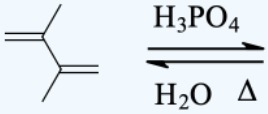
2) How does the cyclopropane group affect the reaction?



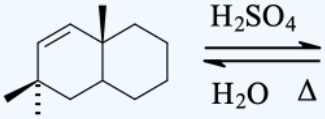
3) (Hint: What is different about this problem?)



4) (Hint: Consider stereochemistry.)

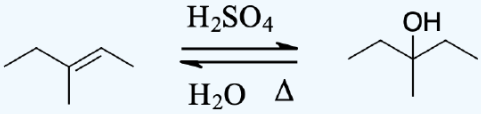


5) Indicate any shifts as well as the major product:

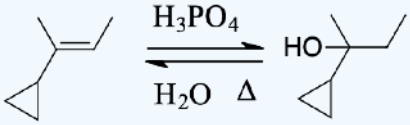


Answer

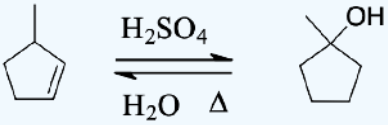
1) This is a simple electrophilic hydration.



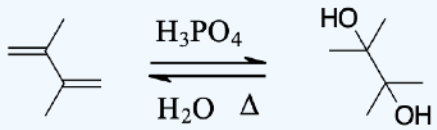
2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3° carbon will remain as such).



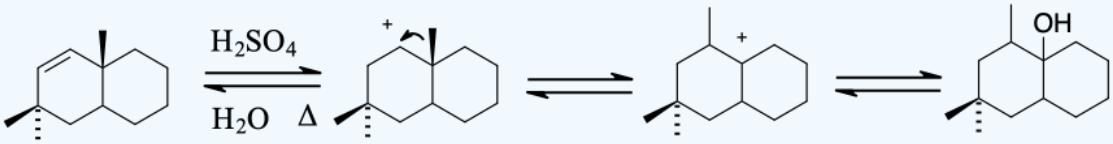
3) A hydride shift actually occurs from the 3 carbon of the 3-methylcyclopentene to where the carbocation had formed.



4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.



5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.



This page titled 8.4: Hydration of Alkenes - Addition of H₂O by Oxymercuration is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, Krista Cunningham, Aliza Bother Duke University, Lauren Reutenauer, & Lauren Reutenauer.

8.5: HYDRATION OF ALKENES - ADDITION OF H_2O BY HYDROBORATION

OBJECTIVES

After completing this section, you should be able to

- identify hydroboration (followed by oxidation) as a method for bringing about the (apparently) non-Markovnikov addition of water to an alkene.
- write an equation for the formation of a trialkylborane from an alkene and borane.
- write an equation for the oxidation of a trialkylborane to an alcohol.
- draw the structure of the alcohol produced by the hydroboration, and subsequent oxidation, of a given alkene.
- determine whether a given alcohol should be prepared by oxymercuration-demercuration or by hydroboration-oxidation, and identify the alkene and reagents required to carry out such a synthesis.
- write the detailed mechanism for the addition of borane to an alkene, and explain the stereochemistry and regiochemistry of the reaction.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- hydroboration

STUDY NOTES

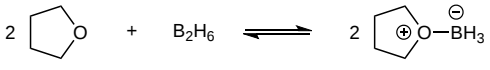
The two most important factors influencing organic reactions are polar (or electronic) effects and steric effects.

Hydroboration-oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. Furthermore, the borane acts as a Lewis acid by accepting two electrons in its empty p orbital from an alkene that is electron rich. This process allows boron to have an electron octet. A very interesting characteristic of this process is that it does not require any activation by a catalyst. The hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific (***syn addition),*** meaning that the hydroboration takes place on the same face of the double bond, this leads ***cis*** stereochemistry.

INTRODUCTION

Hydroboration-oxidation of alkenes has been a very valuable laboratory method for the stereoselectivity and regioselectivity of alkenes. An additional feature of this reaction is that it occurs without rearrangement.

First off it is very important to understand little bit about the structure and the properties of the **borane** molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula B_2H_6 (diborane). Additionally, the dimer B_2H_6 ignites spontaneously in air. Borane is commercially available in ether and tetrahydrofuran (THF), in these solutions the borane can exist as a Lewis acid-base complex, which allows boron to have an electron octet.

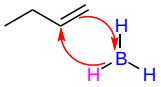


tetrahydrofuran (THF) (BH_3 • THF)

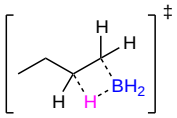
THE MECHANISM

STEP 1

- Part 1: Hydroboration of the alkene. In this first step the addition of the borane to the alkene is initiated and proceeds as a concerted reaction because bond breaking and bond formation occurs at the same time. This part consists of the vacant 2p orbital of the boron electrophile pairing with the electron pair of the pi bond of the nucleophile.

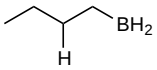


Transition state



*** Note that a carbocation is not formed. Therefore, no rearrangement takes place.**

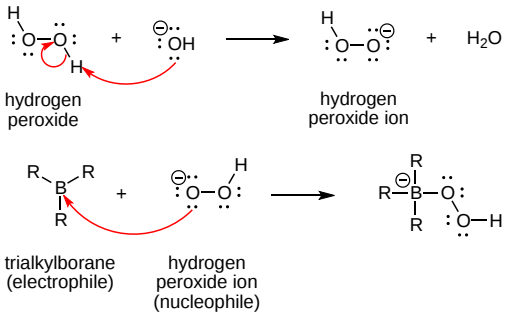
- Part 2: The Anti Markovnikov addition of Boron. The boron adds to the less substituted carbon of the alkene, which then places the hydrogen on the more substituted carbon. Both, the boron and the hydrogen add simultaneously on the same face of the double bond (syn addition).



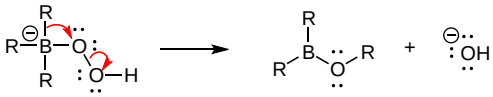
OXIDATION OF THE TRIALKYLBORANE BY HYDROGEN PEROXIDE

STEP 2

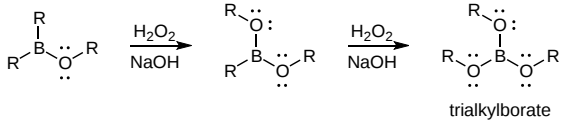
- Part 1: The first part of this mechanism deals with the donation of a pair of electrons from the hydrogen peroxide ion. the hydrogen peroxide is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from hydroboration.



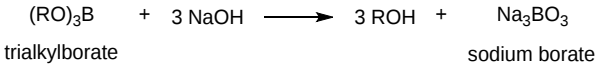
- Part 2: In this second part of the mechanism, a rearrangement of an R group with its pair of bonding electrons to an adjacent oxygen results in the removal of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



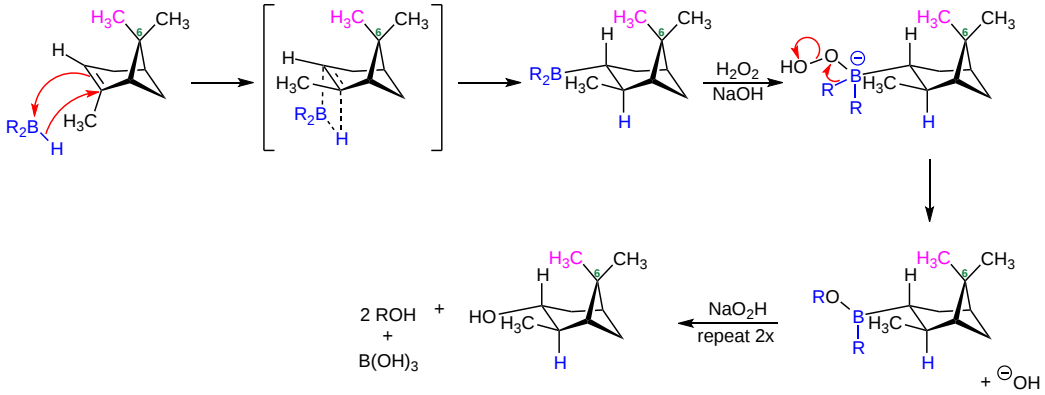
- Part 3: This is the final part of the oxidation process. In this part the trialkylborate reacts with aqueous NaOH to give the alcohol and sodium borate.



If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided here that will take you to other pages and media that are very helpful as well.

STEREOCHEMISTRY OF HYDROBORATION

The hydroboration reaction is among the few simple addition reactions that proceed cleanly in a *syn* fashion. As noted above, this is a single-step reaction. Since the bonding of the double bond carbons to boron and hydrogen is concerted, it follows that the geometry of this addition must be syn. Furthermore, rearrangements are unlikely inasmuch as a discrete carbocation intermediate is never formed. These features are illustrated for the hydroboration of α-pinene.

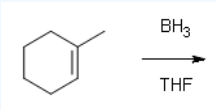


Since the hydroboration procedure is most commonly used to hydrate alkenes in an anti-Markovnikov fashion, we also need to know the stereoselectivity of the second oxidation reaction, which substitutes a hydroxyl group for the boron atom. Independent study has shown this reaction takes place with retention of configuration so the overall addition of water is also syn.

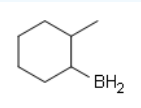
The hydroboration of α-pinene also provides a nice example of steric hindrance control in a chemical reaction. In the less complex alkenes used in earlier examples the plane of the double bond was often a plane of symmetry, and addition reagents could approach with equal ease from either side. In this case, one of the methyl groups bonded to C-6 (colored purple in the equation) covers one face of the double bond, blocking any approach from that side. All reagents that add to this double bond must therefore approach from the side opposite this methyl.

? EXERCISE 8.5.1

What are the products of this reactions?

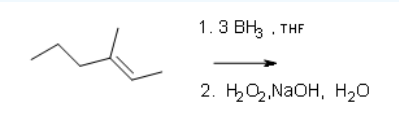


Answer

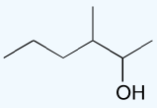


? EXERCISE 8.5.2

What are the products of this reactions?

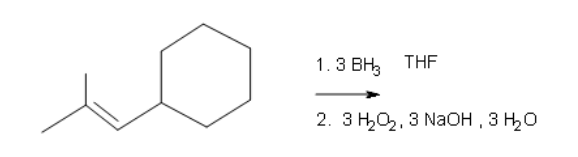


Answer

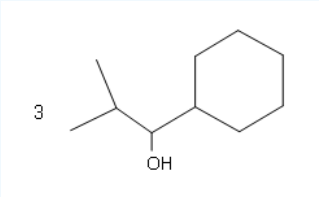


EXERCISE 8.5.3

What are the products of this reactions?

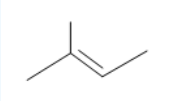


Answer

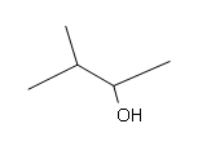


EXERCISE 8.5.4

Draw the structural formulas for the alcohols that result from hydroboration-oxidation of this alkene.



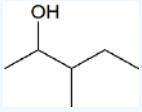
Answer



EXERCISE 8.5.5

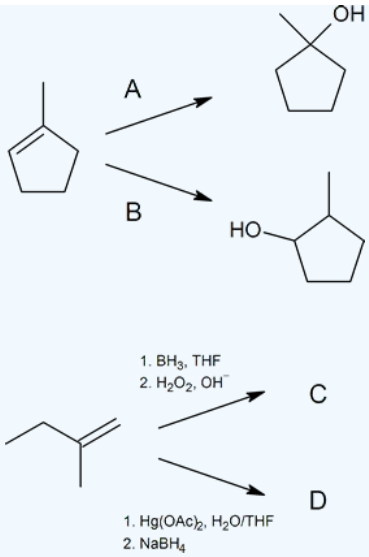
Draw the structural formulas for the alcohols that result from hydroboration-oxidation of (E)-3-methyl-2-pentene. If you need clarification or a reminder on the nomenclature of alkenes refer to the link below on naming the alkenes.

Answer



EXERCISE 8.5.6

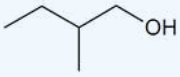
Write out the reagents or products (A–D) shown in the following reaction schemes.

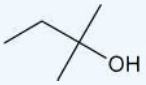


Answer

A 1. $Hg(OAc)_2$, H_2O/THF
2. $NaBH_4$

B 1. BH_3, THF
2. H_2O_2, OH^-

C 

D 

REFERENCES

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Foote, S. Christopher, and William H. Brown. Organic Chemistry. 5th. Belmont, CA: Brooks/Cole Cengage Learning, 2005.
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4. Bergbreiter E. David , and David P. Rainville. Stereochemistry of hydroboration-oxidation of terminal alkenes. *J. Org. Chem.*, 1976, 41 (18), pp 3031–3033
5. Ilich, Predrag-Peter; Rickertsen, Lucas S., and Becker Erienne. Polar Addition to C=C Group: Why Is Anti-Markovnikov Hydroboration-Oxidation of Alkenes Not "Anti-"? Journal of Chemical Education., 2006, v83, n11, pg 1681-1685

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8.6: REDUCTION OF ALKENES - HYDROGENATION

OBJECTIVES

After completing this section, you should be able to

- write an equation for the catalytic hydrogenation of an alkene.
- identify the product obtained from the hydrogenation of a given alkene.
- identify the alkene, the reagents, or both, required to prepare a given alkane by catalytic hydrogenation.
- describe the mechanism of the catalytic hydrogenation of alkenes.
- explain the difference between a heterogeneous reaction and a homogeneous reaction.
- recognize that other types of compounds containing multiple bonds, such as ketones, esters, nitriles and aromatic compounds, do not react with hydrogen under the conditions used to hydrogenate alkenes.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Adams' catalyst
- hydrogenation

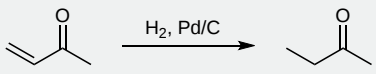
STUDY NOTES

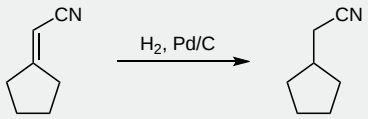
Chemical reactions that are heterogeneous have reactants that are in at least two different phases (e.g. gas with a solid), whereas homogeneous reactions occur in a single phase (e.g. gas with another gas).

Some confusion may arise from the description of the catalyst used in the reaction between alkenes and hydrogen. Three metals—nickel, platinum and palladium—are commonly used, but a chemist cannot simply place a piece of one of these metals in a mixture of the alkene and hydrogen and get a reaction. Each metal catalyst must be prepared in a special way:

- nickel is usually used in a finely divided form called "Raney nickel." It is prepared by reacting a Ni-Al alloy with NaOH.
- palladium is obtained commercially "supported" on an inert substance, such as charcoal, (Pd/C). The alkene is usually dissolved in ethanol when Pd/C is used as the catalyst.
- platinum is used as PtO_2, Adams' catalyst, although it is actually platinum metal that is the catalyst. The hydrogen used to add to the carbon-carbon double bond also reduces the platinum(IV) oxide to finely divided platinum metal. Ethanol or acetic acid is used as the solvent for the alkene.

Other types of compounds containing multiple bonds, such as ketones, esters, and nitriles, do not react with hydrogen under the conditions used to hydrogenate alkenes. The examples below show reduction of an alkene, but the ketone and nitrile groups present remain intact and are not reduced.





Aromatic rings are also not reduced under the conditions used to reduce alkenes, although these rings appear to contain three carbon-carbon double bonds. As you will see later, aromatic rings do not really contain any double bonds, and many chemists prefer to represent the benzene ring as a hexagon with a circle inside it

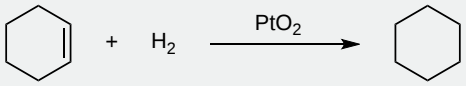


rather than as a hexagon with three alternating double bonds.

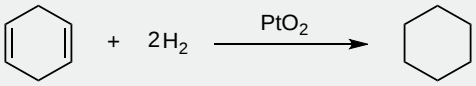


The representation of the benzene ring will be discussed further in Section 15.2.

The reaction between carbon-carbon double bonds and hydrogen provides a method of determining the number of double bonds present in a compound. For example, one mole of cyclohexene reacts with one mole of hydrogen to produce one mole of cyclohexane:



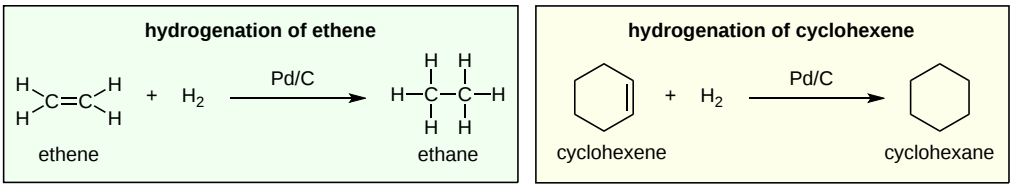
but one mole of 1,4-cyclohexadiene reacts with two moles of hydrogen to form one mole of cyclohexane:



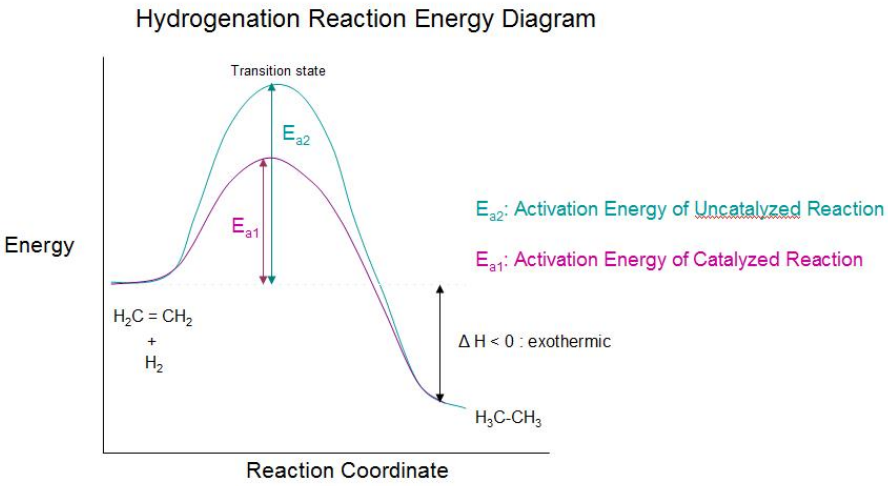
A chemist would say that cyclohexene reacts with one equivalent of hydrogen, and 1,4-cyclohexadiene reacts with two equivalents of hydrogen. If you take a known amount of an unknown, unsaturated hydrocarbon and determine how much hydrogen it will absorb, you can readily determine the number of double bonds present in the hydrocarbon (see question 2, below).

Addition of hydrogen to a carbon-carbon double bond is called hydrogenation. The overall effect of such an addition is the reductive removal of the double bond functional group. Regioselectivity is not an issue, since the same group (a hydrogen atom) is bonded to each of the double bond carbons. The simplest source of two hydrogen atoms is molecular hydrogen (H_2), but mixing alkenes with hydrogen does not result in any discernible reaction. Although the overall hydrogenation reaction is exothermic, a high activation energy prevents it from taking place under normal conditions. This restriction may be circumvented by the use of a catalyst, as shown in the reaction coordinate diagram below.

An example of an alkene addition reaction is a process called hydrogenation. In a hydrogenation reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus it is exothermic (heat is released). The heat released is called the heat of hydrogenation, which is an indicator of a molecule's stability.



Catalysts are substances that changes the rate (velocity) of a chemical reaction without being consumed or appearing as part of the product. Catalysts act by lowering the activation energy of reactions, but they do not change the relative potential energy of the reactants and products. Finely divided metals, such as platinum, palladium and nickel, are among the most widely used hydrogenation catalysts. Catalytic hydrogenation takes place in at least two stages, as depicted in the diagram. First, the alkene must be adsorbed on the surface of the catalyst along with some of the hydrogen. Next, two hydrogens shift from the metal surface to the carbons of the double bond, and the resulting saturated hydrocarbon, which is more weakly adsorbed, leaves the catalyst surface. The exact nature and timing of the last events is not well understood.

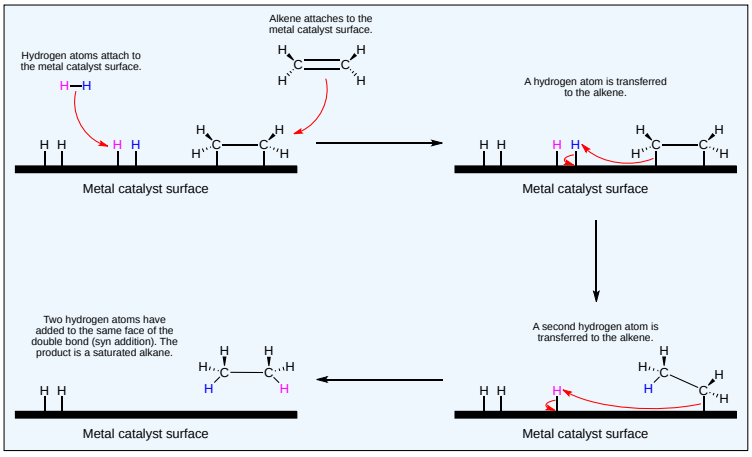


A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

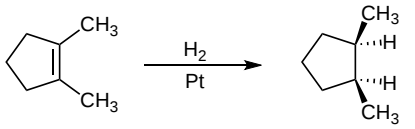
As shown in the energy diagram, the hydrogenation of alkenes is exothermic, and heat is released corresponding to the ΔH in the diagram. This heat of reaction can be used to evaluate the thermodynamic stability of alkenes having different numbers of alkyl substituents on the double bond. For example, the following table lists the heats of hydrogenation for three C_5H_{10} alkenes which give the same alkane product (2-methylbutane). Since a larger heat of reaction indicates a higher energy reactant, these heats are inversely proportional to the stabilities of the alkene isomers. To a rough approximation, we see that each alkyl substituent on a double bond stabilizes this functional group by a bit more than 1 kcal/mole.

Alkene Isomer	$(CH_3)_2CHCH=CH_2$ 3-methyl-1-butene	$CH_2=C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C=CHCH_3$ 2-methyl-2-butene
Heat of Reaction (ΔH°)	–30.3 kcal/mole	–28.5 kcal/mole	–26.9 kcal/mole

Catalytic Hydrogenation Mechanism



From the mechanism shown here we would expect the addition of hydrogen to occur with syn-stereoselectivity. This is often true, but the hydrogenation catalysts may also cause isomerization of the double bond prior to hydrogen addition, in which case stereoselectivity may be uncertain.



(cis product only)

EXERCISE 8.6.1

In the reaction

$$H_2C{=}CH_2 \quad + \quad H_2 \xrightarrow{PtO_2} H_3C{-}CH_3$$

a. 0.500 mol of ethene reacts with _____ mol of hydrogen. Thus a chemist might say that ethene reacts with one _____ of hydrogen.
b. ethene is being _____; while _____ is being oxidized.
c. the oxidation number of carbon in ethene is _____; in ethane it is _____.

Answer

a. 0.500 mol of ethene reacts with 0.500 mol of hydrogen. Thus a chemist might say that ethene reacts with one equivalent of hydrogen.
b. ethene is being reduced; while hydrogen is being oxidized.
c. the oxidation number of carbon in ethene is −2; in ethane it is −3.

EXERCISE 8.6.2

When 1.000 g of a certain triglyceride (fat) is treated with hydrogen gas in the presence of Adams' catalyst, it is found that the volume of hydrogen gas consumed at 99.8 kPa and 25.0°C is 162 mL. A separate experiment indicates that the molar mass of the fat is 914 g mol^{-1}. How many carbon-carbon double bonds does the compound contain?

Answer

Amount of hydrogen consumed

$= n \text{ mol}$

$= \frac{PV}{RT}$ $^{-1} \cdot K^{-1} \times 298\ K = 6.53 \times 10^{-3}$ mol H_2

$= \frac{99.8\ \text{kPa} \times 0.162\ \text{L}}{8.31\ \text{kPa} \cdot \text{msup}}$

Amount of fat used

Math input error

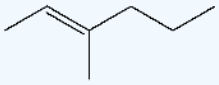
Ratio of moles of hydrogen consumed to moles of fat

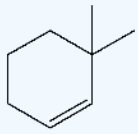
Math input error

Thus, the fat contains six carbon-carbon double bonds per molecule.

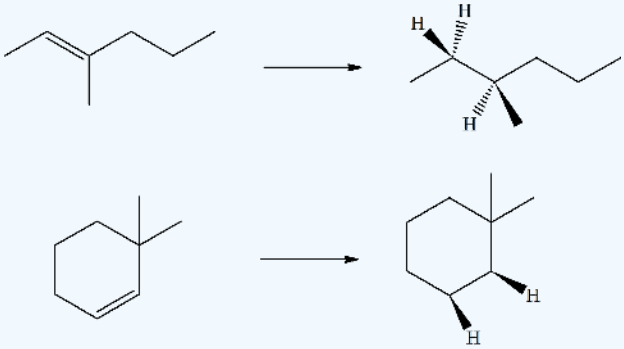
EXERCISE 8.6.3

Predict the products if the following alkenes were reacted with catalytic hydrogen.





Answer



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8.7: OXIDATION OF ALKENES - EPOXIDATION AND HYDROXYLATION

OBJECTIVES

After completing this section, you should be able to

- write the equation for the epoxidation of an alkene using meta-chloroperoxybenzoic acid.
- identify the alkene, reagents, or both, that must be used to prepare a given epoxide.
- write the equation for the hydroxylation of an alkene using osmium tetroxide, and draw the structure of the cyclic intermediate.
- draw the structure of the diol formed from the reaction of a given alkene with osmium tetroxide.
- identify the alkene, the reagents, or both, that must be used to prepare a given 1,2-diol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- diol
- glycol
- hydroxylation

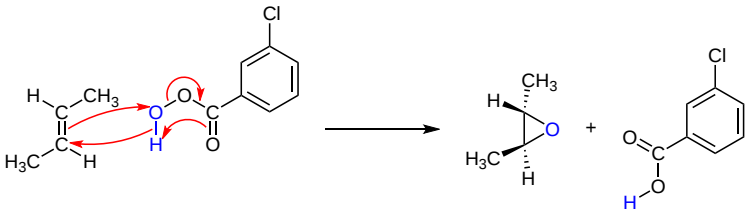
The previous section discussed the reduction of a double bond, so adding hydrogen to the the double bond. This section will discuss oxidation. In organic chemistry, this is a reaction that where the carbon atom loses electron density, which happens when new bond to a more electronegative atom occurs or when a double bond is broken between a carbon and a less electronegative atom. A simplified to say this is in organic chemistry a reduction is more bonds to hydrogen and oxidation is more bonds to oxygen often.

OXACYCLOPROPANE SYNTHESIS BY PEROXYCARBOXYLIC ACID

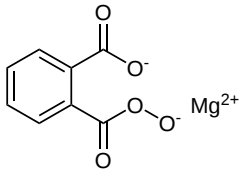
One way to oxidized a double bond is to produce an oxacyclopropane ring. Oxacyclopropane rings, also called epoxide rings, are useful reagents that may be opened by further reaction to form anti vicinal diols. One way to synthesize oxacyclopropane rings is through the reaction of an alkene with peroxycarboxylic acid. Oxacyclopropane synthesis by peroxycarboxylic acid requires an alkene and a peroxycarboxylic acid as well as an appropriate solvent. The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the COOH group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the COOH group becomes COH.

MECHANISM

Peroxycarboxylic acids are generally unstable. An exception is meta-chloroperoxybenzoic acid, shown in the mechanism above. Often abbreviated MCPBA, it is a stable crystalline solid. Consequently, MCPBA is popular for laboratory use. However, MCPBA can be explosive under some conditions.

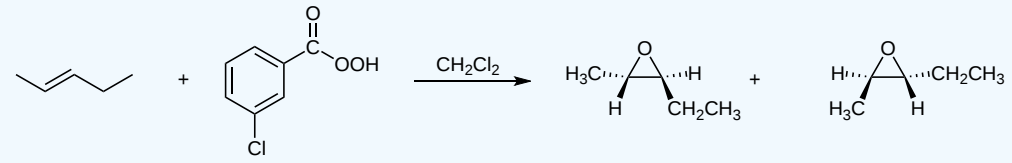


Peroxycarboxylic acids are sometimes replaced in industrial applications by monoperphthalic acid, or the monoperoxyphthalate ion bound to magnesium, which gives magnesium monoperoxyphthalate (MMPP). In either case, a nonaqueous solvent such as chloroform, ether, acetone, or dioxane is used. This is because in an aqueous medium with any acid or base catalyst present, the epoxide ring is hydrolyzed to form a vicinal diol, a molecule with two OH groups on neighboring carbons. (For more explanation of how this reaction leads to vicinal diols, see below.) However, in a nonaqueous solvent, the hydrolysis is prevented and the epoxide ring can be isolated as the product. Reaction yields from this reaction are usually about 75%. The reaction rate is affected by the nature of the alkene, with more nucleophilic double bonds resulting in faster reactions.



magnesium monoperoxyphthalate, MMPP

EXAMPLE 8.7.1



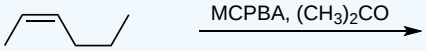
trans-2-pentene MCPBA mixture of enantiomers of *trans*-3-ethyl-2-methyloxacyclopropane

Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen is inserted on top. (See the product of the above reaction.) One way the epoxide ring can be opened is by an acid catalyzed oxidation-hydrolysis. Oxidation-hydrolysis gives a vicinal diol, a molecule with OH groups on neighboring carbons. For this reaction, the dihydroxylation is *anti* since, due to steric hindrance, the ring is attacked from the side opposite the existing oxygen atom. Thus, if the starting alkene is trans, the resulting vicinal diol will have one (*S*) and one (*R*) stereocenter. But, if the starting alkene is cis, the resulting vicinal diol will have a racemic mixture of (*S*,*S*) and (*R*,*R*) enantiomers.

EPOXIDATION EXERCISES

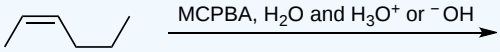
1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

a) in acetone solvent.



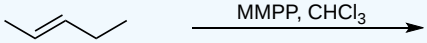
cis-2-hexene

b) in an aqueous medium with acid or base catalyst present.



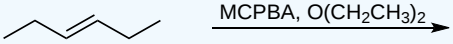
cis-2-hexene

2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



trans-2-pentene

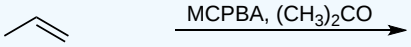
3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.



trans-3-hexene

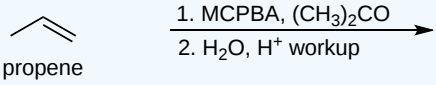
4. Predict the reaction of propene with MCPBA.

a) in acetone solvent

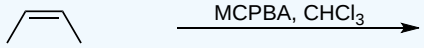


propene

b) after aqueous work-up.

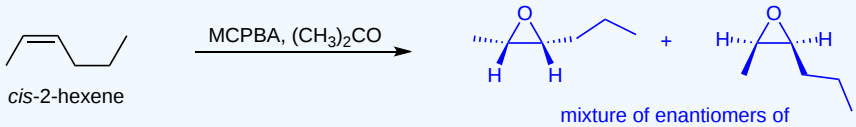


5. Predict the reaction of cis-2-butene in chloroform solvent.

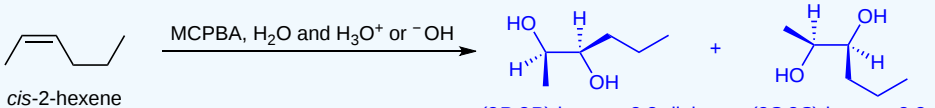


Answers

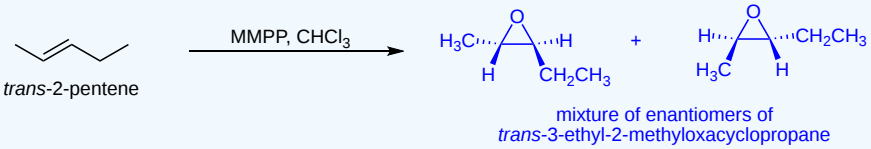
1. a) *Cis*-2-methyl-3-propyloxacyclopropane



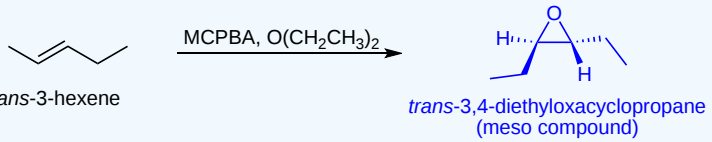
b) Racemic (2*R*,3*R*)-2,3-hexanediol and (2*S*,3*S*)-2,3-hexanediol



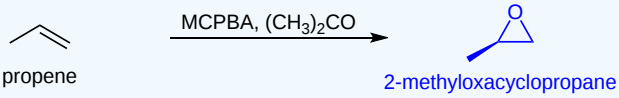
2. *Trans*-3-ethyl-2-methyloxacyclopropane.



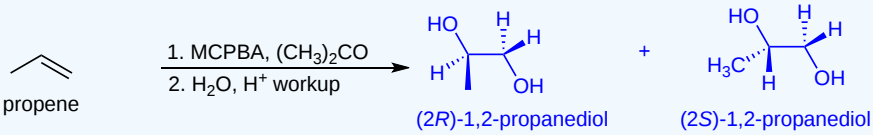
3. *Trans*-3,4-diethyloxacyclopropane.



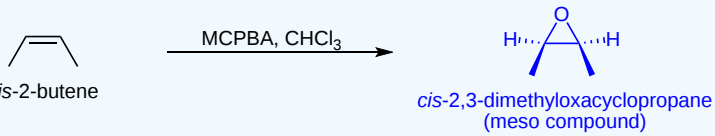
4. a) 2-methyl-oxacyclopropane



b) Racemic (2*S*)-1,2-propandiol and (2*R*)-1,2-propanediol

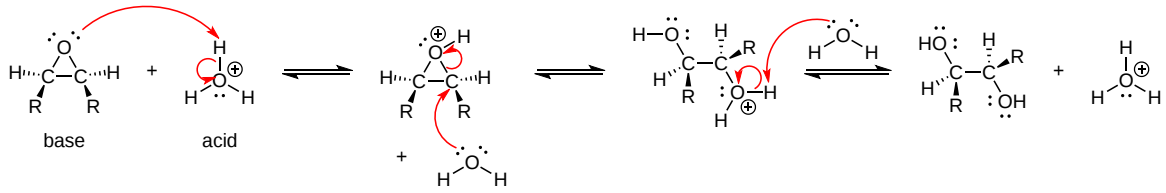


5. *Cis*-2,3-dimethyloxacyclopropane



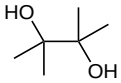
ANTI DIHYDROXYLATION

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction described above. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by nucleophiles such as water in the same way that the cyclic bromonium ion described above undergoes reaction. The result is **anti-hydroxylation** of the double bond, in contrast to the syn-stereoselectivity of the earlier method. In the following equation this procedure is illustrated for a cis-disubstituted epoxide, which, of course, could be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



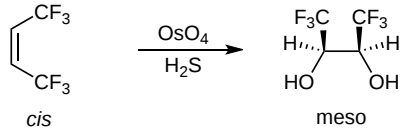
SYN DIHYDROXYLATION

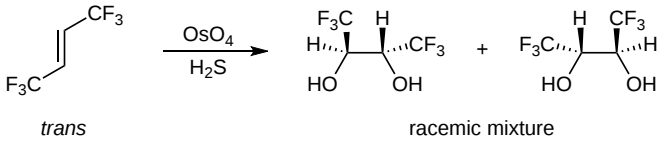
Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.



INTRODUCTION

The reaction with OsO_4 is a concerted process that has a cyclic intermediate and no rearrangements. Vicinal syn dihydroxylation complements the epoxide-hydrolysis sequence which constitutes an *anti* dihydroxylation of an alkene. When an alkene reacts with osmium tetroxide, stereocenters can form in the glycol product. Cis alkenes give meso products and trans alkenes give racemic mixtures.





OsO_4 is formed slowly when osmium powder reacts with gasoues O_2 at ambient temperature. Reaction of bulk solid requires heating to 400 °C:

$$Os(s) + 2\,O_2(g) \rightarrow OS_4$$

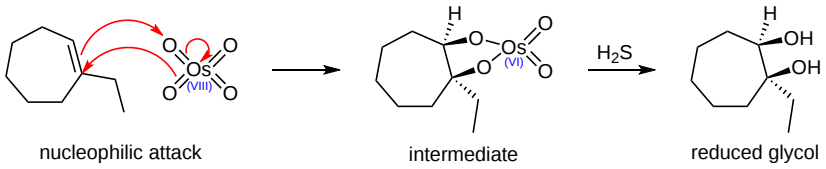
Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of OsO_4 and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of OsO_4 was potassium permanganate, $KMnO_4$. Although syn diols will result from the reaction of $KMnO_4$ and an alkene, potassium permanganate is less useful since it gives poor yields of the product because of **overoxidation**.

MECHANISM

- Electrophilic attack on the alkene
  - Pi bond of the alkene acts as the nucleophile and reacts with osmium (VIII) tetroxide (OsO_4)
  - 2 electrons from the double bond flows toward the osmium metal
    - In the process, 3 electron pairs move simultaneously
  - Cyclic ester with Os (VI) is produced
- Reduction
  - H_2S reduces the cyclic ester

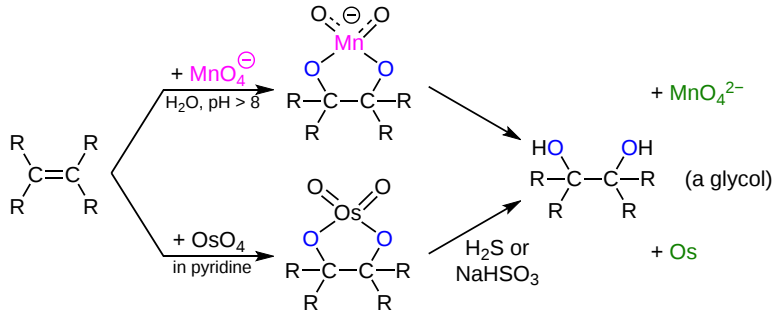
- $NaHSO_4$ with H_2O may be used
  - Forms the syn-1,2-diol (glycol)

Example: Dihydroxylation of 1-ethyl-1-cycloheptene



HYDROXYLATION OF ALKENES

Dihydroxylated products (glycols) are obtained by reaction with aqueous potassium permanganate (pH > 8) or osmium tetroxide in pyridine solution. Both reactions appear to proceed by the same mechanism (shown below); the metallocyclic intermediate may be isolated in the osmium reaction. In basic solution the purple permanganate anion is reduced to the green manganate ion, providing a nice color test for the double bond functional group. From the mechanism shown here we would expect syn-stereoselectivity in the bonding to oxygen, and regioselectivity is not an issue.



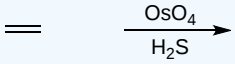
When viewed in context with the previously discussed addition reactions, the hydroxylation reaction might seem implausible. Permanganate and osmium tetroxide have similar configurations, in which the metal atom occupies the center of a tetrahedral grouping of negatively charged oxygen atoms. How, then, would such a species interact with the nucleophilic pi-electrons of a double bond? A possible explanation is that an empty d-orbital of the electrophilic metal atom extends well beyond the surrounding oxygen atoms and initiates electron transfer from the double bond to the metal, in much the same fashion noted above for platinum. Back-bonding of the nucleophilic oxygens to the antibonding π*-orbital completes this interaction. The result is formation of a metallocyclic intermediate, as shown above.

CHEMICAL HIGHLIGHT

Antitumor drugs have been formed by using dihydroxylation. This method has been applied to the enantioselective synthesis of ovalicin, which is a class of fungal-derived products called antiangiogenesis agents. These antitumor products can cut off the blood supply to solid tumors. A derivative of ovalicin, TNP-470, is chemically stable, nontoxic, and noninflammatory. TNP-470 has been used in research to determine its effectiveness in treating cancer of the breast, brain, cervix, liver, and prostate.

? DIHYDROXYLATION EXERCISES

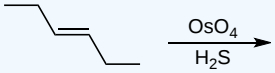
1. Give the major product.



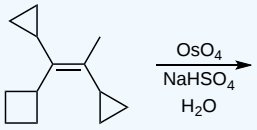
2. What is the product in the dihydroxylation of (Z)-3-hexene?



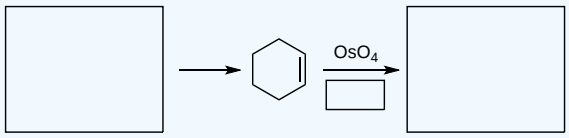
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.

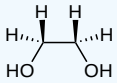


5. Fill in the missing reactants, reagents, and product.

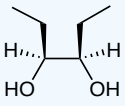


Answers

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.



2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.



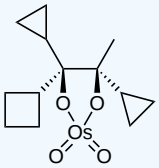
(3*S*,4*R*)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

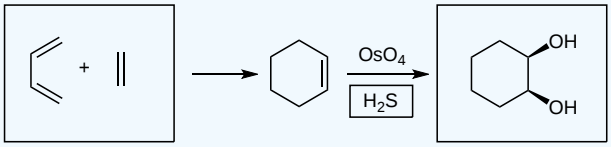


(3*R*,4*R*) (3*S*,4*S*)

4. A cyclic osmic ester is formed.



5. The Diels-Alder cycloaddition reaction is needed in the first box to form the cyclohexene. The second box needs a reagent to reduce the intermediate cyclic ester (not shown). The third box has the product: 1,2-cyclohexanediol.



REFERENCES

1. Dehestani, Ahmad et al. (2005). Ligand-assisted reduction of osmium tetroxide with molecular hydrogen via a [3+2] mechanism. *Journal of the American Chemical Society, 2005, 127 (10)*, 3423-3432.
2. Sorrell, Thomas, N. Organic Chemistry. New York: University Science Books, 2006.
3. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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8.8: OXIDATION OF ALKENES - CLEAVAGE TO CARBONYL COMPOUNDS

OBJECTIVE

After completing this section, you should be able to

- write an equation to describe the cleavage of an alkene by ozone, followed by reduction of the ozonide so formed with either sodium borohydride or zinc and acetic acid.
- predict the products formed from the ozonolysis-reduction of a given alkene.
- write an equation to describe the cleavage of an alkene by potassium permanganate.
- predict the products from the oxidative cleavage of a given alkene by potassium permanganate.
- use the results of ozonolysis-reduction, or cleavage with permanganate, to deduce the structure of an unknown alkene.
- identify the reagents that should be used in the oxidative cleavage of an alkene to obtain a given product or products.
- write the equation for the cleavage of a 1,2-diol by periodic acid, and draw the structure of the probable intermediate.
- predict the product or products that will be formed from the treatment of a given 1,2-diol with periodic acid.
- use the results of hydroxylation/1,2-diol cleavage to deduce the structure of an unknown alkene.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

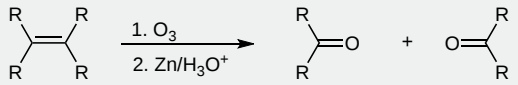
- molozonide
- ozonide
- ozonolysis

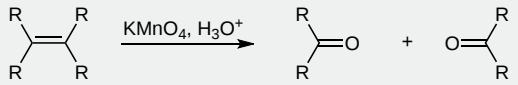
STUDY NOTES

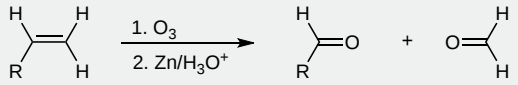
Ozonolysis, or ozonolysis-reduction, refers to the treatment of an alkene with ozone followed by a suitable reducing agent to break down complex double-bond-containing compounds into smaller, more easily identified products. From the identity of the products formed, it may be possible to deduce the structure of the original double-bond-containing substance. Ozonolysis will feature prominently in many of the road-map problems that you will encounter in this course.

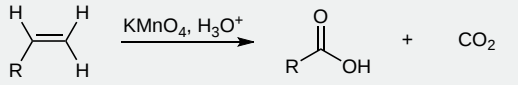
A *molozonide* is an unstable, cyclic intermediate that is initially formed when an alkene reacts with ozone.

Alkenes can also be cleaved by other oxidizing agents such as potassium permanganate. However, $KMnO_4$ will carry the oxidation further than ozonolysis, so products can be slightly different. Note within the summary of the following reactions that ozonolysis produces aldehydes and ketones, while $KMnO_4$ can oxidize all the way to to carbon dioxide and carboxylic acid.

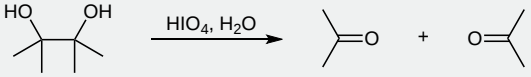




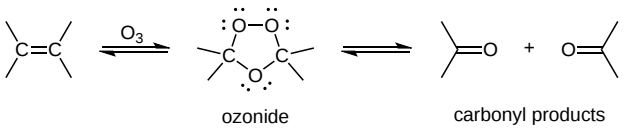




Diol cleavage is another example of a redox reaction; periodic acid, HIO_4, is reduced to iodic acid, HIO_3.



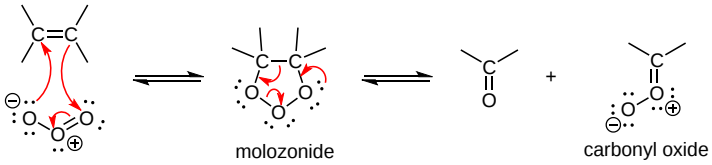
Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen. This reaction is often used to identify the structure of unknown alkenes. by breaking them down into smaller, more easily identifiable pieces. Ozonolysis also occurs naturally and would break down repeated units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.



The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the Carbon-Carbon double bond and is replaced by a Carbon-Oxygen double bond instead.

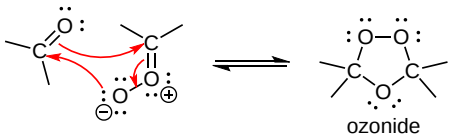
REACTION MECHANISM

Step 1:



The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the Carbon-Carbon double bond, which then form the molozonide intermediate. Due to the unstable molozonide molecule, it continues further with the reaction and breaks apart to form a carbonyl and a carbonyl oxide molecule.

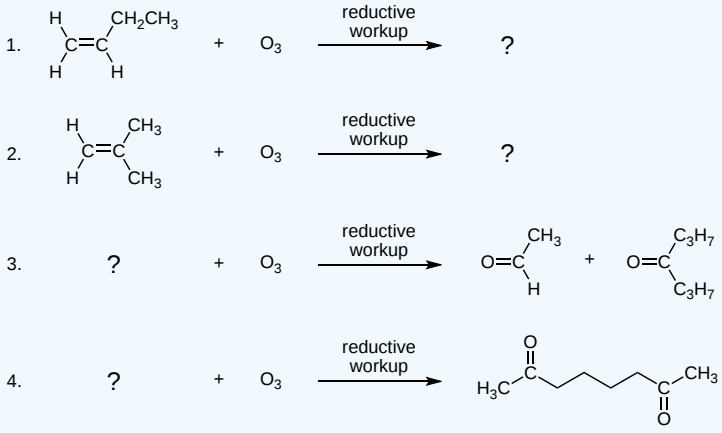
Step 2:



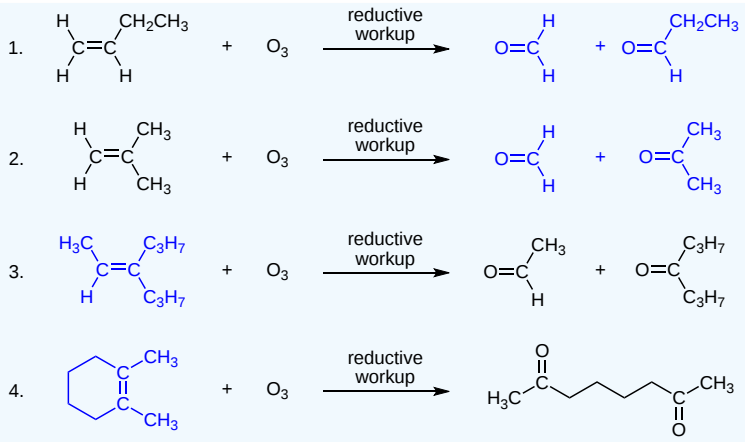
The carbonyl and the carbonyl oxide rearranges itself and reforms to create the stable ozonide intermediate. Since some ozonides are explosive, it is immediately reacted with a reductive workup to then convert the ozonide molecule into the desired carbonyl products. A typical reductive workup is zinc metal in acetic acid. A variety of carbonyl products could result depending on the starting alkene. For example, a tetrasubstituted alkene would yield two ketone products, while a trisubstituted alkene would yield one ketone product and one aldehyde product.

While there are other options for oxidative cleavage of the double bond, this is the most commonly used reaction.

? EXERCISE 8.8.1



Answer



EXERCISE 8.8.2

Draw the structure of the product or products obtained in each of the following reactions:

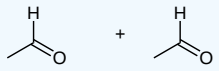
a. *cis*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

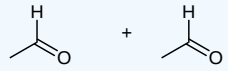
b. *trans*-2-butene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

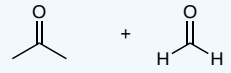
c. 2-methylpropene $\xrightarrow[2.\ Zn/H_3O^+]{1.\ O_3}$

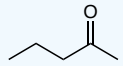
d. 2-methyl-1-pentene $\xrightarrow[KMnO_4]{\text{hot, acidic}}$

Answer

a. 

b. 

c. 

d.  + CO_2

EXERCISE 8.8.3

Exercises 1(*a*) and 1(*b*), above, indicate that it is not possible to distinguish between cis and trans isomers of alkenes using oxidative cleavage.

Answer

Both isomers give the same product or products.

REFERENCES

1. Vollhardt, K., Schore, N. Organic Chemistry: Structure and Function. 5th ed. New York, NY: W. H. Freeman and Company, 2007.
2. Shore, N. Study Guide and Solutions Manual for Organic Chemistry. 5th ed. New York, NY: W.H. Freeman and Company, 2007.

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8.9: ADDITION OF CARBENES TO ALKENES - CYCLOPROPANE SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

- describe, and write the detailed mechanism for, the formation of a carbene, such as dichlorocarbene.
- describe the structure of a carbene in terms of the hybridization of the central carbon atom.
- write an equation for the formation of a substituted cyclopropane from an alkene and a carbene.
- identify the reagents, the alkene, or both, needed to prepare a given substituted cyclopropane by addition of a carbene to a double bond.
- identify the substituted cyclopropane formed from the reaction of a given alkene with the reagents necessary to form a carbene.

KEY TERMS

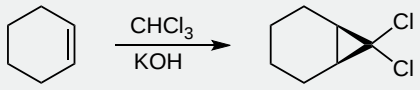
Make certain that you can define, and use in context, the key terms below.

- carbene (R_2C:)
- carbenoid
- Simmons-Smith reaction
- stereospecific

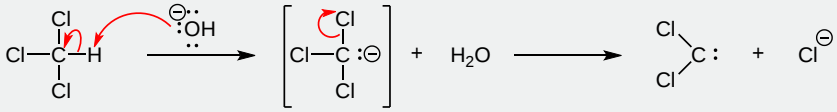
STUDY NOTES

A *carbenoid* is best considered to be a reagent which, while not actually a carbene, behaves as if it were an intermediate of this type.

Dichlorocarbenes can also form cyclopropane structures and are created in situ from reagents such as chloroform and KOH.



The detailed mechanism of the formation of dichlorocarbene is given below. Note that the deprotonation of chloroform generates the trichloromethanide anion, which spontaneously expels the chloride anion.



The highly strained nature of cyclopropane compounds makes them very reactive and interesting synthetic targets. Additionally cyclopropanes are present in numerous biological compounds. One common method of cyclopropane synthesis is the reaction of carbenes with the double bond in alkenes or cycloalkenes. Methylene, H_2C, is simplest carbene, and in general carbenes have the formula R_2C. Other species that will also react with alkenes to form cyclopropanes but do not follow the formula of carbenes are referred to as carbenoids.

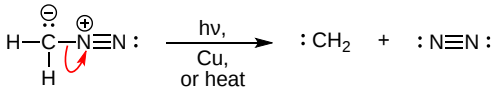
INTRODUCTION

Carbenes were once only thought of as short lived intermediates. The reactions of this section only deal with these short lived carbenes which are mostly prepared in situ, in conjunction with the main reaction. However, there do exist so called persistent carbenes. These persistent carbenes are stabilized by a variety of methods often including aromatic rings or transition metals. In general a carbene is neutral and has 6 valence electrons, 2 of which are non bonding. These electrons can either occupy the same sp^2 hybridized orbital to form a singlet carbene (with paired electrons), or two different sp^2 orbitals to from a triplet carbene (with unpaired electrons). The chemistry of triplet and singlet carbenes is quite different but can be oversimplified to the statement: singlet carbenes usually retain stereochemistry while triplet carbenes do not. The carbenes discussed in this section are singlet and thus retain stereochemistry.

The reactivity of a singlet carbene is concerted and similar to that of electrophilic or nucleophilic addition wheras, triplet carbenes react like biradicals, explaining why sterochemistry is not retained. The highly reactive nature of carbenes leads to very fast reactions in which the rate determining step is generally carbene formation.

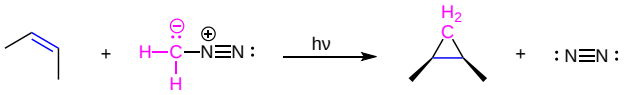
PREPARATION OF METHYLENE

The preparation of methylene starts with the yellow gas diazomethane, CH_2N_2. Diazomethane can be exposed to light, heat or copper to facilitate the loss of nitrogen gas and the formation of the simplest carbene methylene. The process is driven by the formation of the nitrogen gas which is a very stable molecule.

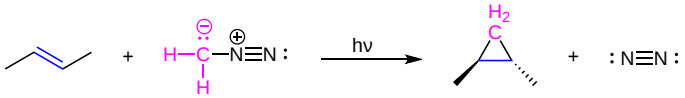


CARBENE REACTION WITH ALKENES

A carbene such as methlyene will react with an alkene which will break the double bond and result with a cyclopropane. The reaction will usually leave stereochemistry of the double bond unchanged. As stated before, carbenes are generally formed along with the main reaction; hence the starting material is diazomethane not methylene.



In the above case *cis*-2-butene is converted to *cis*-1,2-dimethylcyclopropane. Likewise, below the *trans* configuration is maintained. This shows that the reactions are stereospecific, only a single stereoisomer is obtained as the product.



ADDITIONAL TYPES OF CARBENES AND CARBENOIDS

In addition to the general carbene with formula R_2C there exist a number of other compounds that behave in much the same way as carbenes in the synthesis of cyclopropane. **Halogenated carbenes** are formed from halomethanes. An example is dicholorcarbene, Cl_2C. The mechanism for the formation of dichlorocarbene is above in the study notes. These halogenated carbenes will form cyclopropanes in the same manner as methylene but with the interesting presence of two halogen atoms in place of the hydrogen atoms.

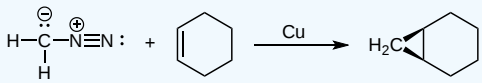
Carbenoids are substances that form cyclopropanes like carbenes but are not technically carbenes. One common example is the stereospecific Simmon-Smith reaction which utilizes the carbenoid - ICH_2ZnI. The (iodomethyl) zinc iodide is formed in situ via the mixing of Zn-Cu with CH_2I_2. If this ICH_2ZnI is in the presence of an alkene, a CH_2 group is transferred to the double bond to create cyclopropane. Since this reacts as a carbene, the same methods can be applied to determine the product.

? EXERCISE 8.9.1

Knowing that cycloalkenes react much the same as regular alkenes what would be the expected structure of the product of cyclohexene and diazomethane facilitated by copper metal?

Answer

The product will be a bicyclic ring, Bicyclo[4.1.0]heptane.



? EXERCISE 8.9.2

What would be the result of a Simmons-Smith reaction that used *trans*-2-pentene as a reagent?

Answer

The stereochemistry will be retained making a cyclopropane with trans methyl and ethyl groups. *Trans*-1-ethyl-2-methylcyclopropane

EXERCISE 8.9.3

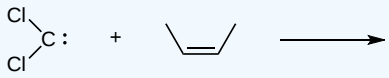
What starting material could be used to form *cis*-1,2-diethylcyclopropane?

Answer

The *cis* configuration will be maintained from reagent to product so we would want to start with *cis*-3-hexene. A Simmons Smith reagent, or methylene could be used as the carbene or carbenoid.

EXERCISE 8.9.4

What would the following reaction yield?



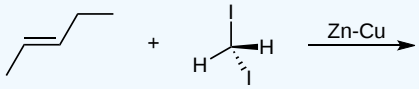
Answer

The halogenated carbene will react the same as methylene yielding, *cis*-1,1-dichloro-2,3-dimethylcyclopropane.



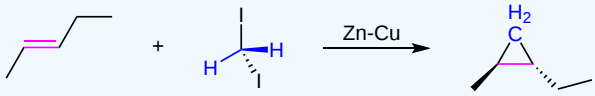
EXERCISE 8.9.5

Draw the product of this reaction. What type of reaction is this?



Answer

This is a Simmons-Smith reaction which uses the carbenoid formed by the CH_2I_2 and Zu-Cu. The reaction results in the same product as if methylene was used and retains stereospecificity. Iodine metal and the Zn-Cu are not part of the product. The product is *trans*-1,2-ethyl-methylcyclopropane.



REFERENCES

1. Vollhardt, K. Peter C. and Schore, Neil E. Organic Chemistry: Structure and Function. New York: Bleyer, Brennan, 2007.
2. Abdel-Wahab, Aboel-Magd A. Ahmed, Saleh A. and Dürr, Heinz. "Carbene Formation by Extrusion of Nitrogen" in CRC Handbook of Organic Photochemistry and Photobiology. CRC Press, 2004.

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8.10: RADICAL ADDITIONS TO ALKENES - CHAIN-GROWTH POLYMERS

OBJECTIVES

After completing this section, you should be able to

- write the detailed mechanism for the radical polymerization of an alkene.
- give examples of some common alkene monomers used in the manufacture of chain-growth polymers.
- identify the alkene monomer used to prepare a specific chain-growth polymer, given the structure of the polymer.

KEY TERMS

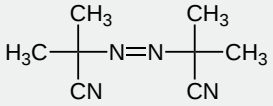
Make certain that you can define, and use in context, the key terms below.

- monomer
- polymer
- vinyl monomer

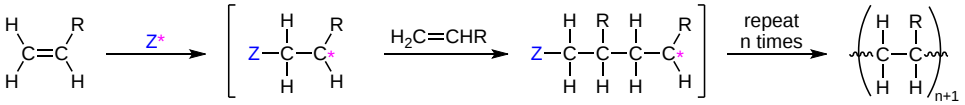
STUDY NOTES

Vinyl monomers are monomers of the type **CH2 = CHX**. Recall that the vinyl group is **CH2 = CH–**.

Although benzoyl peroxide is commonly used as an initiator in free-radical polymerization reactions, an alternative reagent is azobisisobutyronitrile, shown below.



A polymer is a large molecule built of repeat units of many monomers (smaller molecules). An example of this in the biological world is cellulose, which is a polymer composed of repeating glucose monomer units. A synthetic example would be of polyethylene, which is a polymer with ethylene as the repeating unit for the monomer. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.



Z* is an initiating species, where * may be a radical, a cation or an anion

It is useful to distinguish four polymerization procedures fitting this general description.

• Radical Polymerization The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.

• Cationic Polymerization The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.

• Anionic Polymerization The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.

• Coordination Catalytic Polymerization The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

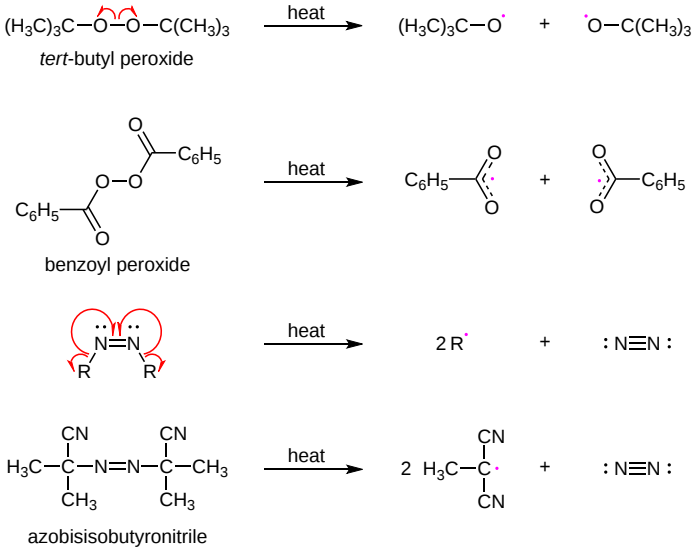
RADICAL CHAIN-GROWTH POLYMERIZATION

Chain-growth polymers are formed in a chain-reaction process. The first step involves an initiator to add to a carbon-carbon double bond in the first monomer, which results in a reactive intermediate. This intermediate reactive intermediate then goes and reacts with a second alkene monomer to yield another reactive intermediate. This process continues to grow the polymer from one monomer to many monomers until the termination step when the radical is consumed.

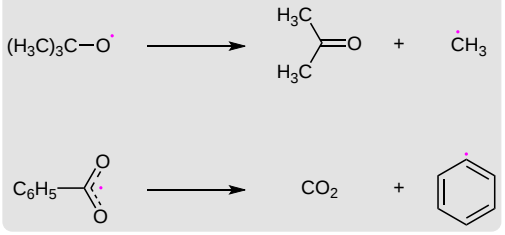
Note: In radical mechanisms, the arrow showing the movement of the electron looks like a "fish hook" or half-arrow as opposed to a full arrow, which indicates the movement of an electron pair.

Initiation: Virtually all of the monomers described above are subject to radical polymerization. Since radical polymerization can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.

Some Radical Initiators



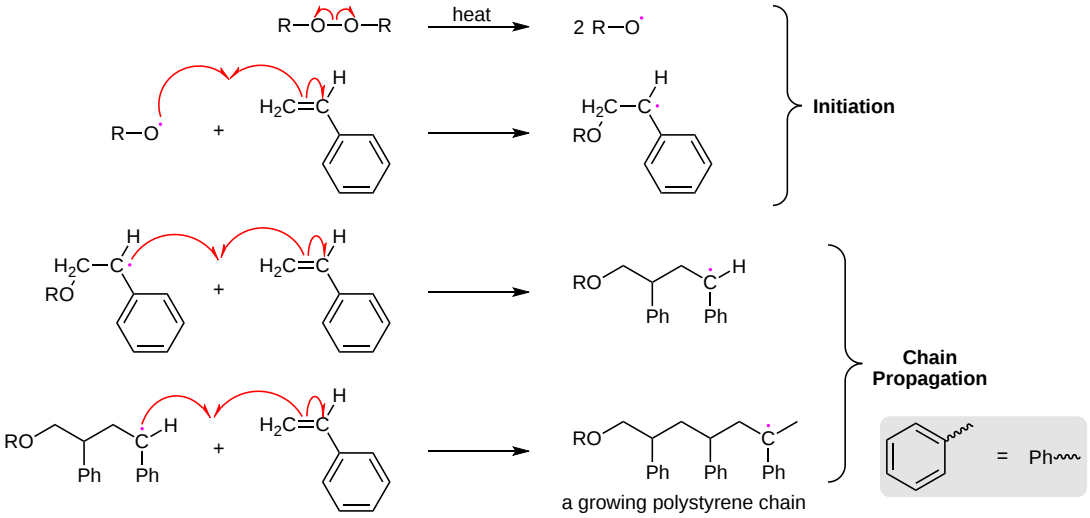
Subsequent Reactions



Propagation: Once the initiator has reacted with the alkene to create the carbon radical intermediate, it adds to another alkene molecule to yield another radical. This process repeats building the polymer chain.

Termination: The chain growing process ends when a reaction that consumes the radical happens. The most common processes are radical combination (two growing chains combine together) and disproportionation.

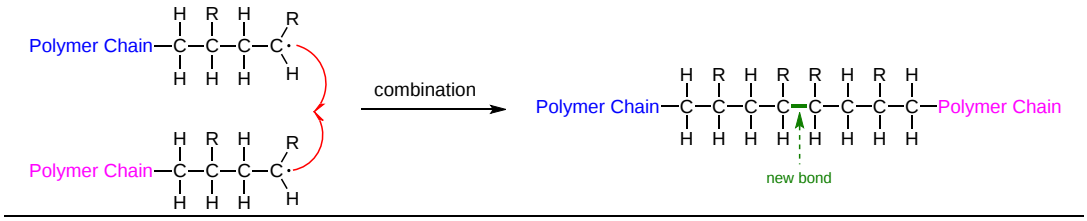
One example of this radical chain-growth polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.

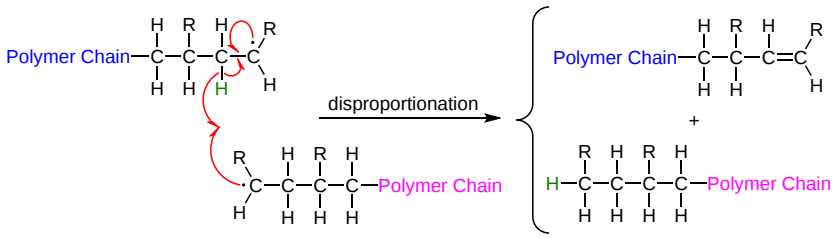


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In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.

Chain Termination Reactions

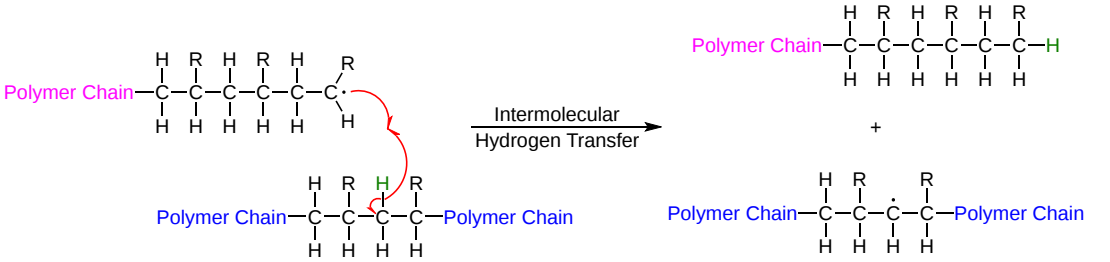


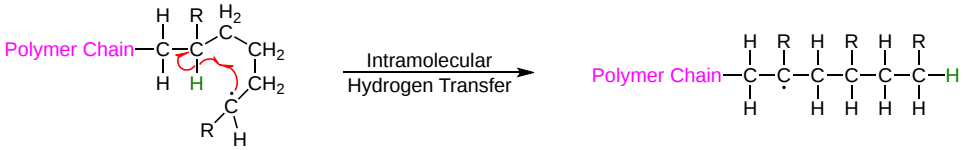


The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations

Chain Transfer Reactions





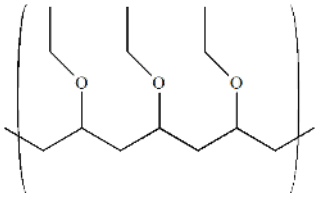
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1°-radical at the end of a growing chain is converted to a more stable 2°-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

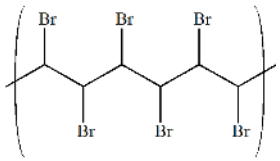
EXERCISES

QUESTIONS

Q8.10.1

Propose the monomer units in the following polymers:





SOLUTIONS

S8.10.1



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8.11: BIOLOGICAL ADDITIONS OF RADICALS TO ALKENES

OBJECTIVE

After completing this section, you should be able to discuss, briefly, some of the addition reactions that take place in nature, and the role of enzymes in such processes.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- enzyme
- coenzyme

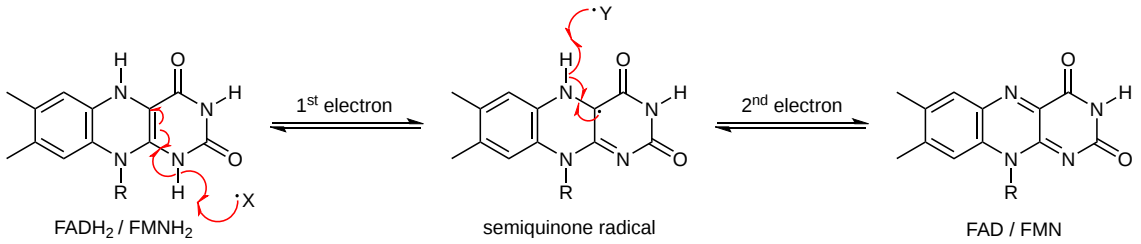
STUDY NOTES

You need not memorize the reaction described in this section of the textbook. However, you should note how the names of enzymes are derived from the reactions they catalyze; for example, ascorbic acid oxidase is the enzyme that catalyzes the oxidation of ascorbic acid (vitamin C).

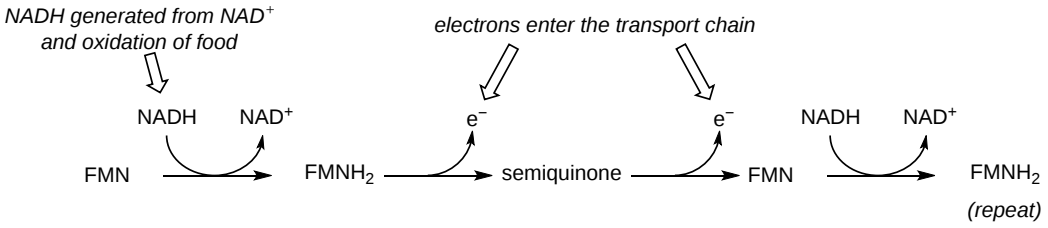
In the previous section (8-10: Radical Additions to Alkenes: Chain-Growth Polymers), very reactive carbon radical intermediates were formed for the alkene polymerizations. The high reactivity of radicals makes it hard to control, though many chemists are currently working on this. Therefore, there is a limit to the usefulness of radical polymerization. Biological reactions do not face this same issue since the enzyme controls the reaction. In an enzyme active site, one monomer at a time enters to react in the proper orientation with all the nearby groups necessary for the reaction to proceed nearby. An example of a radical chain-growth polymerization is discussed next.

RADICAL MECHANISMS FOR FLAVIN-DEPENDENT REACTIONS

Flavin coenzymes, like their nicotinamide adenine dinucleotide (NAD) counterparts, can act as hydride acceptors and donors. In these redox reactions, two electrons are transferred together in the form of a hydride ion. Flavin, however, is also capable of mediating chemical steps in which a single unpaired electron is transferred - in other words, radical chemistry. This is due to the ability of the flavin system to form a stabilized radical intermediate called a **semiquinone**, formed when $FADH_2$ (or $FMNH_2$) donates a single electron, or when FAD (or FMN) accepts a single electron.

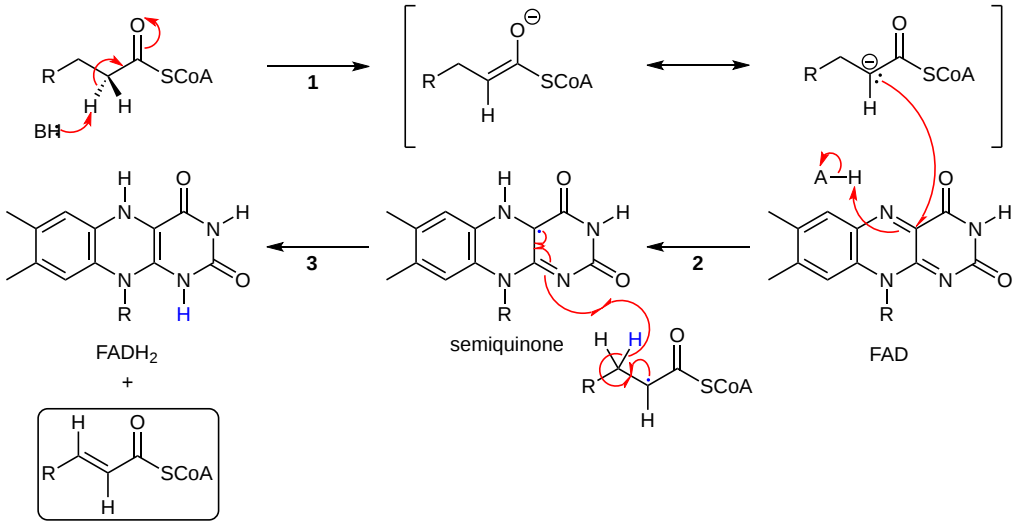


This single-electron transfer capability of flavins is critical to their metabolic role as the entry point of electrons into the electron transport phase of respiration. Electrons 'harvested' from the oxidation of fuel molecules are channeled, *one by one*, by $FMNH_2$ into the electron transport chain, where they eventually reduce molecular oxygen. NADH is incapable of single electron transfer - all it can do is transfer *two* electrons, in the form of a hydride, to FMN; the regenerated $FMNH_2$ is then able to continue sending single electrons into the transport chain.



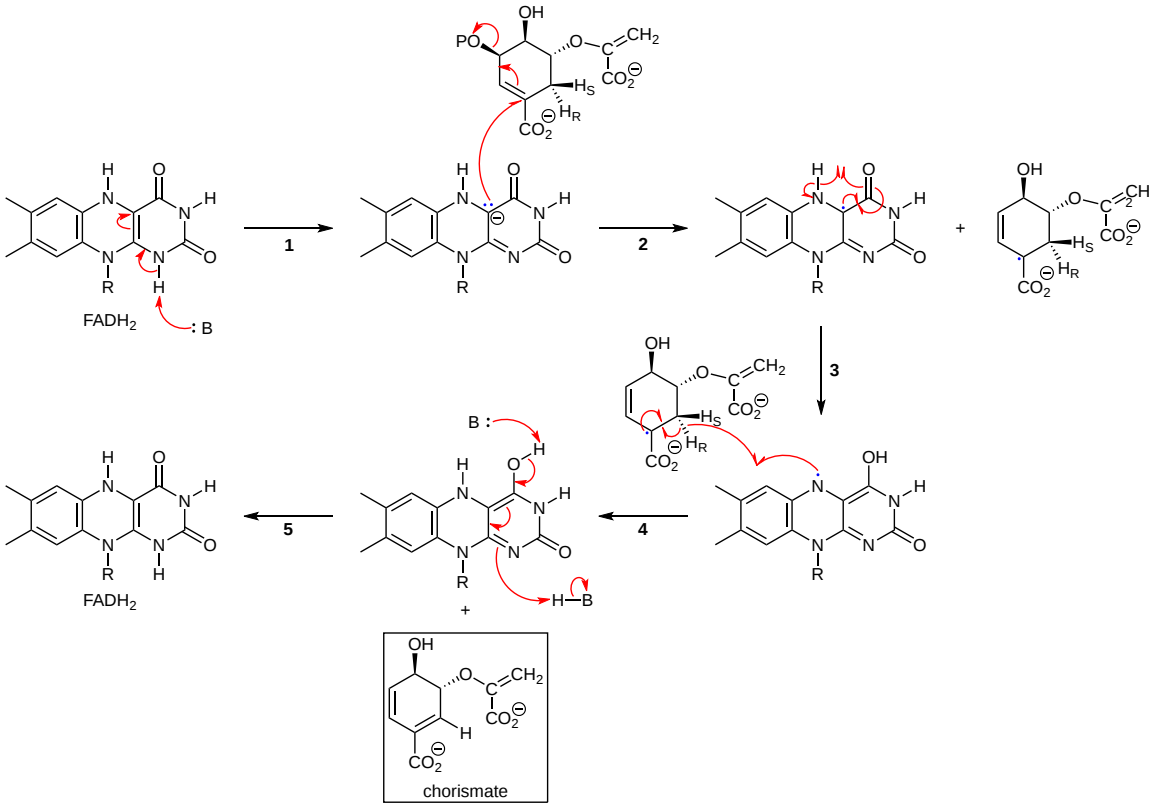
You will learn more details about this process in a biochemistry class.

Because flavins are capable of single-electron as well as two-electron chemistry, the relevant mechanisms of flavoenzyme-catalyzed reactions are often more difficult to determine. Recall the dehydrogenation reaction catalyzed by acyl-CoA dehydrogenase (section 16.5C) - it involves the transfer of two electrons and two protons (ie. a hydrogen molecule) to FAD. Both electrons could be transferred together, with the FAD coenzyme simply acting as a hydride acceptor (this is the mechanism we considered previously). However, because the oxidizing coenzyme being used is FAD rather than NAD^+, it is also possible that the reaction could proceed by a single-electron, radical intermediate process. In the alternate radical mechanism proposed below, for example, the enolate intermediate first donates a *single* electron to FAD, forming a radical semiquinone intermediate (step 2). The second electron is transferred when the semiquinone intermediate abstracts a hydrogen from C_b in a homolytic fashion (step 3).



Scientists are still not sure which mechanism - the hydride transfer mechanism that we saw in section 16.5B or the single electron transfer detailed above - more accurately depicts what is going on in this reaction.

The conjugated elimination catalyzed by chorismate synthase (section 14.3B) is another example of a reaction where the participation of flavin throws doubt on the question of what is the relevant mechanism. This could simply be a conjugated E1' reaction, with formation of an allylic carbocation intermediate. The question plaguing researchers studying this enzyme, however, is why $FADH_2$ is required. This is not a redox reaction, and correspondingly, $FADH_2$ is *not* used up in the course of the transformation - it just needs to be bound in the active site in order for the reaction to proceed. Given that flavins generally participate in single-electron chemistry, this is an indication that radical intermediates may be involved. Recently an alternative mechanism, involving a flavin semiquinone intermediate, has been proposed (*J. Biol. Chem* **2004**, *279*, 9451). Notice that a single electron is transferred from substrate to coenzyme in step 2, then transferred back in step 4.



CONTRIBUTORS AND ATTRIBUTIONS

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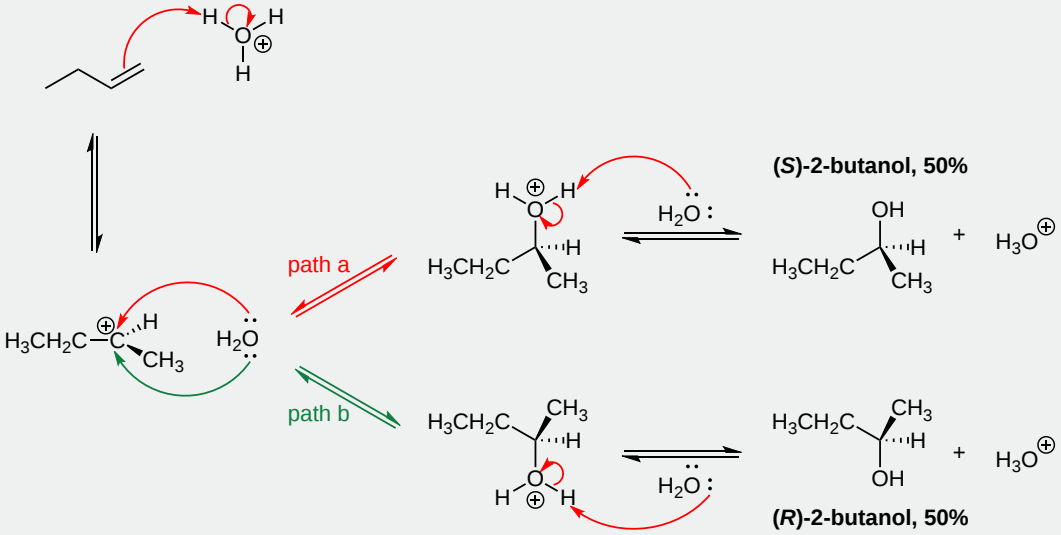
8.12: STEREOCHEMISTRY OF REACTIONS - ADDITION OF H_2O TO AN ACHIRAL ALKENE

OBJECTIVE

After completing this section, you should be able to account for the stereochemistry of the product of the addition of water to an alkene in terms of the formation of a planar carbocation.

STUDY NOTES

Organic reactions in the laboratory or in living systems can produce chiral centres. Consider reaction of 1-butene with water (acid catalyzed). Markovnikov regiochemistry occurs and the OH adds to the second carbon. However, both (*R*) and (*S*) products occur giving a racemic (50/50) mixture of 2-butanol. How does this occur? The proton addition to 1-butene results in a planar carbocation intermediate. A molecule of water is then equally likely to attack from the top (path a) or the bottom (path b) of this cation to produce either (*S*)-2-butanol or (*R*)-2-butanol, respectively.



As a reminder, a chiral center is a carbon that is bonded to four different groups. Organic reactions whether taking place in the body or in the laboratory can result in the product having a chiral center. The example in the study notes uses 1-butene to yield a product that contains a carbon with four different groups attached. Does this mean we get just one stereoisomer? Do we get a mixture of enantiomers? What is the stereochemistry of the reaction?

The product formed from 1-butene acid-catalyzed hydration reaction is a racemic mixture of 2-butanol. So, both R and S enantiomers are present. For more clarity, we can look into the mechanism for this reaction. The first step protonates 1-butene to yield a carbocation. The carbocation has an sp^2-hybridized carbon in a trigonal planar geometry. The planarity of the carbocation allows the nucleophlic water to attack from either side of the plane equally. Many refer to this as top and bottom attack.

One thing to consider is you cannot create chirality from something that is achiral. 1-butene is achiral as is the carbocation intermediate. Therefore, our product must also be achiral and to do this with a molecule that does contain a chiral center means that both enantiomers must be present. In other words, the product is formed as a racemic mixture. While this may be true in the laboratory, biological reactions can give a single enantiomeric product. This is because the enzyme catalyzing the reaction itself is chiral and can therefore yield a chiral product. An example of this is *cis*-aconitate, which is achiral, to (2R,3S)-isocitrate, which is chiral. In this case, aconitase is the enzyme that holds the *cis*-actonitate in a chiral environment, which does create a chemically distinct way for the addition to occur yielding the chiral product, (2R,3S)-isocitrate.

CONTRIBUTORS AND ATTRIBUTIONS

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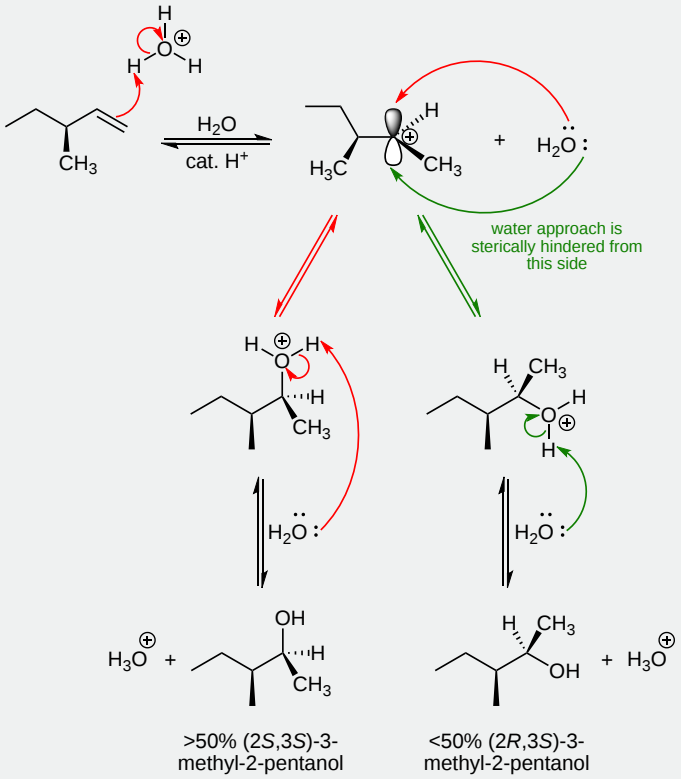
8.13: STEREOCHEMISTRY OF REACTIONS - ADDITION OF H_2O TO A CHIRAL ALKENE

OBJECTIVE

After completing this section, you should be able to explain why the addition of H_2O to a chiral alkene leads to unequal amounts of diastereomeric products.

STUDY NOTES

In the previous section, the addition of water to the achiral alkene produced a racemic mixture of two enantiomeric alcohols. They are produced in equal amounts so the mixture is optically inactive. What would occur if we carried out a similar reaction on a chiral alkene? Consider (*S*)-3-methyl-1-pentene reacting with water (acid catalyzed). Proton addition produces a carbocation intermediate that is chiral (* denotes stereogenic centre). That intermediate does not have a plane of symmetry and therefore attack by water is not equal from the top and bottom. This ultimately produces *R* and *S* products in a non 50:50 ratio.



In the previous section (8.12), an achiral alkene yielded a racemic mixture product. In this section, the starting alkene is chiral. If we consider (S)-3-methyl-1-pentene, it contains a chiral center, thus is optically active. When (S)-3-methyl-1-pentene undergoes acid-catalyzed hydration, it creates a second chiral center. There is the possibility of four products. Do they all form? The do not. Let's see why.

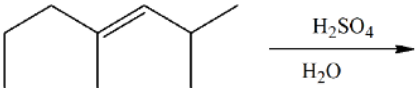
In the reaction, only one site is being reacted at. The S-configuration at C3 just goes along for the ride never participating in the actual mechanism. If you do not react at that site, then the stereochemistry will remain the unchanged, so it will stay with the S-configuration. However, at C2 we are reacting and water can still approach the planar carbocation from either side. Therefore at the C2 site, there will be some R-configuration and some S-configuration. The final product with be a mixture of enantiomers of 2-pentanol. Since the carbocation does not have a plane of symmetry (as was the case in the previous section), there will not be equal attack on either face. One of the faces may be slightly hindered due to sterics, which would result in a little less nucleophilic attack. Instead of obtaining a 50:50 diasteriomeric mixture of products, it would have a slightly different ratio of R to S due to this unequal attack.

EXERCISES

QUESTIONS

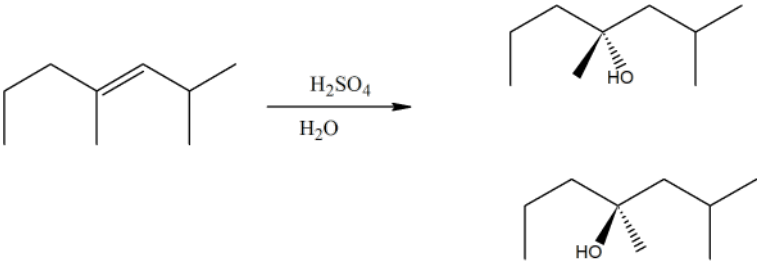
Q8.13.1

Predict the products of the following reaction showing stereochemistry.



SOLUTIONS

S8.13.1



The products (Markovnikov) are diastereomers of one another.

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8.S: ALKENES - REACTIONS AND SYNTHESIS (SUMMARY)

CONCEPTS & VOCABULARY

8.1 Preparing Alkenes: A Preview of Elimination Reactions

- Alkenes can be prepared by either E1 or E2 elimination reactions of alkyl halides.

8.2 Halogenation of Alkenes: Addition of X_2

- Halogen molecules can react as **electrophiles** due to polarization of the halogen-halogen bond.
- During **electrophilic addition** of halogens to pi bonds, an intermediate halonium ion is formed.
- During electrophilic halogenation, ring opening of the halonium intermediate causes **anti** stereochemistry of the halogen atoms in the dihalide product.

8.3 Halohydrins from Alkenes: Addition of HOX

- **Halohydrins** have a halogen and a hydroxide on adjacent carbon atoms. Bromohydrin and chlorohydrin are the specific types of halohydrins where the halogen is bromine or chlorine respectively.
- In **halohydrin** formation a carbocation intermediate is formed on the more substituted carbon (when available). This causes the hydroxide to be added to the more substituted carbon of the original alkene and the halogen to add to the less substituted carbon.

8.4 Hydration of Alkenes: Addition of H_2O by Oxymercuration

- Electrophilic hydration is the addition of water to an alkene with one carbon adding a hydrogen and the other carbon a hydroxide.
- The mechanism begins with addition of a proton, yielding the more substituted **carbocation**.
- Carbocations can undergo **hydride shifts** and **alkyl shifts** to form a more stable **carbocation** when possible.
- **Markovnikov** addition through acid and water or oxymercuration-demercuration yields the more substituted alcohol product (when the two sides of the alkene are not equally substituted).
- Oxymercuration-demercuration avoids carbocation rearrangements through mercurinium ion bridge.

8.5 Hydration of Alkenes: Addition of H_2O by Hydroboration

- Hydroboration-oxidation proceeds through anti-**Markovnikov** addition of water to an alkene, yielding the less substituted alcohol.

8.6 Reduction of Alkenes: Hydrogenation

- Hydrogenation reactions increase the number of carbon-hydrogen bonds, therefore are reduction reactions.
- Addition of hydrogen to carbon-carbon pi bonds is called hydrogenation.
- Hydrogenation requires a catalyst to lower the activation energy allowing the reaction to proceed (commonly nickel, palladium or platinum).
- Hydrogenation reactions occur primarily with syn addition of the two hydrogen atoms, though potential for isomerization makes this uncertain.

8.7 Oxidation of Alkenes: Epoxidation and Hydroxylation

- **Epoxidation** can be carried out by reacting an alkene with a peroxy acid such as MCPBA.
- Anti **dihydroxylation** is achieved by ring opening an epoxide with water under acidic or basic conditions.
- Vicinal diols have hydroxy groups on adjacent carbon atoms.
- Syn dihydroxylation occurs through reaction with osmium tetraoxide, followed by reduction of the intermediate with sulfur compounds.

8.8 Oxidation of Alkenes: Cleavage to Carbonyl Compounds

- Ozonolysis is the cleavage of an alkene resulting in carbonyls at each carbon of the alkene.
- Alkenes can be cleaved by potassium permanganate, which also results in carbonyls at each alkene carbon, though potassium permanganate will oxidize every carbon-hydrogen bonds on the alkene to a carbon-oxygen bond.

8.9 Addition of Carbenes to Alkenes: Cyclopropane Synthesis

- Organic molecules that have a carbon with only two bonds and a lone pair of electrons are called carbenes.
- Most carbenes are highly reactive and short-lived and are often created *in situ*.
- Carbenes can be formed from diazo compounds by reacting wtih a copper catalyst.
- Carbenes will react with alkenes to form cyclopropane rings.

8.10 Radical Addition to Alkenes: Chain-Growth Polymers

- Monomers are units that repeat to form a polymer.

- In radical polymerization, the polymer chain reaction is initiated by a radical.
- Polymer chain reactions occur through a series of steps beginning with **initiation**, continuing through **propagation**, and ending in **termination**.

8.11 Biological Additions of Radicals to Alkenes

8.12 Reaction Stereochemistry: Addition of H_2O to an Achiral Alkene

- Since addition of water to an alkene proceeds through a planar carbocation intermediate, achiral alkenes lead to a racemic mixture of alcohol products.

8.13 Reaction Stereochemistry: Additon of H_2O to a Chiral Alkene

- Addition of water to alkenes which also contain a stereocenter does not lead to a 50:50 mixture of R and S products as the chiral center can reduce reactivity from one side of the carbocation. The products of this type of reaction will be diastereomers, since the original stereocenter will not change and the product will have an additional stereocenter.

SKILLS TO MASTER

- Skill 8.1 Draw accurate Electrophilic Addition Mechanisms incorporating halonium intermediates.
- Skill 8.2 Draw accurate Electrophilic Addition Mechanisms incorporating carbocation intermediates.
- Skill 8.3 Draw Markovnikov products of alkene additions based on the most substituted carbocation intermediate.
- Skill 8.4 Draw hydrogenation products of alkenes.
- Skill 8.5 Draw appropriate epoxidation products including sterechemistry.
- Skill 8.6 Describe how to prepare syn and anti diols from alkenes.
- Skill 8.7 Draw products of oxidative cleavage reactions.
- Skill 8.8 Describe radical chain reactions to form polymers.

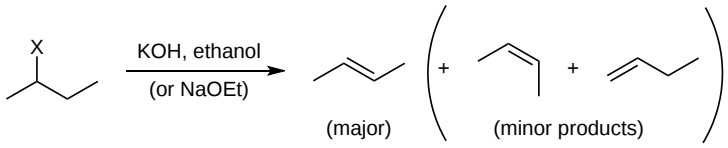
MEMORIZATION TASKS

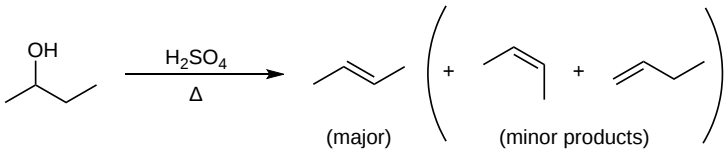
MT 8.1 Memorize reagents for alkene reactions.

MT 8.2 Memorize stability order of carbocations.

SUMMARY OF REACTIONS

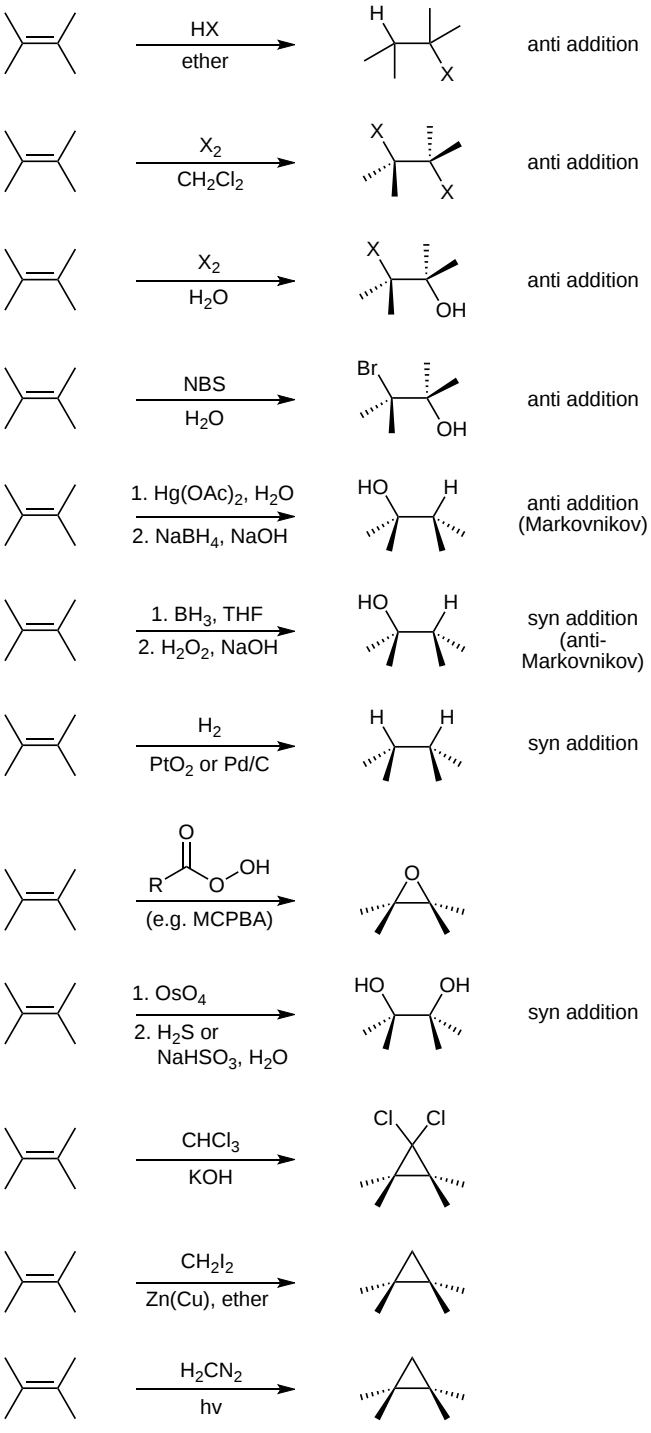
Preparation of Alkenes



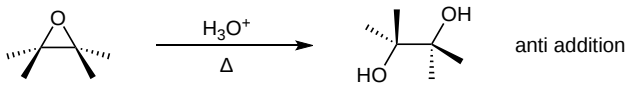


Addition Reactions

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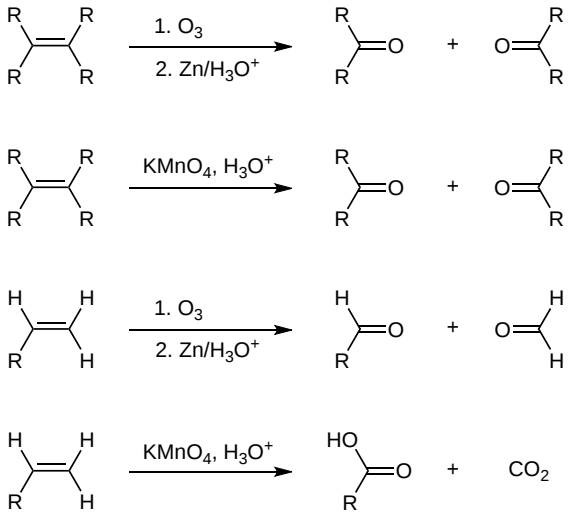


Anti-hydroxylation

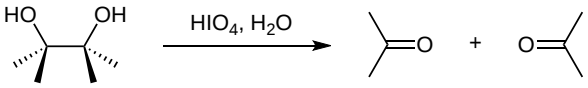


Oxidative Cleavage

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Diol Cleavage



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CHAPTER OVERVIEW

9: ALKYNES - AN INTRODUCTION TO ORGANIC SYNTHESIS

LEARNING OBJECTIVES

After you have completed Chapter 9, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems involving any of the reactions introduced to this point.
3. design multistep syntheses using any of the reactions introduced to this point, and determine the viability of a given synthesis.
4. define, and use in context, the key terms introduced.

Addition reactions not only dominate the chemistry of alkenes, they are also the major class of reaction you will encounter. This chapter discusses an important difference between (terminal) alkynes and alkenes, that is, the acidity of the former; it also addresses the problem of devising organic syntheses. Once you have completed this chapter you will have increased the number of organic reactions in your repertoire, and should be able to design much more elaborate multistep syntheses. As you work through Chapter 9, you should notice the many similarities among the reactions described here and those in Chapters 7 and 8.

9.0: Chapter Objectives
9.1: Naming Alkynes
9.2: Preparation of Alkynes - Elimination Reactions of Dihalides
9.3: Reactions of Alkynes - Addition of HX and X_2
9.4: Hydration of Alkynes
9.5: Reduction of Alkynes
9.6: Oxidative Cleavage of Alkynes
9.7: Alkyne Acidity - Formation of Acetylide Anions
9.8: Alkylation of Acetylide Anions
9.9: An Introduction to Organic Synthesis
9.S: Alkynes - An Introduction to Organic Synthesis (Summary)

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9.0: CHAPTER OBJECTIVES

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9.1: NAMING ALKYNES

OBJECTIVES

After completing this section, you should be able to

- provide the correct IUPAC name of an alkyne, given its Kekulé, condensed or shorthand structure.
- provide the correct IUPAC name of a compound containing both double and triple bonds, given its Kekulé, condensed or shorthand structure.
- draw the structure of a compound containing one or more triple bonds, and possibly one or more double bonds, given its IUPAC name.
- name and draw the structure of simple alkynyl groups, and where appropriate, use these names as part of the IUPAC system of nomenclature.

STUDY NOTES

Simple alkynes are named by the same rules that are used for alkenes (see Section 7.3), except that the ending is *-yne* instead of *-ene*. Alkynes cannot exhibit *E*,*Z* (cis-trans) isomerism; hence, in this sense, their nomenclature is simpler than that of alkenes.

Alkynes are organic molecules made of the functional group carbon-carbon triple bonds and are written in the empirical formula of C_nH_{2n-2}. They are unsaturated hydrocarbons. Like alkenes have the suffix –ene, alkynes use the ending –yne; this suffix is used when there is only one alkyne in the molecule.

$$HC{\equiv}CH$$

INTRODUCTION

Here are the molecular formulas and names of the first ten carbon straight chain alkynes.

Name	Molecular Formula
Ethyne	C_2H_2
Propyne	C_3H_4
1-Butyne	C_4H_6
1-Pentyne	C_5H_8
1-Hexyne	C_6H_{10}
1-Heptyne	C_7H_{12}
1-Octyne	C_8H_{14}
1-Nonyne	C_9H_{16}
1-Decyne	$C_{10}H_{18}$

The more commonly used name for ethyne is acetylene, which used industrially.

NAMING ALKYNES

Like previously mentioned, the IUPAC rules are used for the naming of alkynes.

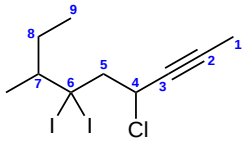
RULE 1

Find the longest carbon chain that includes both carbons of the triple bond.

RULE 2

Number the longest chain starting at the end closest to the triple bond. A 1-alkyne is referred to as a terminal alkyne and alkynes at any other position are called internal alkynes.

For example:

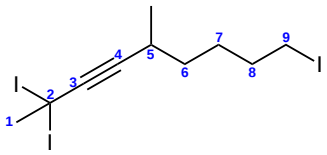


4-chloro-6,6-diiodo-7-methylnon-2-yne

RULE 3

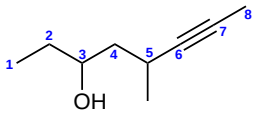
After numbering the longest chain with the lowest number assigned to the alkyne, label each of the substituents at its corresponding carbon. While writing out the name of the molecule, arrange the substituents in alphabetical order. If there are more than one of the same substituent use the prefixes di, tri, and tetra for two, three, and four substituents respectively. These prefixes are not taken into account in the alphabetical order.

For example:



2,2,9-triiodo-5-methylnon-3-yne

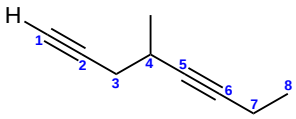
If there is an alcohol present in the molecule, number the longest chain starting at the end closest to it, and follow the same rules. However, the suffix would be –ynol, because the alcohol group takes priority over the triple bond.



5-methyl-6-octyn-3-ol

When there are two triple bonds in the molecule, find the longest carbon chain including both the triple bonds. Number the longest chain starting at the end closest to the triple bond that appears first. The suffix that would be used to name this molecule would be –diyne.

For example:

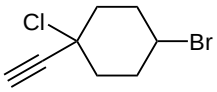


4-methyl-1,5-octadiyne

RULE 4

Substituents containing a triple bond are called alkynyl.

For example:



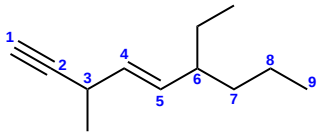
4-bromo-1-chloro-1-ethynylcyclohexane

Here is a table with a few of the alkynyl substituents:

Name	Molecule
Ethynyl	-C≡CH
2- Propynyl	$-CH_2C{\equiv}CH$
2-Butynyl	$-CH_3C{\equiv}CH_2CH_3$

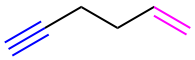
RULE 5

A molecule that contains both double and triple bonds is called an alkenyne. The chain can be numbered starting with the end closest to the functional group that appears first. For example:



(*E*)-6-ethyl-3-methyl-non-4-en-1-yne

If both functional groups are the exact same distance from the ending of the parent chain, the alkene takes precedence in the numbering.

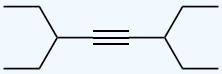


hex-1-en-5-yne

? EXERCISE 9.1.1

Name the following compounds:

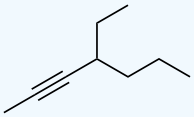
a)



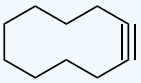
b)



c)



d)



Answer

a. 3,6-diethyl-4-octyne
b. 3-methylbutyne
c. 4-ethyl-2-heptyne
d. cyclodecyne

? EXERCISE 9.1.2

How many isomers are possible for C_5H_8? Draw them.

Answer

2 possible isomers

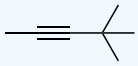


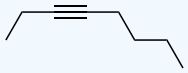
? EXERCISE 9.1.3

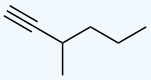
Draw the following compounds:

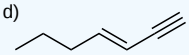
a. 4,4-dimethyl-2-pentyne
b. 3-octyne
c. 3-methyl-1-hexyne
d. *trans* 3-hepten-1-yne

Answer

a) 

b) 

c) 

d) 

EXERCISE 9.1.4

Do alkynes show cis-trans isomerism? Explain.

Answer

No. A triply bonded carbon atom can form only one other bond and has linear electron geometry so there are no "sides". Allkenes have two groups attached to each inyl carbon with a trigonal planar electron geometry that creates the possibility of cis-trans isomerism.

REFERENCE

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th Edition. New York: W. H. Freeman & Company, 2007.

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9.2: PREPARATION OF ALKYNES - ELIMINATION REACTIONS OF DIHALIDES

OBJECTIVES

After completing this section, you should be able to

- write an equation to describe the preparation of an alkyne by the dehydrohalogenation of a vicinal dihalide or vinylic halide.
- identify the alkyne produced from the dehydrohalogenation of a given vicinal dihalide or vinylic halide.
- write a reaction sequence to show how the double bond of an alkene can be transformed into a triple bond.
- identify the vicinal dihalide (or vinylic halide) needed to synthesize a given alkyne by dehydrohalogenation.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

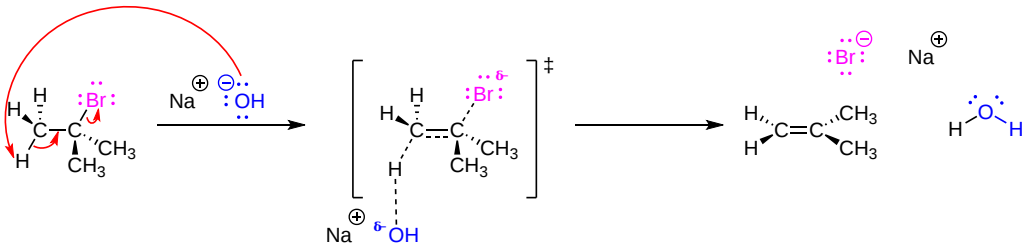
- vicinal dihalide
- vinylic halide

Alkynes can be a useful functional group to synthesize due to some of their antibacterial, antiparasitic, and antifungal properties. One simple method for alkyne synthesis is by double elimination from a dihaloalkane.

E2 MECHANISM

Section 8.2 discussed that alkenes can be formed through an elimination reaction. In particular, the synthesis of alkynes will utilize the E2 elimination reaction. During the mechanism of an E2 reaction, a strong base removes a hydrogen adjacent to a halogen. The electrons from the broken C-H bond move to form the C=C double bond. Doing this causes the halogen to be ejected from the compound. Overall, a hydrogen and a halogen are eliminated from the compound to form an alkene. During this mechanism there is a stereoelectronic requirement that the adjacent hydrogen and the halogen be adjacent to each other.

E2 reaction will be discussed in greater detail in **Section 11.10**.

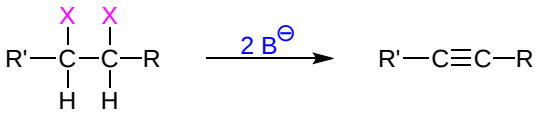


1. The base will deprotonate the haloalkane.
2. The leaving group will depart from the molecule.
3. The deprotonated carbon will rehybridize from sp^3 to sp^2.

ALKYNE FORMATION THROUGH DIHALOALKANE ELIMINATION

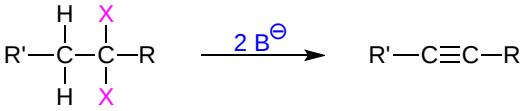
Alkynes are frequently prepared through a double E2 reaction using 2 halides that are vicinal (meaning on adjacent carbons) or geminal (meaning on the same carbon). Because the E2 reaction takes place twice 2 π bonds are formed thus creating an Alkyne. Although hydroxide and alkoxide bases could be used for the strong base required for an E2 reaction, their used opens the possibility of position rearrangement in the alkyne product. Because of this, the stronger base sodium amide in ammonia ($NaNH_2/NH_3$) is commonly used.

GENERAL REACTION



Vicinal dihalide converted to an alkyne

or

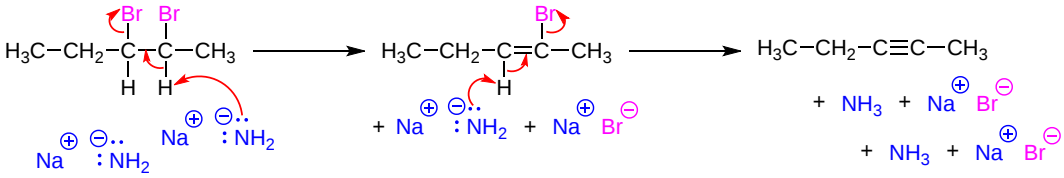


Geminal dihalide converted to an alkyne

Note! If a terminal alkyne is formed during the reaction, 3 equivalents of base are required instead of 2 as discussed below.

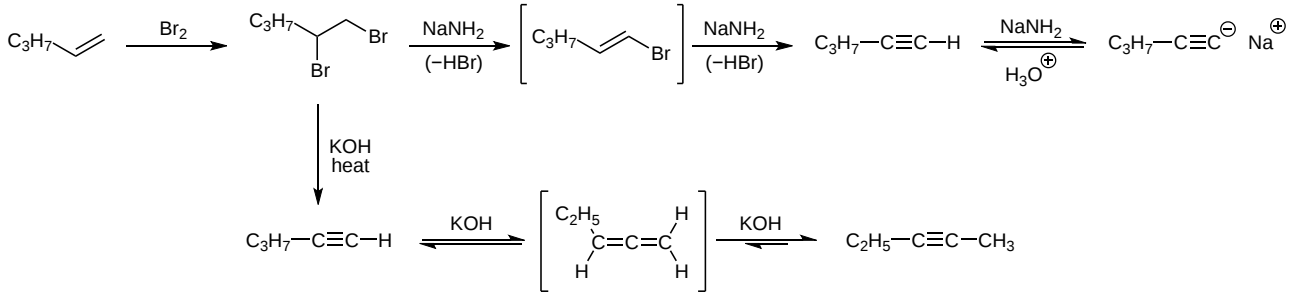
MECHANISM

The following mechanism represents the reaction between 2,3-Dibromopentane with sodium amide in liquid ammonia to form pent-2-yne. During this mechanism an intermediate alkene is formed. Notice that in the alkene intermediate, the remaining hydrogen and halogen are anti to each other due to the stereoelectronic requirements of the E2 mechanism. The intermediate alkene is converted to an alkyne by a second E2 elimination of a hydrogen and halogen.



TERMINAL ALKYNES

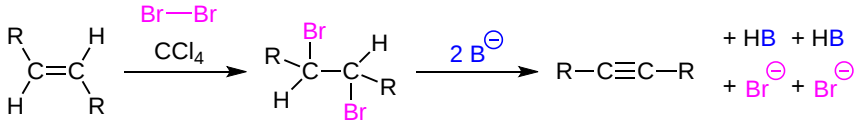
The acidity of terminal alkynes also plays a role in product determination when vicinal (or geminal) dihalides undergo base induced dielimination reactions. The following example illustrates eliminations of this kind starting from 1,2-dibromopentane, prepared from 1-pentene by addition of bromine. The initial elimination presumably forms 1-bromo-1-pentene, since base attack at the more acidic and less hindered 1°-carbon should be favored. The second elimination then produces 1-pentyne. If the very strong base such as sodium amide is used, the terminal alkyne is trapped as its sodium salt, from which it may be released by mild acid treatment. However, if the weaker base KOH with heat is used for the elimination, the terminal alkyne salt is not formed, or is formed reversibly, and the initially generated 1-pentyne rearranges to the more stable 2-pentyne via an allene intermediate. Even though terminal alkynes can be generated using sodium amide as a base, most chemists will prefer to use S_N2 nucleophilic substitution instead of elimination when trying to form a terminal alkyne.



PREPARATION OF ALKYNES FROM ALKENES

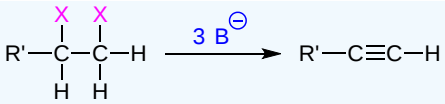
An simple method for the preparation of alkynes utilizes alkenes as starting material. The process begins with the electrophilic addition of a halogen to the alkene bond to form the dihaloalkane. Then the double E2 elimination process is used to form the 2 π bonds of an alkyne.

This first process is gone over in much greater detail in the page on halogenation of an alkene. In general, chlorine or bromine is used with an inert halogenated solvent like chloromethane to create a vicinal dihalide from an alkene. The vicinal dihalide formed is the reactant needed to produce the alkyne using double elimination, as covered previously on this page.



? EXERCISE 9.2.1

Why would we need three bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?



Answer

Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

EXERCISE 9.2.2

What are the major products of the following reactions:

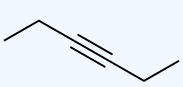
a. 1,2-Dibromopentane with sodium amide in liquid ammonia
b. 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide (Na^+ $^-O\text{-}CH_2CH_3$)

Answer

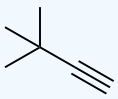
a. 1-Pentyne
b. 1-Pentyne

EXERCISE 9.2.3

What would be good starting molecules for the synthesis of the following molecules:

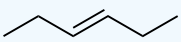
a. 

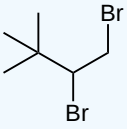
from an alkene

b. 

from a dihaloalkane

Answer

a. 

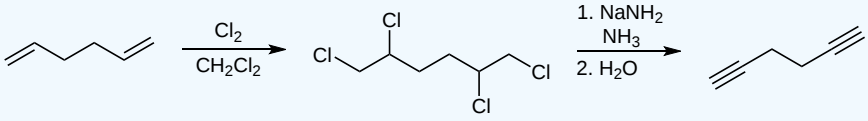
b. 

EXERCISE 9.2.4

Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answer

Bromine or chlorine can be used with different inert solvents for the halogenation. This can be done using many different bases. Liquid ammonia is used as a solvent and needs to be followed by an aqueous work-up.



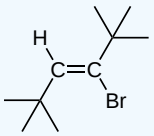
EXERCISE 9.2.5

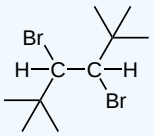
Identify the vinyl halide or halides and the vicinal dihalide or dihalides that could be used in the synthesis of:

a. 2,2,5,5-Tetramethyl-3-hexyne.
b. 4-Methyl-2-hexyne.

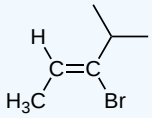
Answer

a)

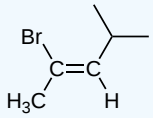


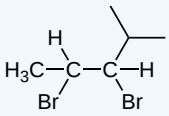


b)



or





REFERENCES

1. Vollhardt, Peter, and Neil Shore. Organic Chemistry: Structure and Function. 5th. New York: W.H. Freeman and Company, 2007.
2. Daley, Richard, and Sally Daley. "13.8 Elimination of Organohalogens." Organic Chemistry. Daley. 5 July 2005. 21 Feb. 2009. <https://studylib.net/doc/8721401/13-elimination-reactions>.

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9.3: REACTIONS OF ALKYNES - ADDITION OF HX AND X_2

OBJECTIVES

After completing this section, you should be able to

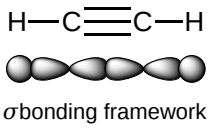
- describe the bonding and geometry of the carbon-carbon triple bond in terms of the *sp*-hybridization of the carbon atoms involved.
- explain the reactivity of alkynes based on the known strengths of carbon-carbon single, double and triple bonds.
- write equations for the reaction of an alkyne with one or two equivalents of halogen (chlorine or bromine) or halogen acid (HCl, HBr or HI).
- draw the structure of the product formed when an alkyne reacts with one equivalent of the halogens and halogen acids listed in Objective 3.
- identify the alkyne which must have been used in an addition reaction with a halogen or halogen acid, given the product of such a reaction.

STUDY NOTES

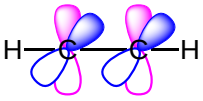
You might find it useful to review Section 1.9 before you begin work on this chapter. If necessary, construct a molecular model of a simple alkyne. Notice the similarity between the behaviour of alkenes and that of alkynes. In the laboratory, you will observe that alkynes readily decolourize a solution of bromine in dichloromethane. Section 9.7 describes a test that allows you to distinguish between a terminal alkyne (i.e., one in which the triple bond occurs between the last two carbons in the chain) and nonterminal alkynes and alkenes.

THE ALKYNE TRIPLE BOND

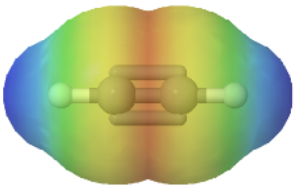
As discussed in **Section 1-9**, the carbon-carbon triple bonds of alkynes are created by the the overlap of orbitals on two sp hybridized carbon atoms. The molecule acetylene (HCCH) is said to contain three sigma bonds and two pi bonds. The C-C sigma bond of acetylene is formed by the overlap an *sp* hybrid orbital from each of the carbon atoms. The two C-H sigma bonds are formed by the overlap of the second *sp* orbital on each carbon atom with a 1*s* orbital from a hydrogen. Each carbon atom still has two half-filled P orbitals, which are perpendicular both to each other and to the line formed by the sigma bonds. These two perpendicular pairs of *p* orbitals form two pi bonds between the carbons, resulting in a triple bond overall (one sigma bond plus two pi bonds). The electrostatic potential map of acetylene shows that the pi electrons of the triple bond form a negative belt (shown in red) around the center of the molecule.



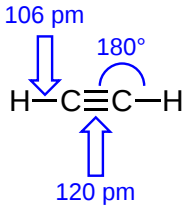
σbonding framework



πoverlap



Acetylene is linear, as predicted by VSEPR, with all four atoms lying in a straight line and both H-C-C bond angles being 180°. The triple bond in acetylene is the shortest (120 pm) and the strongest (964 kJ/mol) carbon-carbon bond known.

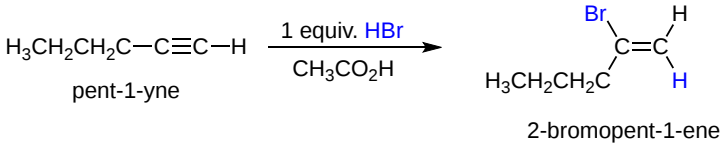


ELECTROPHILIC ADDITION OF HX TO ALKYNES

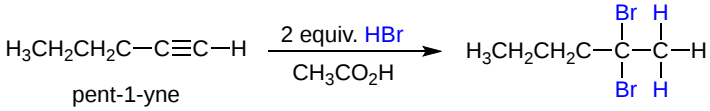
Alkynes undergo electrophilic addition in much the same manner as alkenes, however, the presence to two pi bonds allows for the possibly of the addition happening twice. The addition of one equivalent of hydrogen chloride or hydrogen bromide converts alkynes to haloalkenes. The addition of two or more equivalents of HCl or HBr converts alkynes to geminal dihalides through an haloalkene intermediate. These

additions are regioselective and follow Markovnikov's rule. The double bonds formed during the reaction with internal alkynes tend to have Z stereochemistry although not always.

HBR ADDITION TO A TERMINAL ALKYNE

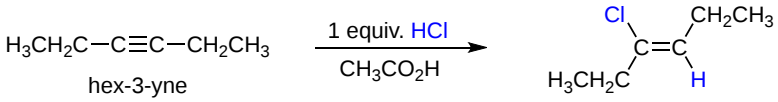


2-bromopent-1-ene

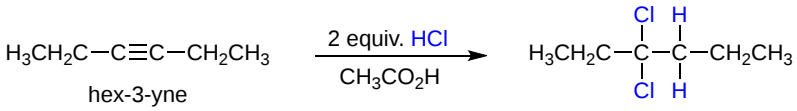


2,2-dibromopentane

HCL ADDITION TO A SYMMETRICAL INTERNAL ALKYNE



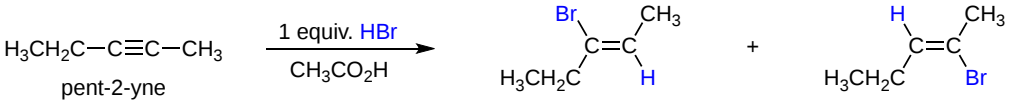
(Z)-4-chlorohex-3-ene



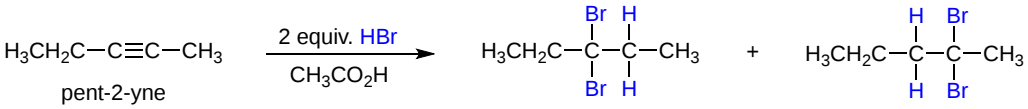
3,3-dichlorohexane

HBR ADDITION TO AN ASYMMETRICAL INTERNAL ALKYNE

The addition of HX to an asymmetrical internal alkyne tend to make a mixture of isomers as products.



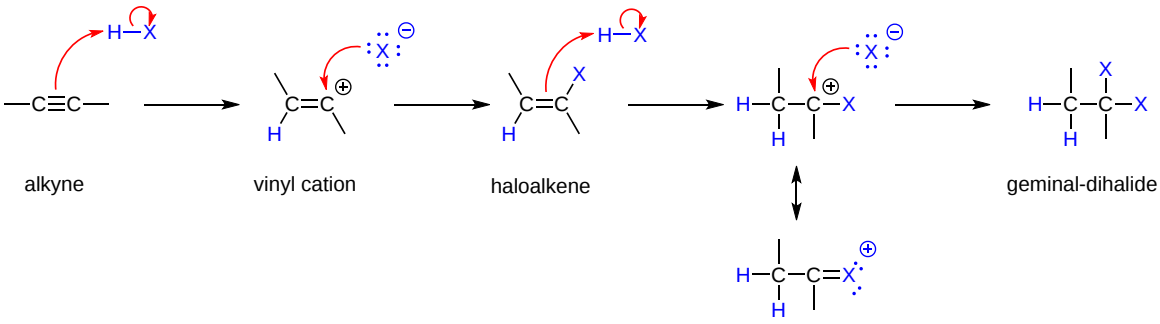
(Z)-3-bromopent-2-ene (Z)-2-bromopent-2-ene



3,3-dibromopentane 2,2-dibromopentane

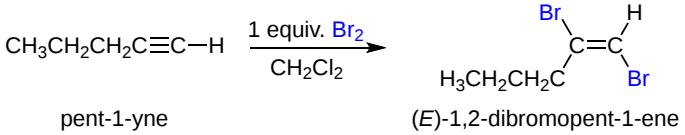
MECHANISM

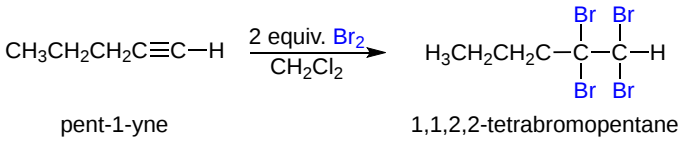
The mechanism for the electrophilic addition of HX to an alkyne is analogous to the HX addition to an alkene. The presence of two pi bonds in the alkyne allows for the addition of HX to occur twice. The addition of H^+ to the alkyne forms a vinyl cation will preferably form on the more substituted side of the alkyne following Markovnikov's rule. The subsequent addition of Br^- forms a haloalkene which undergoes electrophilic addition to a second H^+. The carbocation form will preferably form on the carbon attached to the halogen already in place. The carbocation is stabilized by the halogen through the creation of a resonance structure which obeys the octet rule. This stabilizing effect ensures that a geminal-dihalide is the sole product and no vicinal-dihalide is formed.



ELECTROPHILIC ADDITION OF X_2 TO ALKYNES

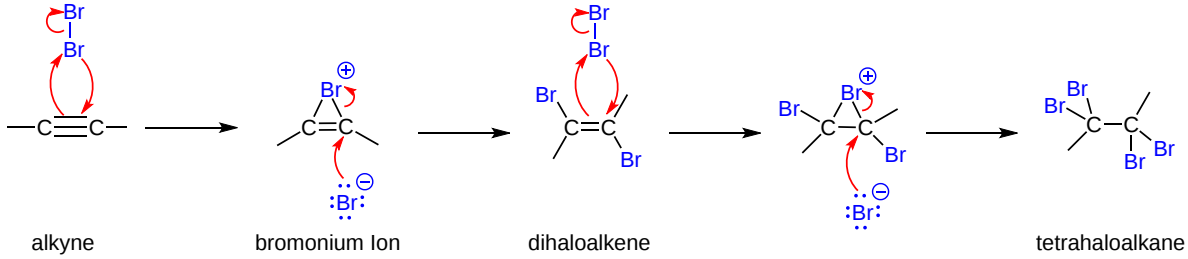
Alkynes undergo the same type of electrophilic addition with chloride and bromine as alkenes. However, with alkynes the halogen addition can occur once or twice depending on the molar equivalents of halogen used in the reaction. If one molar equivalent of halogen is used, a dihaloalkene is formed. The anti addition of the reaction mechanism causes the halogens to be trans in the resulting alkene. The addition of two or more molar equivalents of halogen converts the alkyne to a tetrahaloalkane through a dihaloalkene intermediate.





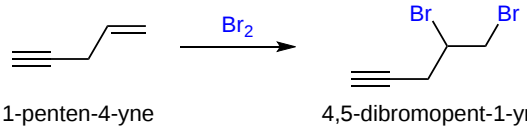
MECHANISM

The alkyne undergoes electrophilic addition with bromine to form a bromonium ion in a three-membered ring. The ejected bromide ion performs an S_N2 reaction with the bromonium ion causing the ring to open and the bromines in the resulting alkene to be in a *trans* configuration. The process is repeated with a second pi bond creating a tetrahaloalkane as a product.



RELATIVE REACTIVITY OF ALKYNES AND ALKENES TO ELECTROPHILIC REAGENTS

When the addition reactions of electrophilic reagents, such as strong Brønsted acids and halogens, to alkynes are studied there is a curious paradox. The reactions of alkynes are even more exothermic than the additions to alkenes, and yet the rate of addition to alkynes is slower by a factor of 100 to 1000. This concept is shown in the reaction of one equivalent of bromine with 1-penten-4-yne to produce 4,5-dibromopent-1-yne as the chief product.

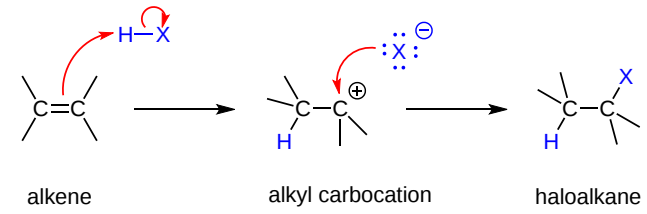


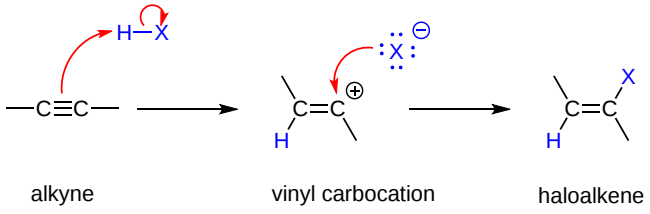
Why are the reactions of alkynes with electrophilic reagents more sluggish than the corresponding reactions of alkenes? Typically, addition reactions to alkynes are more exothermic than additions to alkenes, and there would seem to be a higher π-electron density about the triple bond (two π-bonds versus one). Two factors are significant in explaining this apparent paradox. First, although there are more π-electrons associated with the triple bond, the sp-hybridized alkyne carbons are more electronegative than the sp^2-hybridized alkene carbons. The

alkyne carbons exert a strong attraction for their π-electrons, which are consequently bound more tightly to the functional group than are the π-electrons of a double bond. This is seen in the ionization potentials of ethylene and acetylene. Remember an **ionization potential** is the minimum energy required to remove an electron from a molecule of a compound. Since the initial interaction between an electrophile and an alkene or alkyne involves the donation of electrons, the relatively slower reactions of alkynes becomes understandable.

Acetylene	$HC{\equiv}CH + Energy \rightarrow [HC{\equiv}CH\ ^{\bullet(+)} + e^{(-)}$	$\Delta H = +264$ kcal/mole
Ethylene	$H_2C{=}CH_2 + Energy \rightarrow [H_2C{=}CH_2]\ ^{\bullet(+)} + e^{(-)}$	$\Delta H = +244$ kcal/mole

A second factor is presumed to be the stability of the carbocation intermediate generated by sigma-bonding of a proton or other electrophile to one of the triple bond carbon atoms. When comparing the mechanism for the addition of HBr to an alkene and an alkyne, the alkyne reaction creates a vinyl carbocation which is less stable than the alkyl carbocation made during the alkene reaction.

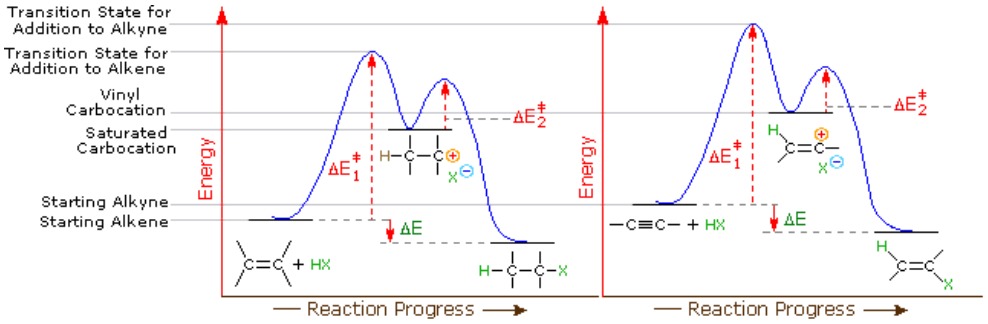




Indeed, we can modify our earlier ordering of carbocation stability to include these vinyl cations in the manner shown below.

Substitution	**Methyl**		**1°-Vinyl**		**1°**		**2°-Vinyl**		**2°**		**1°-Allyl**		**3°**
Stability	$CH_3^{(+)}$	≈	$RCH{=}CH^{(+)}$	<	$RCH_2^{(+)}$	≈	$RCH{=}CR^{(+)}$	<	$R_2CH^{(+)}$	≈	$CH_2{=}CH\text{-}CH_2^{(+)}$	<	$R_3C^{(+)}$

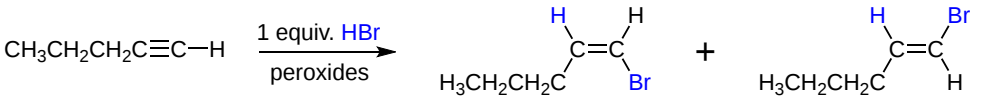
Application of the Hammond postulate indicates that the activation energy for the generation of a vinyl cation intermediate would be higher than that for a lower energy intermediate. Thus, electrophilic reactions with alkenes have a lower activation energy and process faster than the corresponding reaction with an alkyne. This is illustrated for alkenes versus alkynes by the following energy diagrams. Despite these differences, electrophilic additions to alkynes have emerged as exceptionally useful synthetic transforms.



A Comparison of Energy Profiles for Electrophilic Addition to Alkenes and Alkynes

ELECTROPHILIC ADDITION OF HX WITH PEROXIDES TO ALKYNES

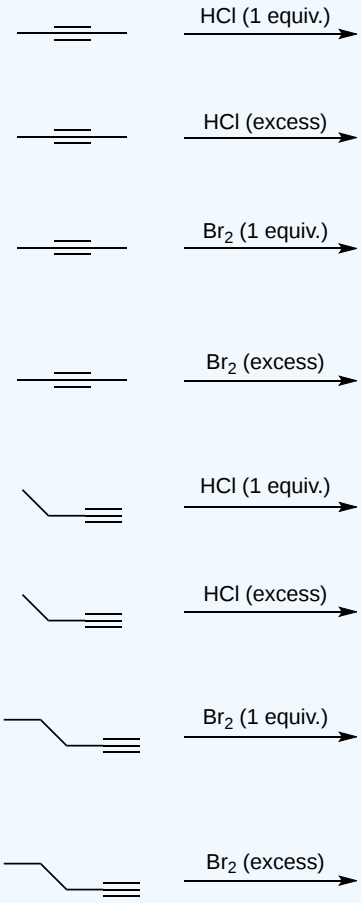
When 1 equivalent of HBr is reacted with alkynes in the presence of peroxides and Anti-Markovnikov addition occurs. The use of peroxides causes the reaction to occur via a free radical mechanism. The bromine adds to the less substituted alkyne carbon while the hydrogen adds to the more substituted creating a haloalkene. Typically, H and Br are added in a syn or anti manner creating a mixture of products.



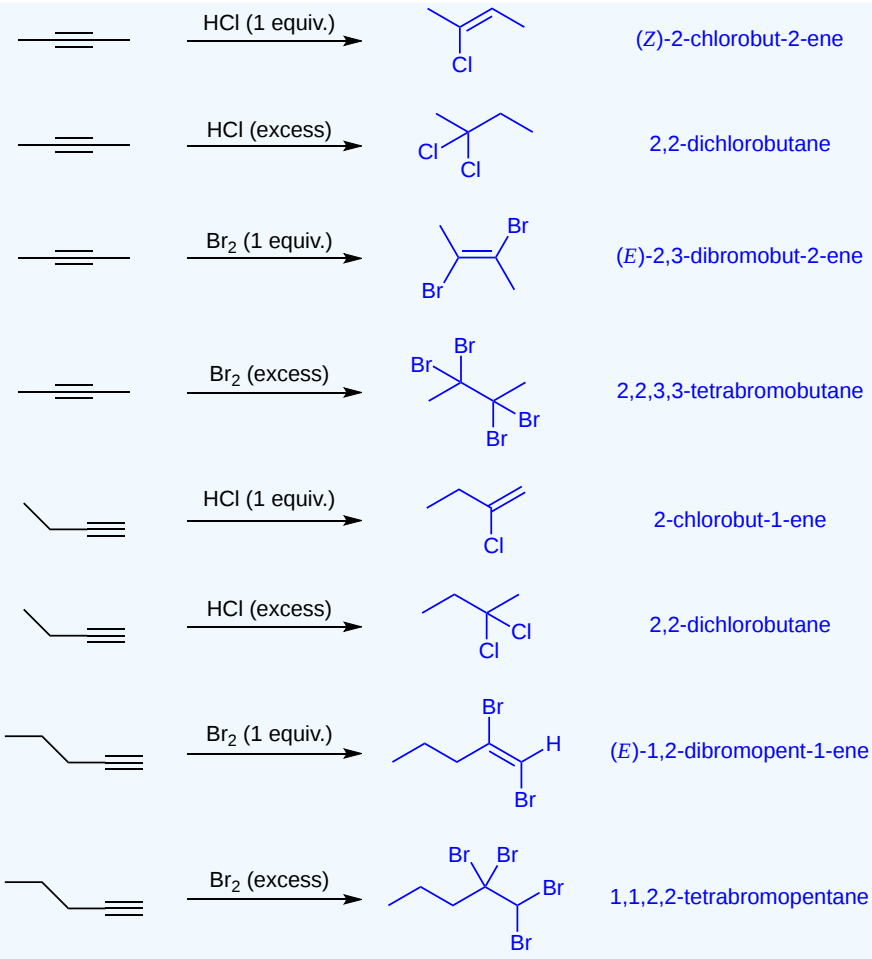
pent-1-yne (*Z*)-1-bromopent-1-ene (*E*)-1-bromopent-1-ene

EXERCISE 9.3.1

Draw the structure and give the IUPAC name of the product formed in each of the reactions listed below:



Answer



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9.4: HYDRATION OF ALKYNES

OBJECTIVES

After completing this section, you should be able to

- write the equation for the reaction of water with an alkyne in the presence of sulfuric acid and mercury(II) sulfate.
- describe keto-enol tautomerism.
- predict the structure of the ketone formed when a given alkyne reacts with sulfuric acid in the presence of mercury(II) sulfate.
- identify the reagents needed to convert a given alkyne to a given ketone.
- identify the alkyne needed to prepare a given ketone by hydration of the triple bond.
- write an equation for the reaction of an alkyne with borane.
- write the equation for the reaction of a vinylic borane with basic hydrogen peroxide or hot acetic acid.
- identify the reagents, the alkyne, or both, needed to prepare a given ketone or a given cis alkene through a vinylic borane intermediate.
- identify the ketone produced when a given alkyne is reacted with borane followed by basic hydrogen peroxide.
- identify the cis alkene produced when a given alkyne is reacted with borane followed by hot acetic acid.
- explain why it is necessary to use a bulky, sterically hindered borane when preparing vinylic boranes from terminal alkynes.
- predict the product formed when the vinylic borane produced from a terminal alkyne is treated with basic hydrogen peroxide.
- identify the alkyne needed to prepare a given aldehyde by a vinylic borane.

KEY TERMS

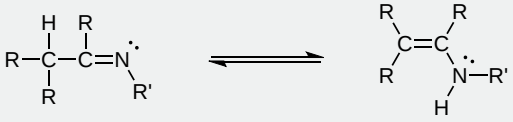
Make certain that you can define, and use in context, the key terms below.

- enol
- keto-enol tautomeric equilibrium
- tautomerism
- tautomers

STUDY NOTES

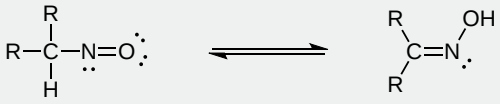
Rapid interconversion between tautomers is called **tautomerism**; however, as the two tautomers are in equilibrium, the term *tautomeric equilibrium* may be used. This section demonstrates the equilibrium between a ketone and an enol; hence, the term *keto-enol tautomeric equilibrium* is appropriate. The term “enol” indicates the presence of a carbon-carbon double bond and a hydroxyl (i.e., alcohol) group. Later in the course, you will see the importance of keto-enol tautomerism in discussions of the reactions of ketones, carbohydrates and nucleic acids.

It is important to note that tautomerism is not restricted to keto-enol systems. Other examples include imine-enamine tautomerism



imine enamine

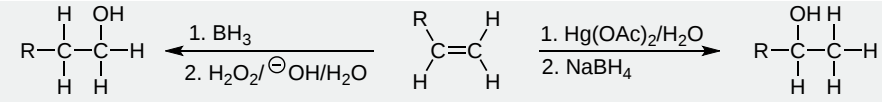
and nitroso-oxime tautomerism

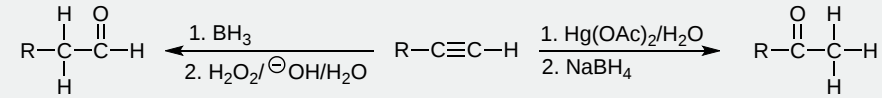


nitroso oxime

However, at the moment you need only concern yourself with keto-enol tautomerism.

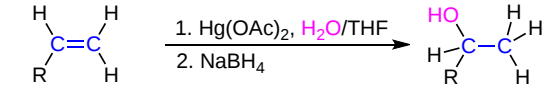
Notice how hydroboration complements hydration in the chemistry of both alkenes and alkynes.



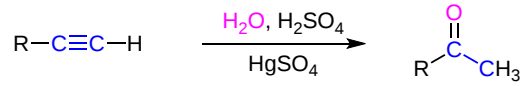


MERCURY(II)-CATALYZED HYDRATION OF ALKYNES

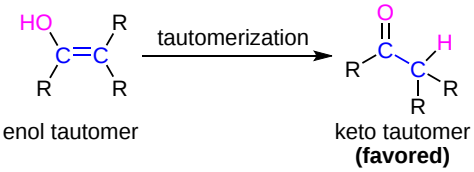
As with alkenes, hydration (addition of water) of alkynes requires a strong acid, usually sulfuric acid, and is facilitated by the mercuric ion (Hg^{2+}). However, the hydration of alkynes gives ketone products while the hydration of alkenes gives alcohol products. Notice that the addition of oxygen in both reactions follows Markovnikov rule.



During the hydration of an alkyne, the initial product is an enol intermediate (a compound having a hydroxyl substituent attached to a double-bond), which immediately rearranges to the more stable ketone through a process called **enol-keto tautomerization**.

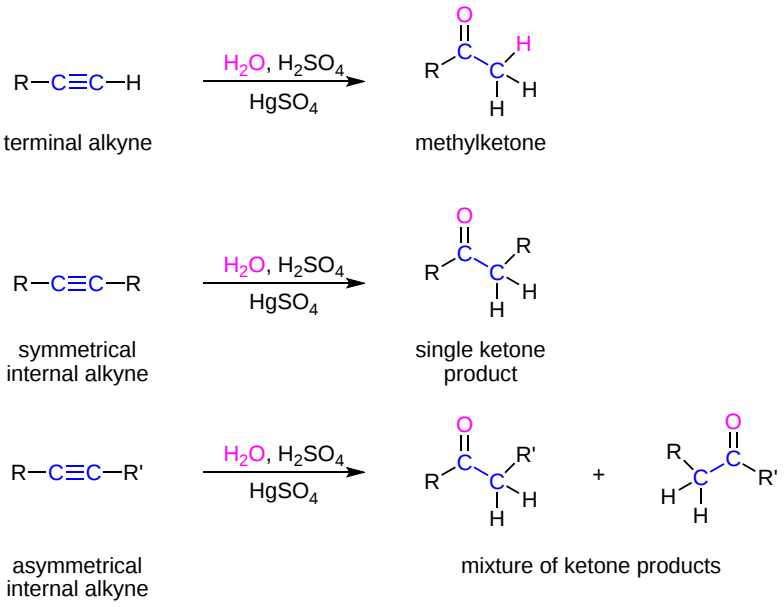


Tautomers are defined as rapidly inter-converted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom and a differently located double bond. The keto and enol tautomers are in equilibrium with each other and with few exceptions the keto tautomer is more thermodynamically stable and therefor favored by the equilibrium. This mechanism for tautomerization will be discussed in greater detail in **Section 22-1**.



GENERAL REACTION

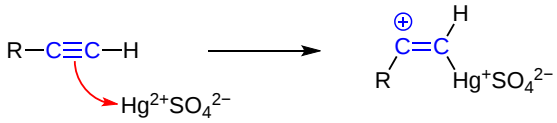
For terminal alkynes, the addition of water follows the Markovnikov rule, and the final product is a methyl ketone. For internal alkynes the addition of water is not regioselective. Hydration of symmetrical internal alkynes produces a single ketone product. However, hydration of asymmetrical alkynes, (i.e. if R & R' are not the same) produces two isomeric ketone products.



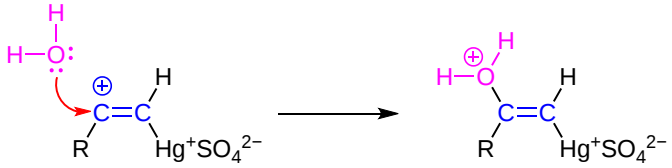
MECHANISM

The mechanism starts with the electrophilic addition of the mercuric ion (Hg^{2+}) to the alkyne producing a mercury-containing vinylic carbocation intermediate. Nucleophilic attack of water on the vinylic carbocation forms a C-O bond to produce a protonated enol. Deprotonation of the enol by water then produces a organomercury enol. The mercury is substituted with H^+ to produced a neutral enol and regenerate the Hg^{2+} catalyst. The enol is converted to the ketone product through keto-enol tautomerization the mechanism of which is provided in **Section 22-1**.

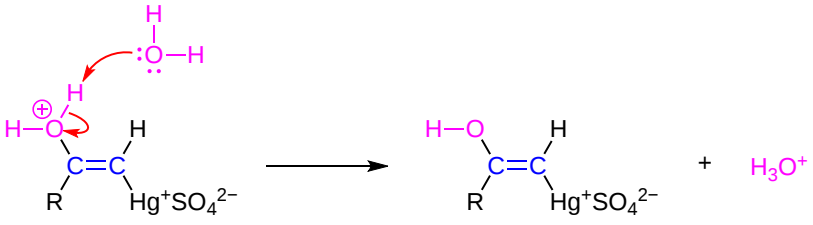
Step 1: Electrophilic addition of Hg^{2+}



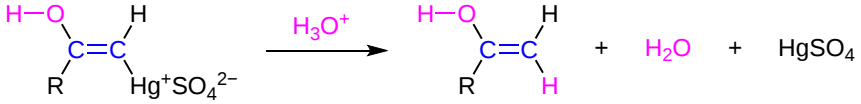
Step 2: Nucleophilic attack by water



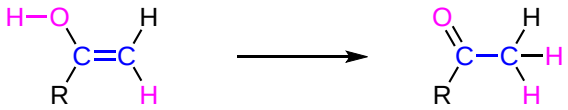
Step 3: Deprotonation



Step 4: Substitution

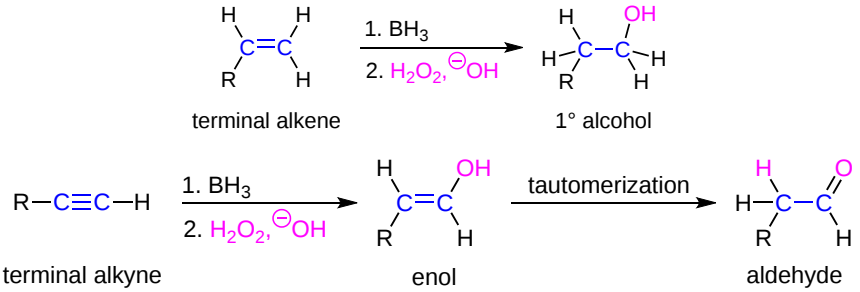


Step 5: Tautomerization

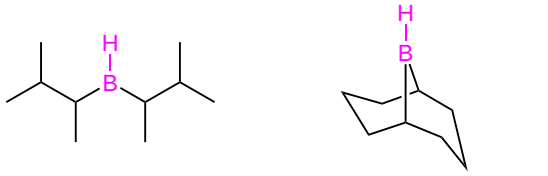


HYDROBORATION–OXIDATION OF ALKYNES

The hydroboration-oxidation of alkynes is analagous to the reaction with alkenes. However, where alkenes for alcohol products, alkynes for aldehyde or ketone products. In both cases the addition is anti-Markovnikov and an oxygen is placed on the less alkyl substituted carbon. With the hydroboration of an alkyne the presences of a second pi bond allows the initial product to under tautomerization to become the final aldehyde product.

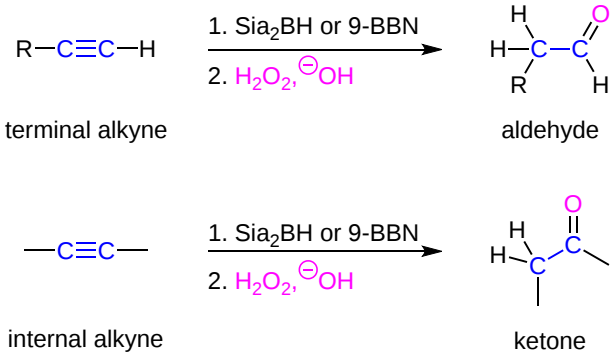


Alkynes have two pi bonds both of which are capable of reacting with borane (BH_3). To limit the reactivity to only one alkyne pi bond, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance which enhances the anti-Markovnikov regioselective of the reaction. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for this hydroboration reaction. The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes.



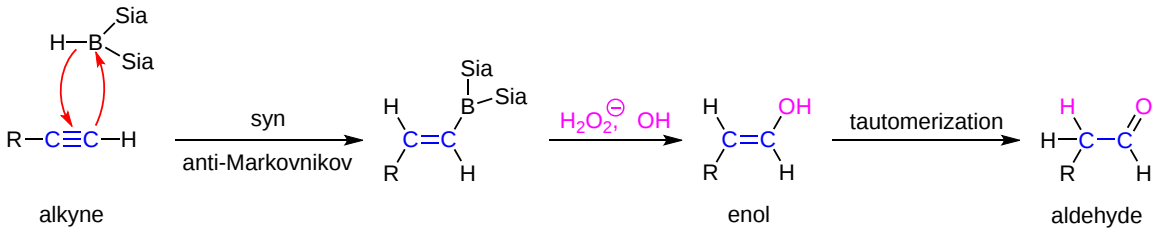
GENERAL REACTION

The hydroboration of terminal alkynes produces aldehyde products while internal alkynes produce ketone products. The hydroboration of symmetrical alkynes produces one ketone product and asymmetrical alkynes produce a mixture of product ketones.



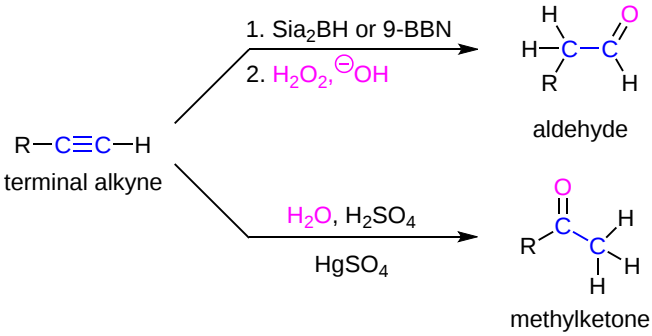
MECHANISM

The mechanism starts with the electrophilic addition of the B-H bond of the borane. The hydrogen atom and the borane all on the same side of the alkyne creating a syn addition configuration in the alkene product. Also, the addition is anti-Markovnikov regioselective which means the borane adds to the less substituted carbon of the alkyne and the hydrogen atom adds to the more substituted. The oxidative work-up replaces the borane with a hydroxy group (-OH) creating an enol intermediate. The enol immediately tautomerizes to the product aldehyde for terminal alkynes and the product ketone for internal alkynes.

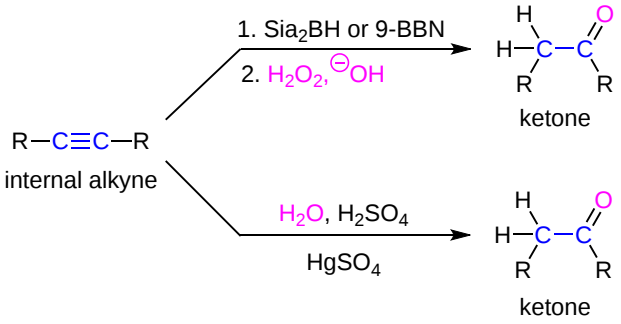


COMPARISON OF MERCURY(II)-CATALYZED HYDRATION AND HYDROBORATION–OXIDATION OF ALKYNES

These two reactions are complementary for the reaction of a terminal alkyne because the produce distinctly different products. The mercury(II) catalyzed hydration of a terminal alkyne produces a methyl ketone, while the hydroboration-oxidation produces an aldehyde.



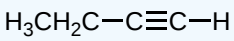
For internal alkynes, the regioslectivity of these reactions are rendered ineffective. The reactions are redundant in that they both produce the same ketone products.



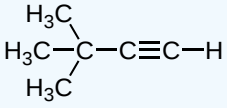
? EXERCISE 9.4.1

Draw the structure of the product formed when each of the substances below is treated with H_2O/H_2SO_4 in the presence of $HgSO_4$.

a)

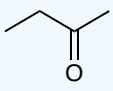


b)

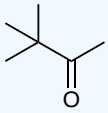


Answer

a)

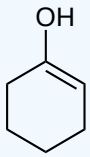


b)

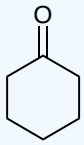


EXERCISE 9.4.2

Draw the structure of the keto form of the compound shown below. Which form would you expect to be the most stable?



Answer

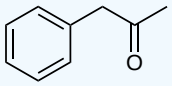


The keto form should be the most stable.

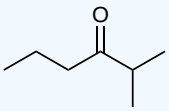
EXERCISE 9.4.3

What alkyne would you start with to gain the following products?

a)

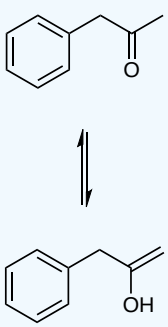


b)

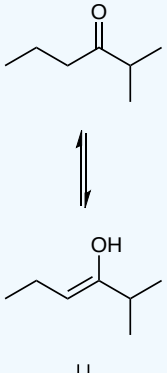


Answer

a)

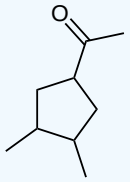


b)

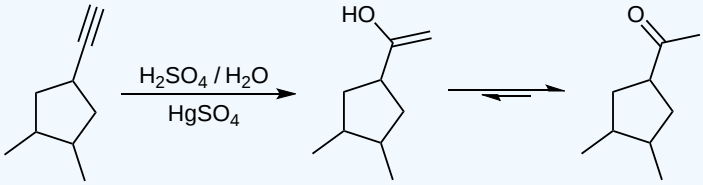


EXERCISE 9.4.4

What alkyne would you start with to gain the following product?

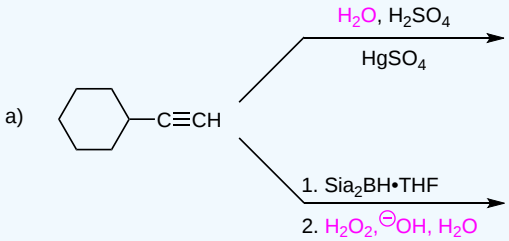


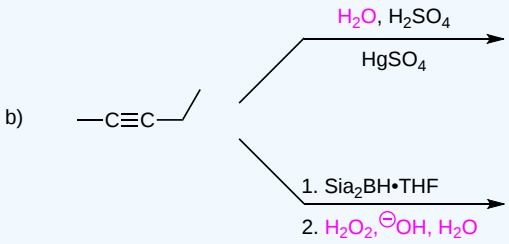
Answer



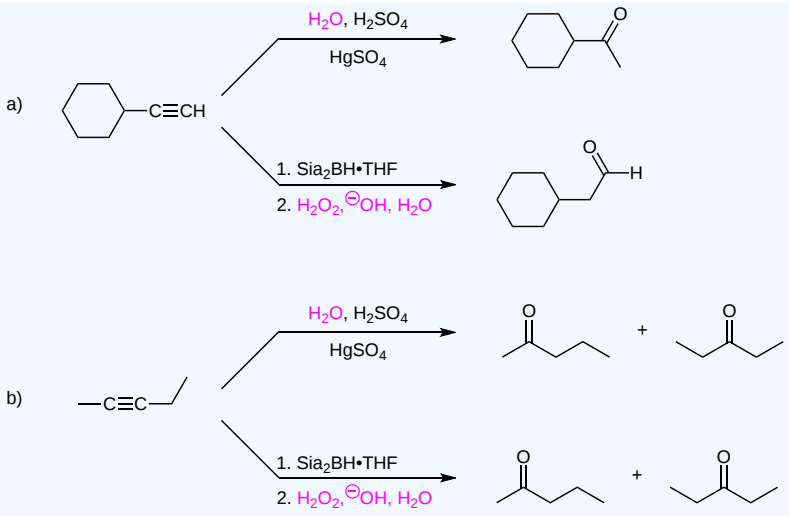
EXERCISE 9.4.5

Draw the product(s) of the following reactions:





Answer



For internal alkynes, there is no difference in the reaction products.

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9.5: REDUCTION OF ALKYNES

OBJECTIVES

After completing this section, you should be able to

1. write equations for the catalytic hydrogenation of alkynes to alkanes and cis alkenes.
2. identify the reagent and catalyst required to produce a given alkane or *cis* alkene from a given alkyne.
3. identify the product formed from the reaction of a given alkyne with hydrogen and a specified catalyst.
4. identify the alkyne that must be used to produce a given alkane or *cis* alkene by catalytic hydrogenation.
5. write the equation for the reduction of an alkyne with an alkali metal and liquid ammonia.
6. predict the structure of the product formed when a given alkyne is reduced with an alkali metal and liquid ammonia.
7. identify the alkyne that must be used to produce a given alkene by reduction with an alkali metal and ammonia.

KEY TERMS

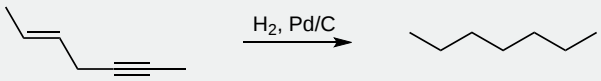
Make certain that you can define, and use in context, the key terms below.

- anion radical
- Lindlar catalyst

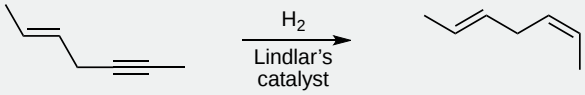
STUDY NOTES

The Lindlar catalyst allows a chemist to reduce a triple bond in the presence of a double bond.

Thus

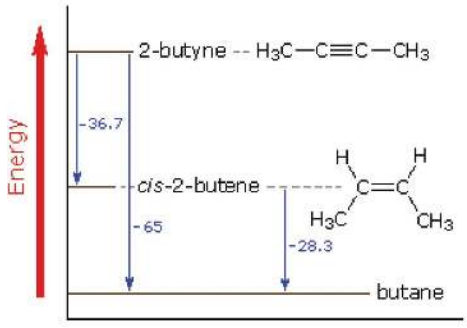


but



HYDROGENATION AND THE RELATIVE STABILITY OF HYDROCARBONS

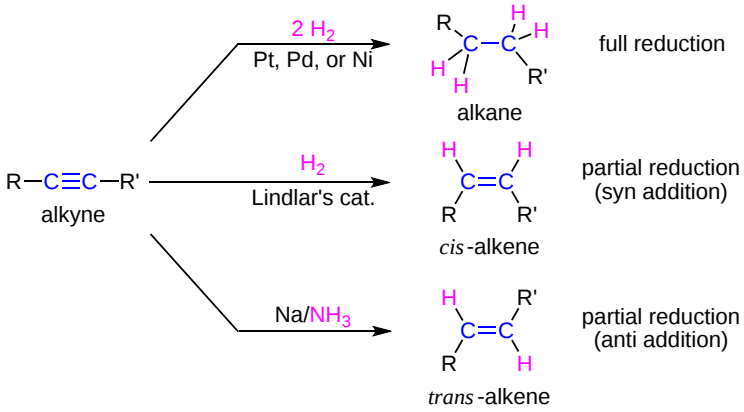
Like alkenes, alkynes readily undergo catalytic hydrogenation partially to *cis*-alkenes or fully to alkanes depending on the reaction employed.



The catalytic addition of hydrogen to 2-butyne provides heat of reaction data that reflect the relative thermodynamic stabilities of these hydrocarbons, as shown above. From the heats of hydrogenation, shown in blue in units of kcal/mole, it would appear that alkynes are thermodynamically less stable than alkenes to a greater degree than alkenes are less stable than alkanes. The standard bond energies for carbon-carbon bonds confirm this conclusion. Thus, a double bond is stronger than a single bond, but not twice as strong. The difference (63 kcal/mole) may be regarded as the strength of the π-bond component. Similarly, a triple bond is stronger than a double bond, but not 50%

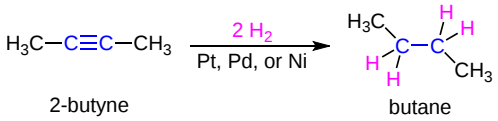
stronger. Here the difference (54 kcal/mole) may be taken as the strength of the second π-bond. The 9 kcal/mole weakening of this second π-bond is reflected in the heat of hydrogenation numbers (36.7 - 28.3 = 8.4).

Alkynes can undergo reductive hydrogenation reactions similar to alkenes. Due to the presence of two pi bonds within alkynes, reductive hydrogenation reactions can be partial to form an alkene or complete to form an alkane. Since partial reductive hydrogenation of an alkyne produces an alkene, the stereochemistry provided by the reaction's mechanism determines whether a *cis*- or *trans*- alkene is formed. The three most significant alkyne reduction reactions are summarized below:

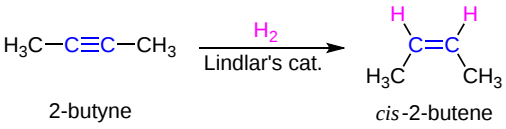


CATALYTIC HYDROGENATION OF AN ALKYNE

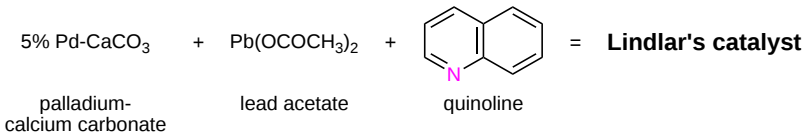
Much like alkenes, alkynes can be fully hydrogenated into alkanes with the help of a platinum, palladium, or nickel catalyst. Because the reaction is catalyzed on the surface of the metal, it is common for these catalysts to be dispersed on carbon (Pd/C) or finely dispersed, such as Raney-Ni. The presence of two pi bonds in the alkyne causes two equivalents of H_2 to be added during the reaction. An alkene intermediate is formed during the reaction but is not isolated.



For catalytic hydrogenation, the Pt, Pd, or Ni catalysts are so effective in promoting the addition of hydrogen to carbon-carbon triple bonds that the alkene intermediate formed cannot be isolated. A less efficient **Lindlar's catalyst**, permits alkynes to be converted to alkenes without further reduction to an alkane. Lindlar's Catalyst transforms an alkyne to a *cis*-alkene because both hydrogen atoms are added to the same side of the alkyne (syn) as shown in the in the previous chapter.

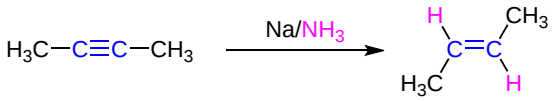


Lindlar's catalyst is prepared by deactivating (or poisoning) a conventional palladium catalyst. Lindlar's catalyst has three components: palladium-calcium carbonate, lead acetate, and quinoline. The quinoline serves to prevent complete hydrogenation of the alkyne to an alkane.



HYDROGENATION OF AN ALKYNE TO A *TRANS*-ALKENE

The anti-addition of hydrogen to an alkyne pi bond occurs through reaction with sodium or lithium metal dissolved in ammonia. This reaction, also called a **dissolving metal reduction**, involves a radical mechanism, and produces a *trans*-alkene product.

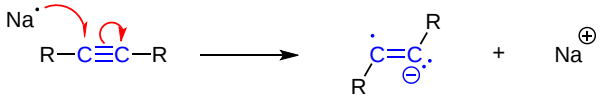


2-Butyne ***Trans*-2-Butene**

MECHANISM

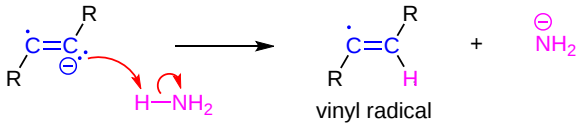
Sodium metal is a powerful reducing agent due to the presence of a $3s^1$ electron in its valence shell. Sodium metal easily gives up this electron to become Na^+. The mechanism start with a sodium atom donating an electron to the alkyne to create an intermediate with a negative charge and an unpaired electron called a radical anion. Next the amine solvent protonates the anion to create a vinyl radical. A second sodium atom then donates an electron to pair the radical to form a vinyl anion. This vinyl anion intermediate rapid interconverts between *cis* and *trans* conformations and determines the stereochemistry of the reaction. The *trans*-vinyl anion is more stable due to reduced steric crowding and is preferentially formed. Finally, the protonation of the *trans*-vinyl anion creates the *trans*-alkene product.

Step 1: Electron Donation



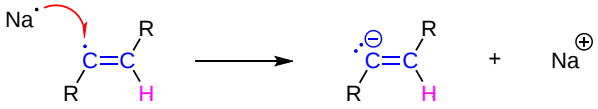
radical anion

Step 2: Protonation



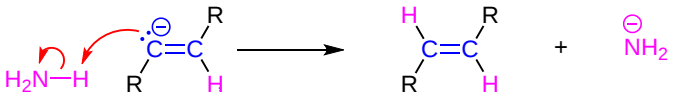
vinyl radical

Step 3: Electron Donation



trans -vinyl anion

Step 4: Protonation

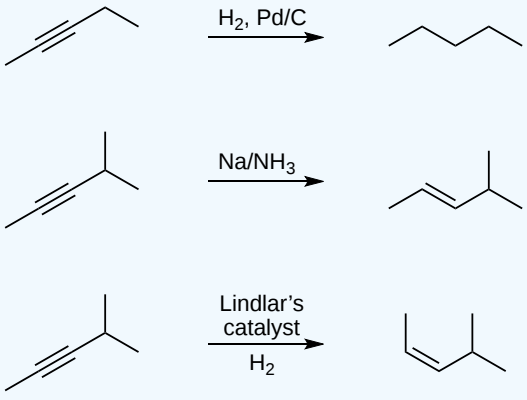


trans -alkene

? EXERCISE 9.5.1

Using any alkyne how would you prepare the following compounds: pentane, *trans*-4-methyl-2-pentene, *cis*-4-methyl-2-pentene.

Answer



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9.6: OXIDATIVE CLEAVAGE OF ALKYNES

OBJECTIVES

After completing this section, you should be able to

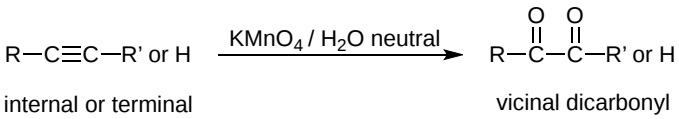
- write an equation to represent the oxidative cleavage of an alkyne with potassium permanganate or ozone.
- identify the products that result from the oxidative cleavage of a given alkyne.
- identify the reagents needed to carry out the oxidative cleavage of an alkyne.
- use the results of an oxidative cleavage to determine the identity of an alkyne of unknown structure.

STUDY NOTES

Compare the oxidative cleavage of alkynes with the oxidative cleavage of alkenes, discussed in Section 8.8.

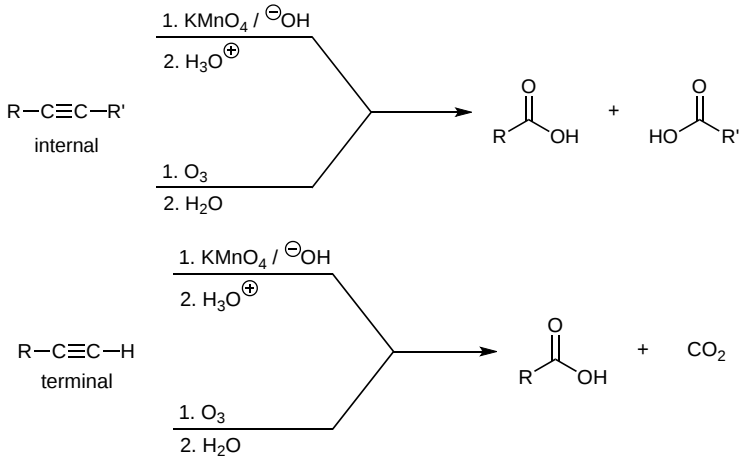
Alkynes, similar to alkenes, can be oxidized gently or strongly depending on the reaction environment. Since alkynes are less stable than alkenes, the reaction conditions can be gentler. For example, alkynes form vicinal dicarbonyls in neutral permanganate solution.

Gentle Alkyne Oxidation



Strong Alkyne Oxidation - Oxidative Cleavage

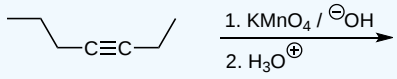
During strong oxidation with ozone or basic potassium permanganate, the alkyne is cleaved into two products. Because at least one of the reaction products is a carboxylic acid, it is important to consider the acid-base chemistry of the product in the reaction solution. Carboxylic acids are deprotonated in basic solutions to carboxylates. A second reaction step is required to protonate the carboxylate to the neutral form of the carboxylic acid.

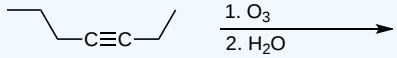


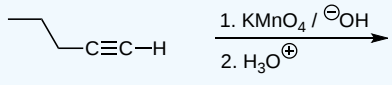
EXERCISE 9.6.1

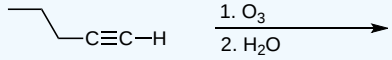
Draw the bond-line structures for the product(s) of the following reactions.

https://chem.libretexts.org/@go/page/31486

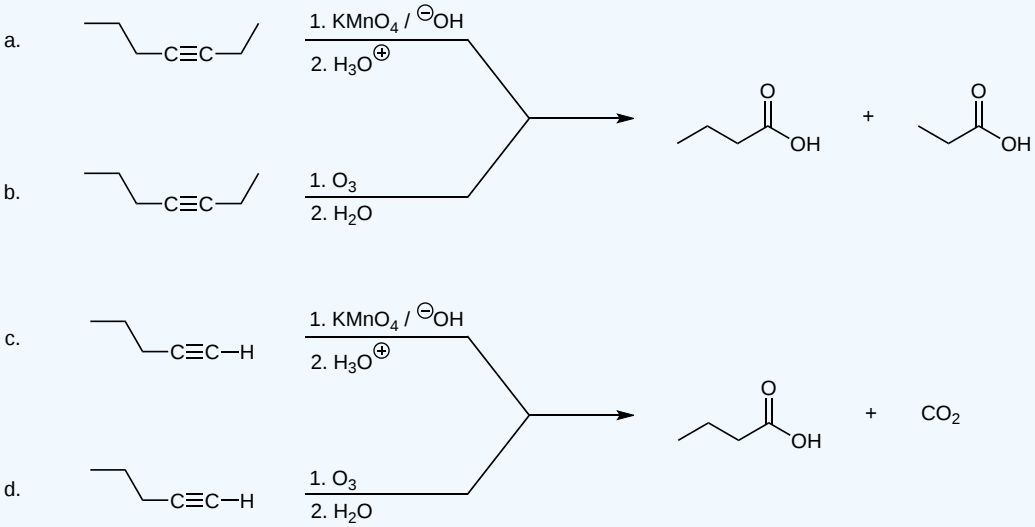
a. 

b. 

c. 

d. 

Answer



Oxidative cleavage of alkynes produces carboxylic acids and/or carbon dioxide. Aldehydes are not produced.

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9.7: ALKYNE ACIDITY - FORMATION OF ACETYLIDE ANIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation for the reaction that occurs between a terminal alkyne and a strong base, such as sodamide, $NaNH_2$.
2. rank a given list of compounds, including water, acetylene and ammonia, in order of increasing or decreasing acidity.
3. rank a given list of hydrocarbons, such as acetylene, ethylene and ethane, in order of increasing or decreasing acidity.
4. describe a general method for determining which of two given compounds is the stronger acid.
5. provide an acceptable explanation of why terminal alkynes are more acidic than alkanes or alkenes.

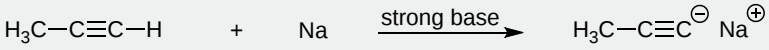
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acetylide anion
- acidity order

STUDY NOTES

An *acetylide anion* is an anion formed by removing the proton from the end carbon of a terminal alkyne:

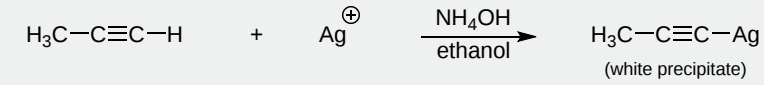


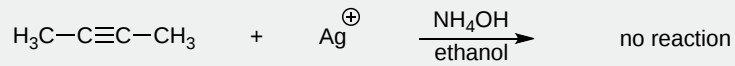
An *acidity order* is a list of compounds arranged in order of increasing or decreasing acidity.

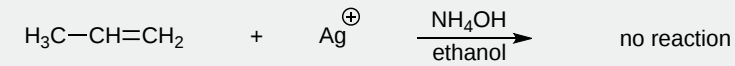
The general ideas discussed in this section should already be familiar to you from your previous exposure to chemistry and from the review in Section 2.8. A slightly different account of why terminal alkynes are stronger acids than are alkenes or alkanes is given below. However, the argument is still based on the differences between *sp*-, sp^2- and sp^3-hybrid orbitals.

The carbons of a triple bond are *sp*-hybridized. An *sp*-hybrid orbital has a 50% *s* character and a 50% *p* character, whereas an sp^2-hybrid orbital is 33% *s* and 67% *p*, and an sp^3-hybrid orbital is 25% *s* and 75% *p*. The greater the *s* character of the orbital, the closer the electrons are to the nucleus. Thus in a C(*sp*)-H bond, the bonding electrons are closer to the carbon nucleus than they are in a C(sp^2)-H bond. In other words, compared to a C(sp^2)-H bond (or a C(sp^3)-H bond), a C(*sp*)-H bond is very slightly polar: $C^{\delta-}$-$H^{\delta+}$. This slight polarity makes it easier for a base to remove a proton from a terminal alkyne than from a less polar or non-polar alkene or alkane.

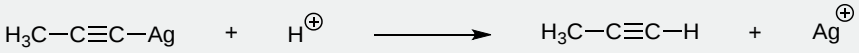
As you will appreciate, the reaction between sodium amide and a terminal alkyne is an acid-base reaction. The sodium acetylide product is, of course, a salt. Terminal alkynes can also form salts with certain heavy-metal cations, notably silver(I) and copper(I). In the laboratory component of this course, you will use the formation of an insoluble silver acetylide as a method for distinguishing terminal alkynes from alkenes and non-terminal alkynes:





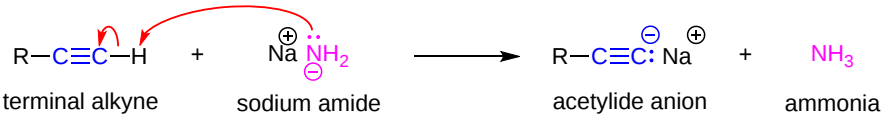


Metal acetylides are explosive when dry. They should be destroyed while still wet by warming with dilute nitric acid:

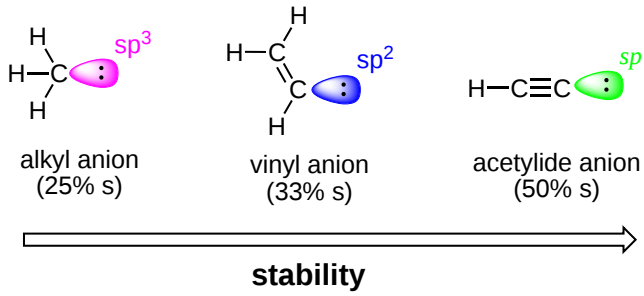


ACIDITY OF TERMINAL ALKYNES: FORMATION OF ACETYLIDE ANIONS

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the terminal proton leads to the formation of an acetylide anion, $RC{\equiv}C{:}^-$.



As discussed in Section 2.10, acidity typically increases with the stability of the corresponding conjugate base. The origin of the enhanced acidity of terminal alkynes can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals increases as the percent s character increases and follows the order sp > sp^2 > sp^3.



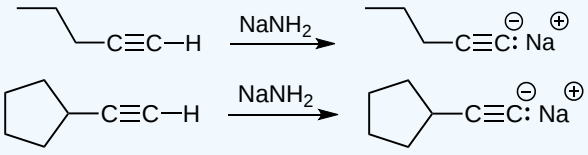
This trend indicates the sp hybridized orbitals of the acetylide anion are more electronegative and better able to stabilize a negative charge than sp^2 or sp^3 hybridized orbitals. There is a strong correlation between s-character in the orbital containing the non-bonding electrons in the anion and the acidity of hydrocarbons. The table below shows how orbital hybridization compares with the identity of the atom when predicting relative acidity. Remember that as the pK_a of a compound decreases its acidity increases.

Table **9.7.1**: Akynes

Compound	Conjugate Base	Hybridization	"s Character"	pKa	C-H BDE (kJ/mol)
CH_3CH_3	$CH_3CH_2^-$	sp^3	25%	50	410
CH_2CH_2	CH_2CH^-	sp^2	33%	44	473
HCCH	HCC^-	sp	50%	25	523

Acetylene, with a pK_a of 25 is shown to be much more acidic than ethylene (pK_a = 44) or ethane (pK_a = 50). Consequently, acetylide anions can be readily formed by deprotonation of a terminal alkynes with a sufficiently strong base. The amide anion (NH_2^-), in the form of sodium amide ($NaNH_2$) is commonly used for the formation of acetylide anions.

✔ EXAMPLE 9.7.1



? EXERCISE 9.7.1

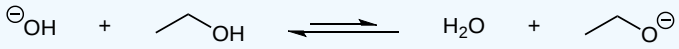
Given that the p*K*a of water is 14.00, would you expect hydroxide ion to be capable of removing a proton from each of the substances listed below? Justify your answers, briefly.

a. ethanol (p*K*a = 16)
b. acetic acid (p*K*a = 4.72)
c. acetylene (p*K*a = 25)

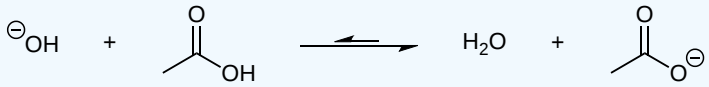
Answer

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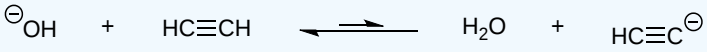
a. No, not very well. The p*K*a of ethanol is greater than that of water, thus the equilibrium lies to the left rather than to the right.Add texts here. Do not delete this text first.



b. Yes, very well. There is a difference of 11 p*K*a units between the p*K*a of water and the p*K*a of acetic acid. The equilibrium lies well to the right.



c. No, hardly at all. The hydroxide ion is too weak a base to remove a proton from acetylene. The equilibrium lies well to the left.



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9.8: ALKYLATION OF ACETYLIDE ANIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the reaction of an acetylide ion with an alkyl halide.
2. discuss the importance of the reaction between acetylide ions and alkyl halides as a method of extending a carbon chain.
3. identify the alkyne (and hence the acetylide ion) and the alkyl halide needed to synthesize a given alkyne.
4. determine whether or not the reaction of an acetylide ion with a given alkyl halide will result in substitution or elimination, and draw the structure of the product formed in either case.

KEY TERMS

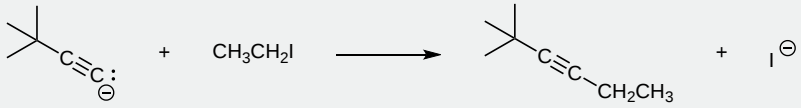
Make certain that you can define, and use in context, the key term below.

- alkylation

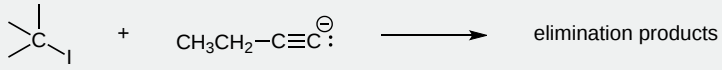
STUDY NOTES

The alkylation of acetylide ions is important in organic synthesis because it is a reaction in which a new carbon-carbon bond is formed; hence, it can be used when an organic chemist is trying to build a complicated molecule from much simpler starting materials.

The alkyl halide used in this reaction must be primary. Thus, if you were asked for a suitable synthesis of 2,2-dimethyl-3-hexyne, you would choose to attack iodoethane with the anion of 3,3- dimethyl-1-butyne



rather than to attack 2-iodo-2-methylpropane with the anion of 1-butyne.



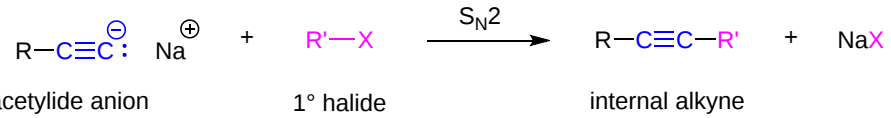
The reasons will be made clear in Chapter 11.

NUCLEOPHILIC SUBSTITUTION REACTIONS OF ACETYLIDES

The presence of lone pair electrons and a negative charge on a carbon, makes acetylide anions are strong bases and strong nucleophiles. Therefore, acetylide anions can attack electrophiles such as alkyl halides to cause a substitution reaction. These substitution reactions will be discussed in detail in **Chapter 11**.

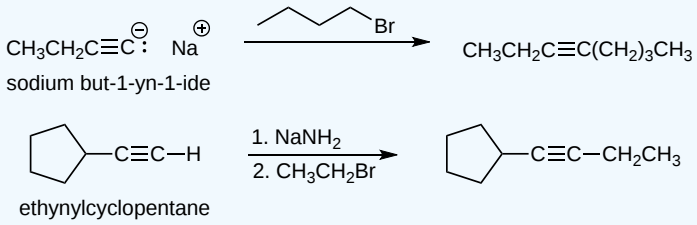
MECHANISM

The C-X bonds in 1º alkyl halides are polarized due to the high electronegativity of the halogen. The electrons of the C-X sigma bond are shifted towards the halogen giving it a partial negative charge. This also causes electrons to be shifted away from the carbon giving it a partial positive and making it electrophilic. During this reaction, the lone pair electrons on the acetylide anion attack the electrophilic carbon in the 1º alkyl halide forming a new C-C bond. The formation of this new bond causes the expulsion of the halogen as what is called a leaving group. Overall, this reaction forms a C-C bond and converts a terminal alkyne into a internal alkyne. Because a new alkyl group is added to the alkyne during this reaction, it is commonly called an alkylation.

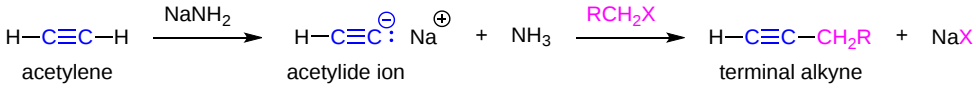


This substitution reaction is often coupled with the acetylide formation, discussed in the previous section, and shown as a single reaction.

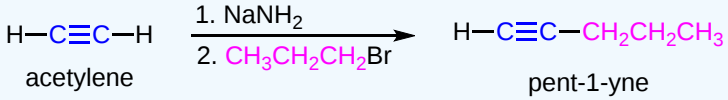
EXAMPLE 9.8.1



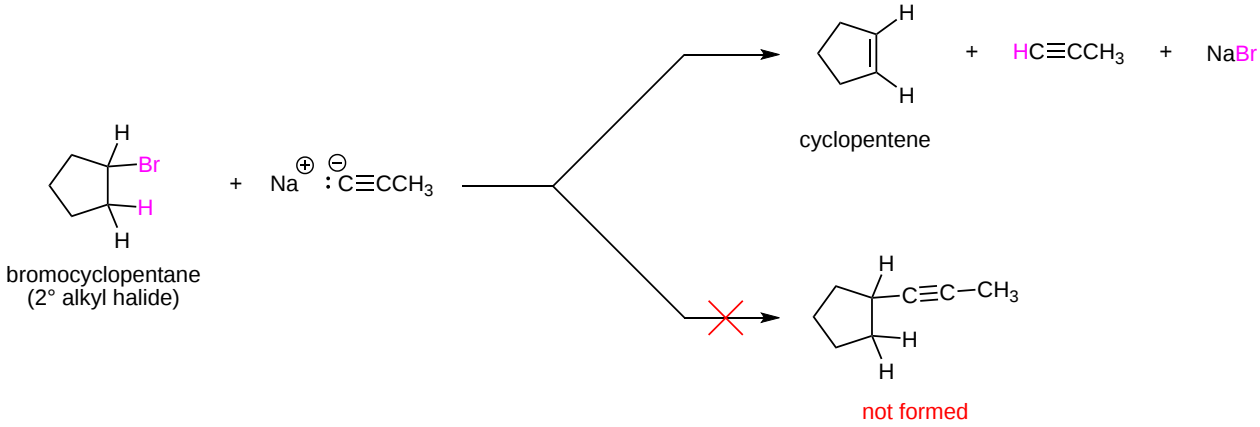
Terminal alkynes can be generated through the reaction of acetylene and a 1° alkyl halide.



EXAMPLE 9.8.2

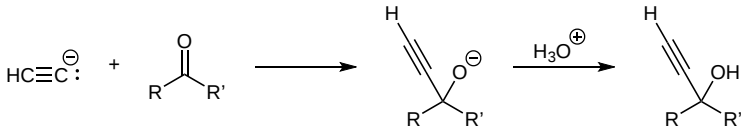


Because the acetylide anion is a very strong base, this substitution reaction is most efficient with methyl or primary halides. Secondary, tertiary, or even bulky primary halogens will give alkenes by the E2 elimination mechanism discussed in **Section 11.10**. An example of this effect is seen in the reaction of bromocyclopentane with a propyne anion. The reaction produces the elimination product cyclopentene rather than the substitution product 1-propynylcyclopentane.



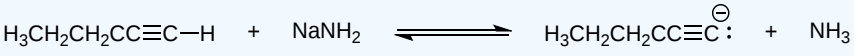
NUCLEOPHILIC ADDITION OF ACETYLIDES TO CARBONYLS

Acetylide anions also add to the electrophilic carbon in aldehydes and ketones to form alkoxides, which, upon protonation, give propargyl alcohols. With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers. These types of reaction will be discussed in more detail in **Chapter 19**.



EXERCISE 9.8.1

The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by sodium amide, as shown below.

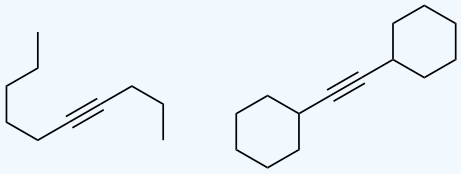


Answer

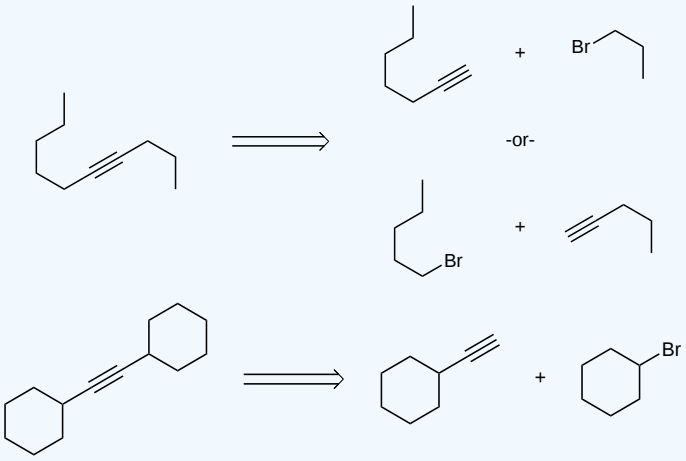
Assuming the pK_a of pent-1-yne is about 25, then the difference in pK_as is 10. Since pentyne is more acidic, the formation of the acetylide will be favored at equilibrium, so the equilibrium constant for the reaction is about 10^{10}.

EXERCISE 9.8.2

Give the possible reactants which could form the following molecules by an alkylation.



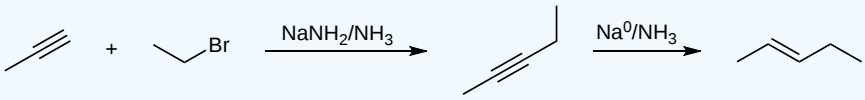
Answer



EXERCISE 9.8.3

Propose a synthetic route to produce 2-pentene from propyne and an alkyl halide.

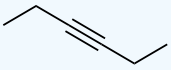
Answer



EXERCISE 9.8.4

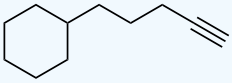
Using acetylene as the starting material, show how you would synthesize the following compounds

a)

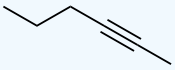


b) but-2-yne

c)

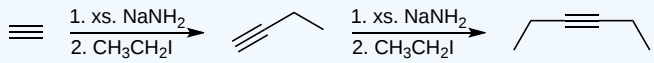


d)



Answer

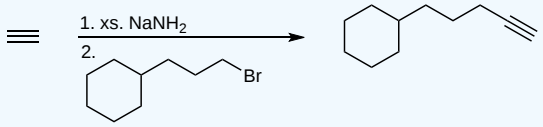
a)



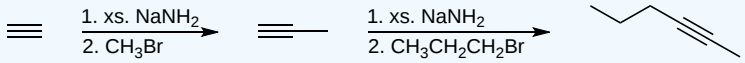
b)



c)

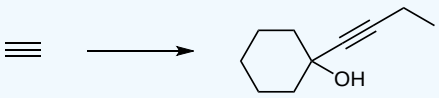


d)

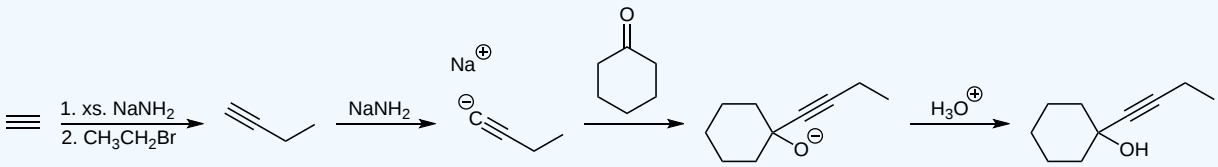


? EXERCISE 9.8.5

Show how you would accomplish the following synthetic transformation.



Answer



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9.9: AN INTRODUCTION TO ORGANIC SYNTHESIS

OBJECTIVE

After completing this section, you should be able to design a multistep synthesis to prepare a given product from a given starting material, using any of the reactions introduced in the textbook up to this point.

STUDY NOTES

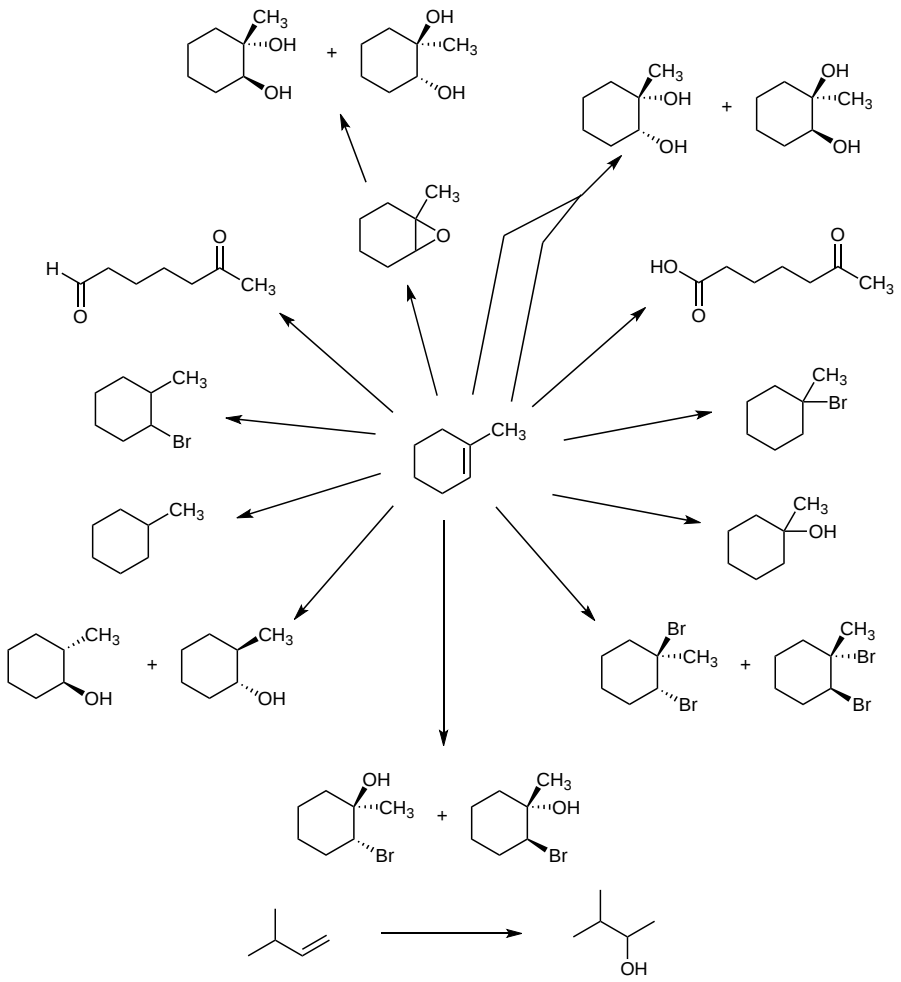
You should have noticed that some of the assigned problems have required that you string together a number of organic reactions to convert one organic compound to another when there is no single reaction to achieve this goal. Such a string of reactions is called an "organic synthesis." One of the major objectives of this course is to assist you in designing such syntheses. To achieve this objective, you will need to have all of the reactions described in the course available in your memory. You will need to recall some reactions much more frequently than others, and the only way to master this objective is to practise. The examples given in this chapter will be relatively simple, but you will soon see that you can devise some quite sophisticated syntheses using a limited number of basic reactions.

INTRODUCTION

The study of organic chemistry introduces students to a wide range of interrelated reactions. Alkenes, for example, may be converted to structurally similar alkanes, alcohols, alkyl halides, epoxides, glycols and boranes; cleaved to smaller aldehydes, ketones and carboxylic acids; and enlarged by carbocation and radical additions as well as cycloadditions. Most of these reactions are shown in the Alkene Reaction Map below. All of these products may be subsequently transformed into a host of new compounds incorporating a wide variety of functional groups. Consequently, the logical conception of a multi-step synthesis for the construction of a designated compound from a specified starting material becomes one of the most challenging problems that may be posed. Functional group reaction maps like the one below for alkenes can be helpful in designing multi-step syntheses. It can be helpful to build and design your own reaction maps for each functional group studied.

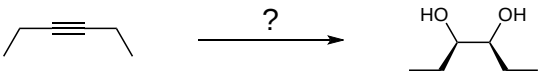
ALKENE REACTION MAP

Please note: The reagents for each chemical transformation have been intentionally omitted so that this map can be used as a study tool. The answers are provided at the end of this section as part of the exercises.

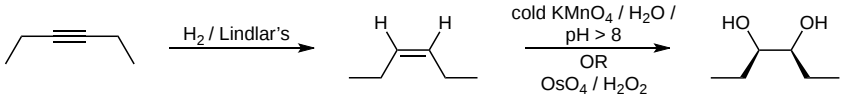


SIMPLE MULTI-STEP SYNTHESES

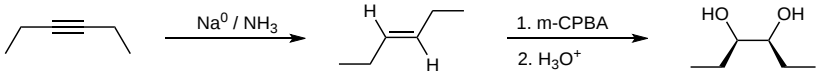
A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.



One approach would be to reduce the alkyne to cis or trans-3-hexene before undertaking glycol formation. Permanaganate or osmium tetroxide hydroxylation of cis-3-hexene would form the desired meso isomer.



From trans-3-hexene, it would be necessary to first epoxidize the alkene with a peracid followed by ring opening with acidic or basic hydrolysis.

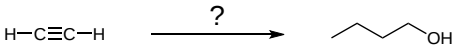


Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope and limitations constraining each of the individual reactions being employed. The skill is acquired by practice, experience, and often trial and error.

THINKING IT THROUGH WITH 3 EXAMPLES

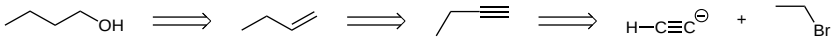
The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. Retro-synthesis is the approach of working backwards from the product to the starting material.

In the first example, we are asked to synthesize 1-butanol from acetylene.

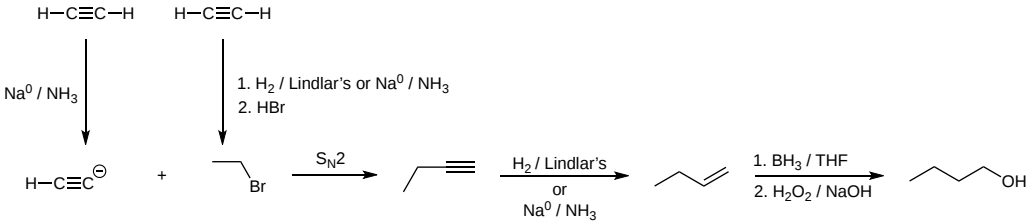


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.

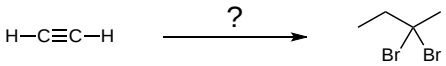
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation identified from the retro-synthesis. The ethylbromide must also be derived from acetylene so multiple reaction pathways are combined as shown below.

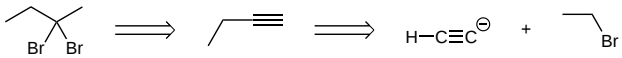


In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.

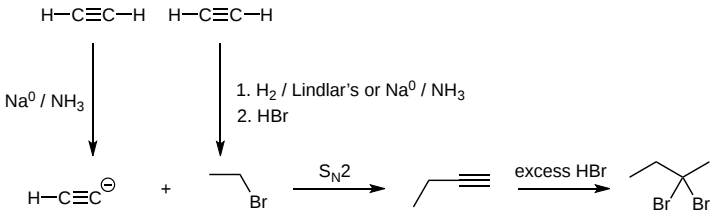


Once again there is an increase in the carbon chain length indicating an acetylide S_N2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne with 1,2-dibromobutane, there is a difference of two H atoms and two Br atoms indicating hydrohalogenation and not halogenation. The addition of both bromine atoms to the same carbon atom also supports the idea that hydrohalogenation occurs on an alkyne and not an alkene. The formation of the geminal dihalide also indicates hydrohalogenation instead of halogenation because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

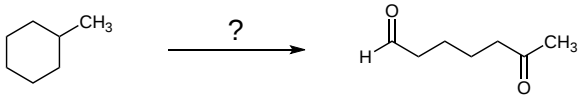
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.



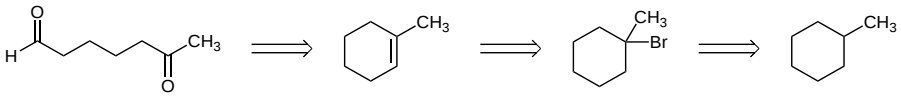
In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.



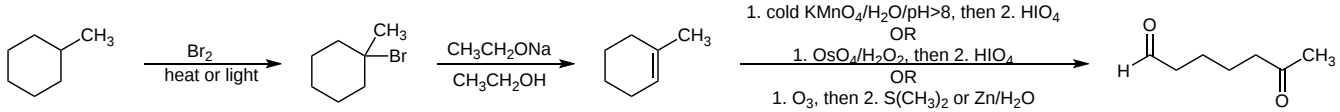
Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We

can burn them as fuel or perform free-radical halogenation to create alkyl halides with excellent leaving groups. With these observations, the following retro-synthesis is reasonable.

Retro-Synthesis



Working forwards, we specify the reagents needed for each reaction. For the initial free-radical halogenation of the alkane, we have the option of chlorine (Cl_2) or bromine (Br_2). Because methylcyclohexane has several different classifications of carbons, the selectivity of Br_2 is more important than the faster reactivity of Cl_2. A strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldehyde group on the final product indicates gentle oxidative cleavage by any of several reaction pathways. These reactions can be combined in to the following multi-step synthesis.

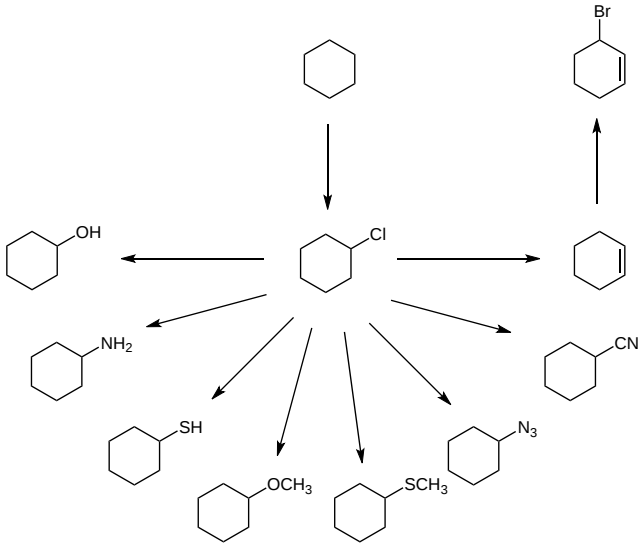


REACTION MAPS TO BUILD FUNCTIONAL GROUP CONVERSION MASTERY

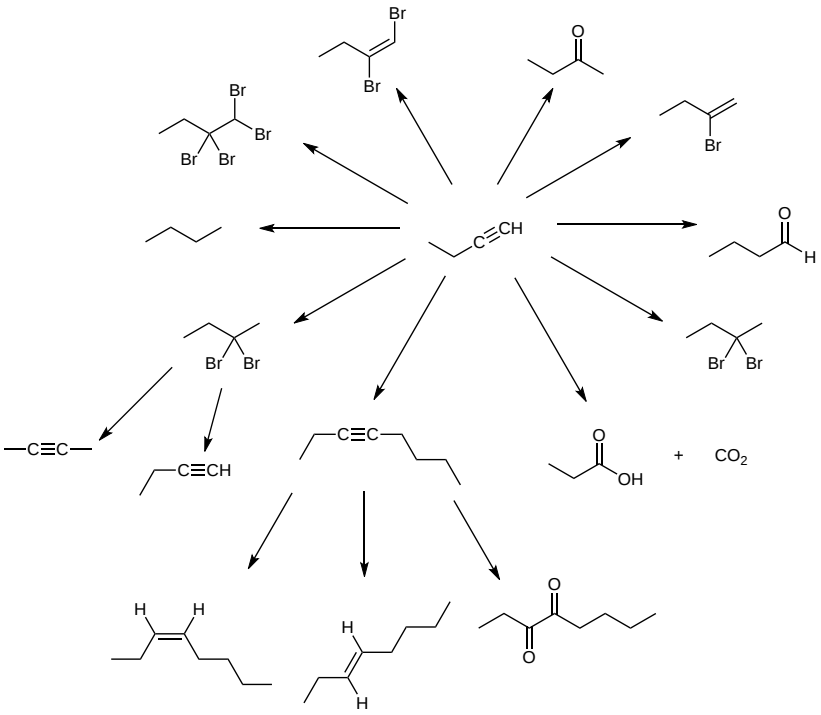
After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

Please note: The reagents for each chemical transformation have been intentionally omitted so that these maps can be used as a study tools. The answers are provided at the end of this section as part of the exercises.

ALKANE AND ALKYL HALIDE REACTION MAP



ALKYNE REACTION MAP



EXERCISE

1) Starting at 3-hexyne predict synthetic routes to achieve:

a) trans-3-hexene

b) 3,4-dibromohexane

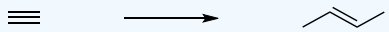
c) 3-hexanol.

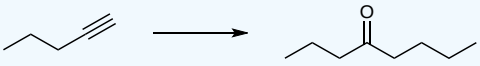
2) Starting with acetylene and any alkyl halides propose a synthesis to make

a) pentanal

b) hexane.

3) Show how you would accomplish the following synthetic transformations.

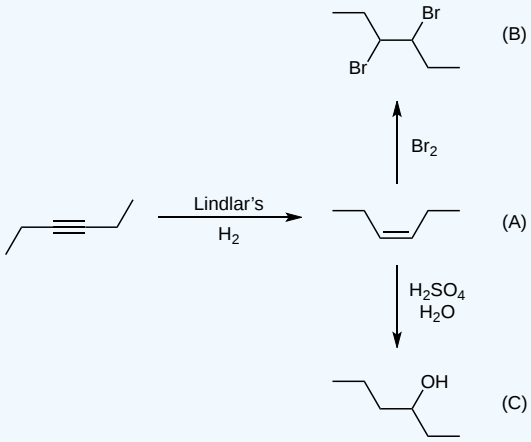
a) 

b) 

Answer

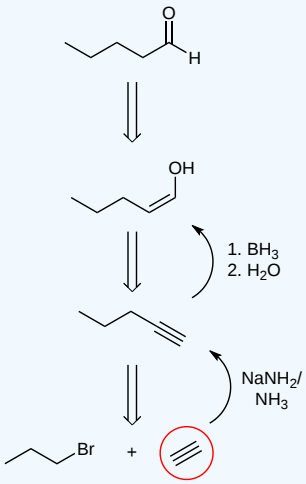
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1)

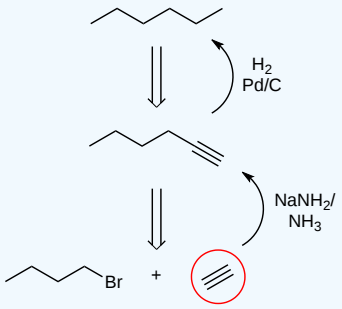


2)

a)

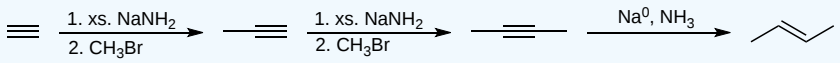


b)

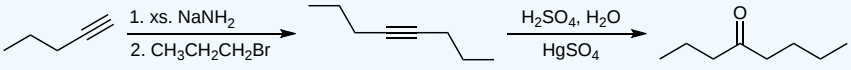


3)

a)



b)



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9.S: ALKYNES - AN INTRODUCTION TO ORGANIC SYNTHESIS (SUMMARY)

CONCEPTS & VOCABULARY

9.1 Naming Alkynes

- Follow IUPAC rules in naming alkynes.

9.2 Preparation of Alkynes - Elimination Reactions of Dihalides

- **Vicinal** describes two groups on adjacent carbon atoms.
- **Geminal** describes two groups on the same carbon atom.
- Alkynes can be prepared by two successive eliminations of HX from either **vicinal** or **geminal** dihalides.

9.3 Reactions of Alkynes - Addition of HX and X_2

- **Alkynes** undergo addition reactions similarly to alkenes yielding Markovnikov products.

9.4 Hydration of Alkynes

- Enols have a hydroxyl group bonded to a sp^2 hybrid carbon (double-bonded carbon).
- Enols are usually not stable and undergo **keto-enol tautomerization** to form a ketone or aldehyde.
- Hydration of alkynes leads to an enol product which then rapidly tautomerizes into a ketone or aldehyde.

9.5 Reduction of Alkynes

- Alkynes can be hydrogenated with hydrogen gas and strong catalysts to yield alkanes.
- Alkynes can be hydrogenated with hydrogen gas and Lindlar's catalyst to yield Z alkenes.
- Alkynes can be hydrogenated with sodium metal and liquid ammonia to yield E alkenes.

9.6 Oxidative Cleavage of Alkynes

- Oxidative cleavage of internal alkynes forms two molecules of carboxylic acids.
- Oxidative cleavage of terminal alkynes forms one molecule of carbon dioxide and one carboxylic acid.

9.7 Alkyne Acidity - Formation of Acetylide Anions

- Terminal alkynes are relatively acidic compared to alkene and alkane carbon-hydrogen bonds.
- Deprotonation of a terminal alkyne forms an acetylide ion, which is a good nucleophile.

9.8 Alkylation of Acetylide Anions

- Acetylide ions can be alkylated by adding to alkyl halides and carbonyl compounds.

9.9 An Introduction to Organic Synthesis

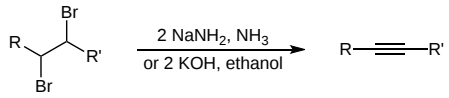
- Desired products cannot always be made from available starting materials through one reaction. Formation of these materials may require multiple reactions completed in sequence. This type of reaction sequence is termed synthesis.

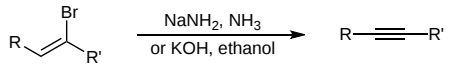
SKILLS TO MASTER

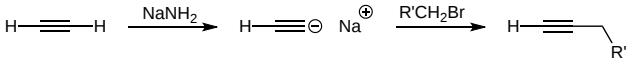
- Skill 9.1 Use IUPAC rules to accurately name alkynes.
- Skill 9.2 Draw elimination mechanisms to form alkynes.
- Skill 9.3 Draw addition mechanisms to alkynes incorporating carbocation intermediates.
- Skill 9.4 Draw addition mechanisms to alkynes incorporating halonium intermediates.
- Skill 9.5 Describe relative stability of enols to ketones and aldehydes.
- Skill 9.6 Draw keto-enol tautomerism mechanism.
- Skill 9.7 Draw products that differentiate between multiple reduction reactions of alkynes.
- Skill 9.8 Draw products of oxidative cleavage of alkynes.
- Skill 9.9 Draw mechanism for deprotonation of terminal alkynes.
- Skill 9.10 Compare acidity of terminal alkynes with other organic compounds.
- Skill 9.11 Draw reaction mechanisms using acetylide ions as nucleophiles.
- Skill 9.12 Describe schemes to accomplish synthesis of organic products given a starting material.

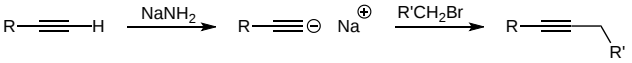
SUMMARY OF REACTIONS

Preparation of Alkynes

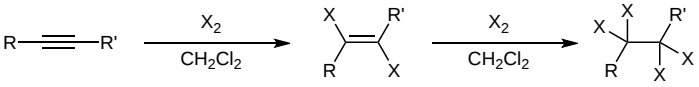


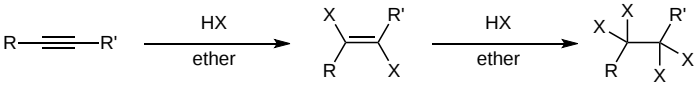


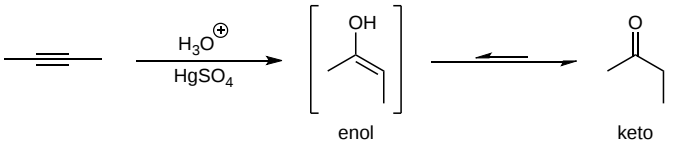


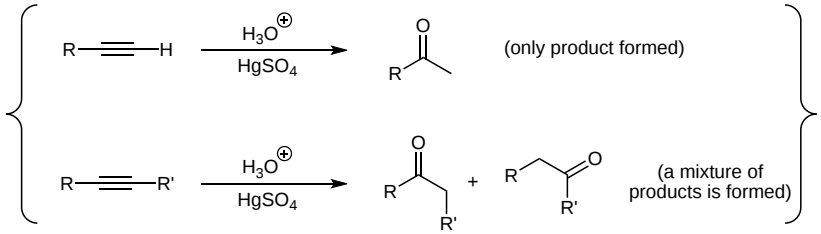


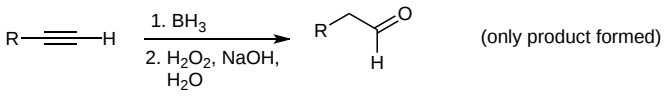
Reactions of Alkynes

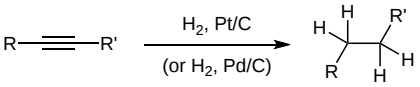


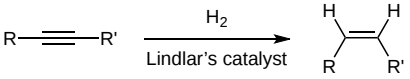


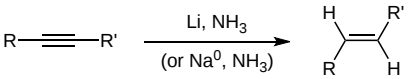












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CHAPTER OVERVIEW

10: ORGANOHALIDES

LEARNING OBJECTIVES

After you have completed Chapter 10, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design a multistep synthesis to prepare a given compound from a given starting material using any of the reactions studied up to this point in the course, including those which involve alkyl halides.
- solve road-map problems requiring a knowledge of any of the reactions or concepts studied up to this point, including those introduced in this chapter.
- define, and use in context, the key terms introduced.

10.0: Introduction to Organohalides
10.1: Names and Properties of Alkyl Halides
10.2: Preparing Alkyl Halides from Alkanes - Radical Halogenation
10.3: Preparing Alkyl Halides from Alkenes - Allylic Bromination
10.4: Stability of the Allyl Radical - Resonance Revisited
10.5: Preparing Alkyl Halides from Alcohols
10.6: Reactions of Alkyl Halides - Grignard Reagents
10.7: Organometallic Coupling Reactions
10.8: Oxidation and Reduction in Organic Chemistry
10.S: Organohalides (Summary)

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10.0: INTRODUCTION TO ORGANOHALIDES

OBJECTIVES

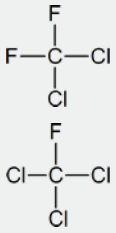
After completing this section, you should be able to

1. list the industrial uses of some important halogenated hydrocarbons including 1,1,1-trichloroethane, tetrafluoroethylene and dichlorodifluoromethane.
2. outline, briefly, how the chemistry of vinyl halides and aryl halides differs from that of the alkyl halides discussed.

STUDY NOTES

There are several different types of halogen-substituted organic compounds, including aryl halides, acyl halides, vinyl halides and alkynyl halides. The primary focus of this chapter is on alkyl halides.

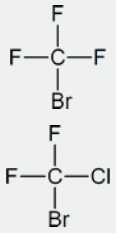
Freons™, also called fluorocarbons or chlorofluorocarbons, have been a source of concern to environmentalists since 1974, when Frank S. Rowland and Mario J. Molina suggested that these substances might be contributing to the destruction of Earth's ozone layer. The stratospheric ozone layer filters out much of the ultraviolet radiation from the sun's rays. It is believed that extensive depletion of this layer, and the consequent increase in the amount of ultraviolet radiation reaching Earth, could result in the destruction of certain crops, in climate modification, and in an increase in the incidence of skin cancer. In recent years, the manufacture and use of freons has declined sharply as the general public has become more aware of the problems that might be caused by these substances.



Note: "Freon" is a DuPont trademark.

Related to the freons are the halons—now used in some fire extinguishers, particularly in areas where foams or dry-chemical extinguishers cannot be used (e.g., in and around computers). If you examine such extinguishers, you will find that the halon is identified by a number; for example, halon 1301 or halon 1211. The first number represents the number of carbon atoms present, the second is the number of fluorines, the third is the number of chlorines and the fourth is the number of bromines.

Thus the halons given as examples above have the following structures:



You need not remember the names of the various freons and halons, but you should be prepared to name them by the IUPAC system according to the rules developed in the next section.

Many organic compounds are closely related to the alkanes. Alkanes react with halogens to produce halogenated hydrocarbons, the simplest of which have a single halogen atom substituted for a hydrogen atom of the alkane. Even more closely related are the cycloalkanes, compounds in which the carbon atoms are joined in a ring, or cyclic fashion.

The reactions of alkanes with halogens produce **halogenated hydrocarbons**, compounds in which one or more hydrogen atoms of a hydrocarbon have been replaced by halogen atoms:



The replacement of only one hydrogen atom gives an **alkyl halide (or haloalkane)**. A wide variety of interesting and often useful compounds have one or more halogen atoms per molecule. For example, methane (CH_4) can react with chlorine (Cl_2), replacing one, two,

three, or all four hydrogen atoms with Cl atoms. Several halogenated products derived from methane and ethane (CH_3CH_3) are listed in Table 10.1, along with some of their uses.

Table 10.1: Some Halogenated Hydrocarbons

Formula	Common Name	IUPAC Name	Some Important Uses
Derived from CH_4			
CH_3Cl	methyl chloride	chloromethane	refrigerant; the manufacture of silicones, methyl cellulose, and synthetic rubber
CH_2Cl_2	methylene chloride	dichloromethane	laboratory and industrial solvent
$CHCl_3$	chloroform	trichloromethane	industrial solvent
CCl_4	carbon tetrachloride	tetrachloromethane	dry-cleaning solvent and fire extinguishers (but no longer recommended for use)
$CBrF_3$	halon-1301	bromotrifluoromethane	fire extinguisher systems
CCl_3F	chlorofluorocarbon-11 (CFC-11)	trichlorofluoromethane	foaming plastics
CCl_2F_2	chlorofluorocarbon-12 (CFC-12)	dichlorodifluoromethane	refrigerant
Derived from CH_3CH_3			
CH_3CH_2Cl	ethyl chloride	chloroethane	local anesthetic
$ClCH_2CH_2Cl$	ethylene dichloride	1,2-dichloroethane	solvent for rubber
CCl_3CH_3	methylchloroform	1,1,1-trichloroethane	solvent for cleaning computer chips and molds for shaping plastics

TO YOUR HEALTH: HALOGENATED HYDROCARBONS

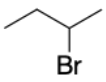
Once widely used in consumer products, many chlorinated hydrocarbons are suspected carcinogens (cancer-causing substances) and also are known to cause severe liver damage. An example is carbon tetrachloride (CCl_4), once used as a dry-cleaning solvent and in fire extinguishers but no longer recommended for either use. Even in small amounts, its vapor can cause serious illness if exposure is prolonged. Moreover, it reacts with water at high temperatures to form deadly phosgene ($COCl_2$) gas, which makes the use of CCl_4 in fire extinguishers particularly dangerous.

Ethyl chloride, in contrast, is used as an external local anesthetic. When sprayed on the skin, it evaporates quickly, cooling the area enough to make it insensitive to pain. It can also be used as an emergency general anesthetic.

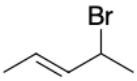
Bromine-containing compounds are widely used in fire extinguishers and as fire retardants on clothing and other materials. Because they too are toxic and have adverse effects on the environment, scientists are engaged in designing safer substitutes for them, as for many other halogenated compounds.

REACTIVITY OF HALIDES

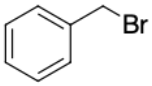
Alkyl halides have an sp^3 carbon atom with a halogen attached, this is also true for allylic halides and benzylic halides. These types of halides are all reactive toward most substitution and elimination reactions. Allyl and benzyl halides tend to form carbocations more easily due to resonance stabilization.



alkyl halide



allyl halide

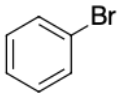


benzyl halide

However, halogens bonded to sp^2 carbon atoms are not typically reactive. Examples of this are vinyl and aryl halides.



vinyl halide



aryl halide

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10.1: NAMES AND PROPERTIES OF ALKYL HALIDES

OBJECTIVES

After completing this section, you should be able to

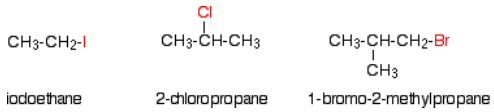
1. write the IUPAC name of a halogenated aliphatic hydrocarbon, given its Kekulé, condensed, or shorthand structure.
2. draw the Kekulé, condensed, or shorthand structure of a halogenated aliphatic hydrocarbon, given its IUPAC name.
3. write the IUPAC name and draw the Kekulé, condensed, or shorthand structure of a simple alkyl halide, given a systematic, non-IUPAC name (e.g., *sec*-butyl iodide).
4. arrange a given series of carbon-halogen bonds in order of increasing or decreasing length and strength.

STUDY NOTES

This section contains little that is new. If you mastered the IUPAC nomenclature of alkanes, you should have little difficulty in naming alkyl halides. Notice that when a group such as CH_2Br must be regarded as a substituent, rather than as part of the main chain, we may use terms such as bromomethyl.

You will find it easier to understand the reactions of the alkyl halides if you keep the polarity of the C-X bond fixed permanently in your mind (see "The Polar C-X Bond" shown in the reading below).

Alkyl halides are also known as haloalkanes. This page explains what they are and discusses their physical properties. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine or iodine). For example:

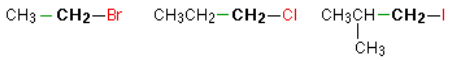


HALIDE DESIGNATIONS

Alkyl halides fall into different classes depending on how many alkyl groups are attached to the carbon which holds the halogen. There are some chemical differences between the various types. When there are **no** alkyl groups attached to the carbon holding the halogen, these are considered methyl halides (CH_3X).

PRIMARY ALKYL HALIDES

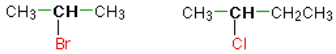
In a primary (1°) haloalkane, the carbon which carries the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

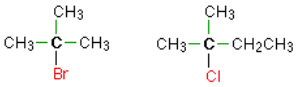
SECONDARY ALKYL HALIDES

In a secondary (2°) haloalkane, the carbon with the halogen attached is joined directly to two other alkyl groups, which may be the same or different. Examples:



TERTIARY ALKYL HALIDES

In a tertiary (3°) haloalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



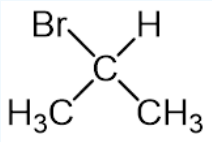
EXAMPLE 10.1.1

Please indicate if the following haloalkanes are methyl, 1°, 2°, or 3°:

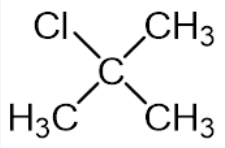
a) CH_3I

b) CH_3CH_2Br

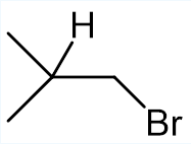
c)



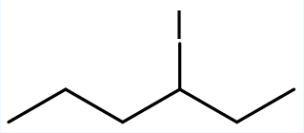
d)



e)



f)



Solution

a) methyl

b) 1°

c) 2°

d) 3°

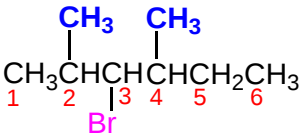
e) 1°

f) 2°

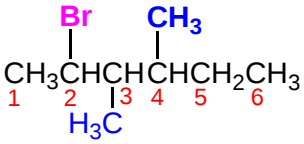
NOMENCLATURE OF ALKYL HALIDES

Alkyl halides are systematically named as alkanes (Section 3-4) where the halogen is a substituent on the parent alkane chain. To summarize the rules discussed in detail in **Section 3-4**, there are three basic steps to naming alkyl halides.

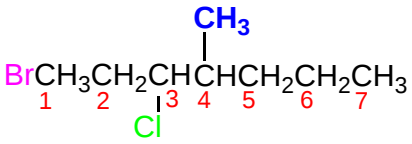
1. Find and name the longest carbon chain and name it as the parent chain. Remember is an alkene or alkyne is present, the parent chain must contain both carbons of the multiple bond.
2. Number the parent chain consecutively, starting at the end nearest a substituent group. Then assign each substituent a number. Remember the IUPAC system uses a prefix to indicate the halogen followed by the suffix -ide. The prefixes are *fluoro-* for fluorine, *chloro-* for chlorine, *bromo-* from bromine, and *iodo-* for iodine. The name of a halogen is preceded by a number indicating the substituent's location on the parent chain.



3-Bromo-2,4-Dimethylhexane

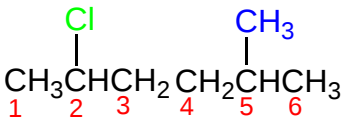


2-Bromo-3,4-Dimethylhexane



1-Bromo-3-Chloro-4-methylheptane

3. If there is an ambiguity in numbering the parent chain, begin on the end which is closer to the substituent which comes first alphabetically.

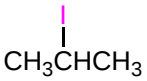


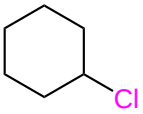
2-Chloro-5-methylhexane
(Not 5-Chloro-2-methylhexane)

COMMON NAMES OF ALKYL HALIDES

Alkyl halides with simple alkyl groups are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names. The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the first syllable of the name of the halogen, with the ending *-ide*. The names of common alkyl groups are listed in Section 3.3.







IUPAC Name:	Bromomethane	2-Iodopropane	Chlorocyclohexane
Common Name:	Methyl bromide	Isopropy iodide	Cyclohexyl chloride

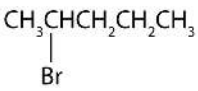
? EXERCISE 10.1.1

1) Give the common and IUPAC names for each compound.

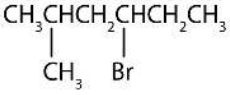
a. $CH_3CH_2CH_2Br$
b. $(CH_3)_2CHCl$
c. CH_3CH_2I
d. $CH_3CH_2CH_2CH_2F$

2) Give the IUPAC name for each compound.

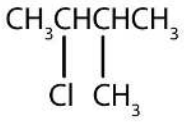
a)



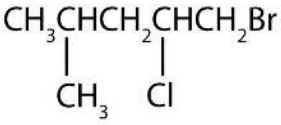
b)



c)



d)



Answer

1) a) The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.

b) The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro*-) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

c) The alkyl group (CH_3CH_2–) is a ethyl group, and the halogen is iodine (I). The common name is therefore ethyl iodide. For the IUPAC name, the prefix for iodine (iodo) is combined with the name for a two-carbon chain (ethane), preceded by a number identifying the carbon atom to which the I atom is attached, so the IUPAC name is 1-iodoethane.

d) The alkyl group ($CH_3CH_2CH_2CH_2$–) is a butyl group, and the halogen is fluorine (F). The common name is therefore butyl fluoride. For the IUPAC name, the prefix for fluorine (Fluoro) is combined with the name for a four-carbon chain (butane), preceded by a number identifying the carbon atom to which the F atom is attached, so the IUPAC name is 1-fluorobutane.

2) a) The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.

b) The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

c) 2-Chloro-3-methylbutane

d) 1-Bromo-2-chloro-4-methylpentane.

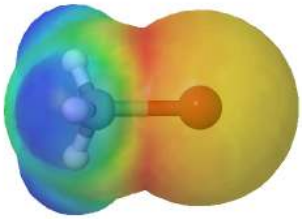
There is a fairly large distinction between the structural and physical properties of haloalkanes and the structural and physical properties of alkanes. As mentioned above, the structural differences are due to the replacement of one or more hydrogens with a halogen atom. The differences in physical properties are a result of factors such as electronegativity, bond length, bond strength, and molecular size.

HALOGENS AND THE CHARACTER OF THE CARBON-HALOGEN BOND

As discussed in Section 6.4, halogens are more electronegative than carbon. This results in a carbon-halogen bond that is polarized with the carbon atom bearing a partial positive charge and the halogen a partial negative charge. This polarity can be distinctly seen when viewing the electrostatic potential map of a methyl halide. Electron density is shown by a red/yellow color which is almost exclusively around the halogen atom. The methyl portion of the compound lacks electron density which is shown by a blue/green color.

The Polar C-X Bond





The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

Electronegativity	I	<	Br	<	Cl	< F

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases, the bonds get longer, and the strength of those bonds decreases.

Bond length	C-F	<	C-Cl	<	C-Br	< C-I
Bond strength	C-I	<	C-Br	<	C-Cl	< C-F
Molecular size	F	<	Cl	<	Br	< I

HALOALKANES HAVE HIGHER BOILING POINTS THAN ALKANES

When comparing alkanes and haloalkanes, we will see that haloalkanes have higher boiling points than alkanes containing the same number of carbons. London dispersion forces are the first of two types of forces that contribute to this physical property. You might recall from general chemistry that London dispersion forces increase with molecular surface area. In comparing haloalkanes with alkanes, haloalkanes exhibit an increase in surface area due to the substitution of a halogen for hydrogen. The increase in surface area leads to an increase in London dispersion forces, which then results in a higher boiling point.

Dipole-dipole interaction is the second type of force that contributes to a higher boiling point. As you may recall, this type of interaction is a coulombic attraction between the partial positive and partial negative charges that exist between carbon-halogen bonds on separate haloalkane molecules. Similar to London dispersion forces, dipole-dipole interactions establish a higher boiling point for haloalkanes in comparison to alkanes with the same number of carbons.

Dipole-Dipole Interaction

$$\overset{\delta^+}{C}-\overset{\delta^-}{X}\cdots\overset{\delta^+}{C}-\overset{\delta^-}{X}$$

The table below illustrates how boiling points are affected by some of these properties. Notice that the boiling point increases when hydrogen is replaced by a halogen, a consequence of the increase in molecular size, as well as an increase in both London dispersion forces and dipole-dipole attractions. The boiling point also increases as a result of increasing the size of the halogen, as well as increasing the size of the carbon chain.

Boiling Points of Haloalkanes (°C)

R	X = H	F	Cl	Br	I
CH_3	-161.7	-78.4	-24.2	3.6	42.4
CH_3CH_2	-88.6	-37.7	12.3	38.4	72.3
$CH_3(CH_2)_2$	-42.1	-2.5	46.6	71.0	102.5
$CH_3(CH_2)_3$	-0.5	32.5	78.4	101.6	130.5
$CH_3(CH_2)_4$	36.1	62.8	107.8	129.6	157.0
$CH_3(CH_2)_7$	125.7	142.0	182.0	200.3	225.5

SOLUBILITY

SOLUBILITY IN WATER

The alkyl halides are at best only slightly soluble in water. For a haloalkane to dissolve in water the attractions between the haloalkane molecules (van der Waals dispersion and dipole-dipole interactions) and hydrogen bonds between water molecules must be broken. Both of these cost energy. Energy is released when new intermolecular forces are generated between the haloalkane molecules and water molecules. These will only be dispersion forces and dipole-dipole interactions. These are not as strong as the original hydrogen bonds in the water, and

so not as much energy is released as was used to separate the water molecules. The energetics of the changes are sufficiently "unprofitable" such that very little dissolves.

SOLUBILITY IN ORGANIC SOLVENTS

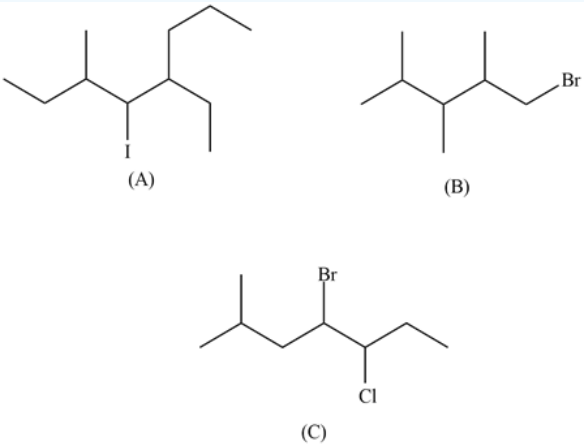
Alkyl halides tend to dissolve in organic solvents because the new intermolecular attractions have roughly the same strength as the ones being broken in the separate haloalkane and solvent.

CHEMICAL REACTIVITY

The pattern in chemical reactiviy lies in the strength of the bond between the carbon atom and the halogen atom. Previously in this section, it was noted that the trend for bond strength increases from C-I to C-Br to C-Cl with C-F bonds being the strongest. To react with the alkyl halides, the carbon-halogen bond has got to be broken. Because that gets easier as you go from fluoride to chloride to bromide to iodide, the compounds get more reactive in that order. Iodoalkanes are the most reactive and fluoroalkanes are the least. In fact, fluoroalkanes are so unreactive that we will ignore them completely from now on in this section!

? EXERCISE 10.1.2

1) Give the names of the following organohalides:



2) Draw the structures of the following compounds:

a) 2-Chloro-3,3-dimethylpentane

b) 1,1-Dichloro-4-isopropylcyclohexane

c) 3-bromo-3-ethylhexane

Answer

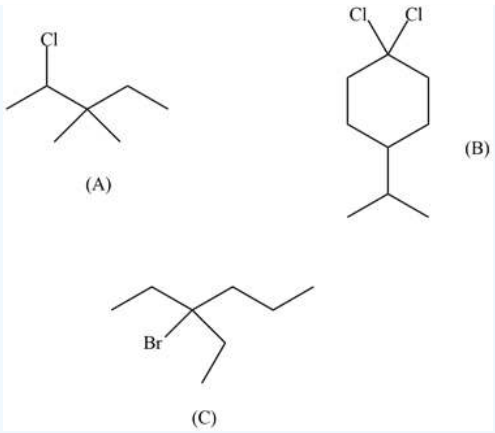
1)

a) 5-ethyl-4-iodo-3-methyloctane

b) 1-bromo-2,3,4-trimethylpentane

c) 4-bromo-5-chloro-2-methylheptane

2)



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10.2: PREPARING ALKYL HALIDES FROM ALKANES - RADICAL HALOGENATION

OBJECTIVES

After completing this section, you should be able to

1. explain why the radical halogenation of alkanes is not usually a particularly good method of preparing pure samples of alkyl halides.
2. use **C — H** bond energies to account for the fact that in radical chlorinations, the reactivity of hydrogen atoms decreases in the order

$$\textbf{tertiary} > \textbf{secondary} > \textbf{primary}.$$

3. predict the approximate ratio of the expected products from the monochlorination of a given alkane.

STUDY NOTES

The following terms are synonymous:

1. methyl hydrogens, primary hydrogens, and 1° hydrogens.
2. methylene hydrogens, secondary hydrogens, and 2° hydrogens.
3. methine hydrogens, tertiary hydrogens, and 3° hydrogens.

Note that in radical chlorination reactions, the reactivity of methine, methylene and methyl hydrogens decreases in the ratio of approximately 5 : 3.5 : 1. This will aid in the prediction of expected products from the monochlorination of a given alkane.

RADICAL HALOGENATION

Alkanes (the simplest of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen (Cl_2 or Br_2) to form a haloalkane. This reaction is very important in organic chemistry because it functionalizes alkanes which opens a gateway to further chemical reactions.

GENERAL REACTION

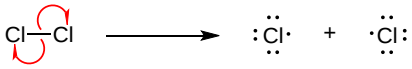
$$CH_4 + Cl_2 + energy \rightarrow CH_3Cl + HCl$$

RADICAL CHAIN MECHANISM

The reaction proceeds through the radical chain mechanism which is characterized by three steps: **initiation**, **propagation,** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining.

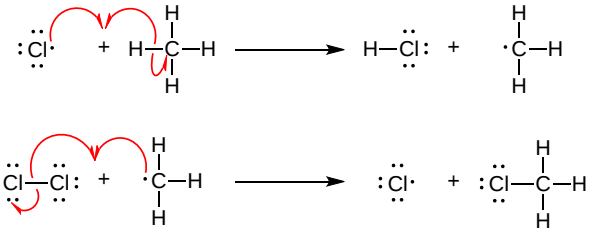
STEP 1: INITIATION

During the initiation step free radicals are created when ultraviolet light or heat causes the X-X halogen bond to undergo homolytic to create two halogen free radicals. It is important to note that this step is not energetically favorable and cannot occur without some external energy input. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy.



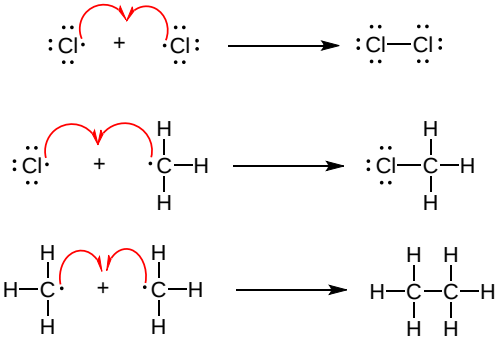
STEP 2: PROPAGATION

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical abstracts hydrogen atom from methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step, the methyl radical reacts with more of the chlorine starting material (Cl_2). One of the chlorine atoms becomes a radical and the other combines with the methyl radical to form the alkyl halide product.

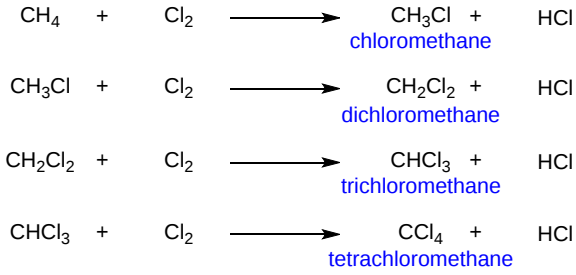


STEP 3: TERMINATION

In the three termination steps of this mechanism, radicals produced in the mechanism an undergo radical coupling to form a sigma bond. These are called termination steps because a free radical is not produced as a product, which prevents the reaction from continuing. Combining the two types of radicals produced can be combined to from three possible products. Two chlorine radicals and couple to form more halogen reactant (Cl_2). A chlorine radical and a methyl radical can couple to form more product (CH_3Cl). An finally, two methyl radicals can couple to form a side product of ethane (CH_3CH_3).



This reaction is a poor synthetic method due to the formation of polyhalogenated side products. The desired product occurs when one of the hydrogen atoms in the methane has been replaced by a chlorine atom. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms to produce a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.

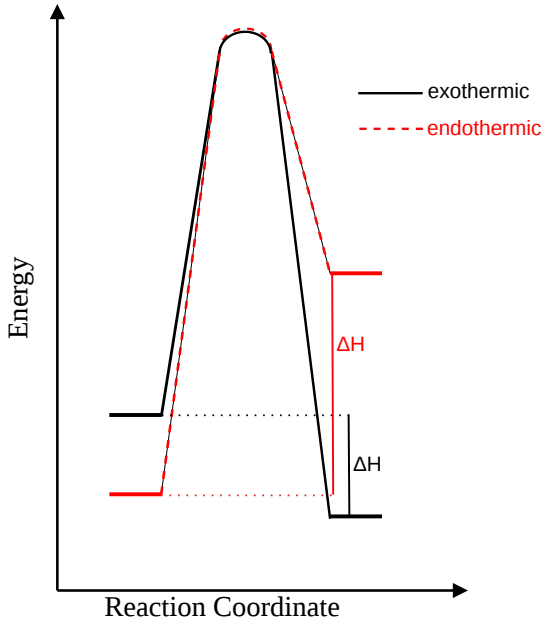


ENERGETICS

Why do these reactions occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy ΔH that occurs when the reaction takes place.

ΔH = (Energy put into reaction) – (Energy given off from reaction)

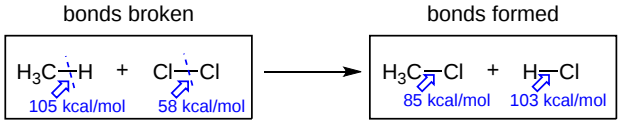
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



change in enthalpy = (105 kcal/mol + 58 kcal/mol) − (85 kcal/mol + 103 kcal/mol)
= −25 kcal/mol

Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

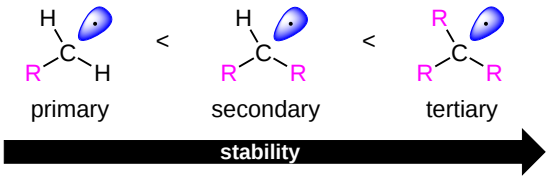
CHLORINATION OF OTHER ALKANES

When alkanes larger than ethane are halogenated, isomeric products are formed. Thus chlorination of propane gives both 1-chloropropane and 2-chloropropane as mono-chlorinated products. The halogenation of propane discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. For example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 ºC gives 45% 1-chloropropane and 55% 2-chloropropane.

$$CH_3\text{-}CH_2\text{-}CH_3 + Cl_2 \rightarrow 45\%\ CH_3\text{-}CH_2\text{-}CH_2Cl + 55\%\ CH_3\text{-}CHCl\text{-}CH_3$$

These results suggest strongly that 2º-hydrogens are inherently more reactive than 1º-hydrogens, by a factor of about 3.5:1. Further experiments showed that 3º-hydrogens are about 5 times more toward halogen atoms 1º-hydrogens. Thus, light-induced chlorination of 2-methylpropane gave predominantly (65%) 2-chloro-2-methylpropane, the substitution product of the sole 3º-hydrogen, despite the presence of nine 1º-hydrogens in the molecule.

$$(CH_3)_3CH + Cl_2 \rightarrow 65\%\ (CH_3)_3CCl + 35\%\ (CH_3)_2CHCH_2Cl$$

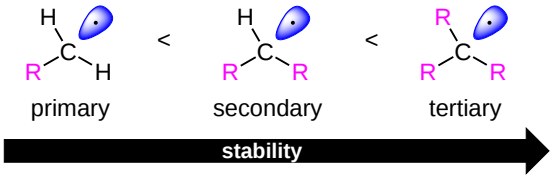


The Relative Reactivity of Hydrogens to Radical Chlorination

This difference in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured. These values are given in the following table.

R (in R–H)	methyl	ethyl	i-propyl	t-butyl
Bond Dissociation Energy (kcal/mole)	103	98	95	93

This data shows that a tertiary C-H bond (93 kcal/mole) is easier to break than a secondary (95 kcal/mole) and primary (98 kcal/mole) C-H bond. These bond dissociation energies can be used to estimate the relative stability of the radicals formed after homolytic cleavage. Because a tertiary C-H bond requires less energy to undergo homolytic cleavage than a secondary or primary C-H bond, it can be inferred that a tertiary radical is more stable than secondary or primary.



Relative Stability of Free Radicals

? EXERCISE 10.2.1

Write out the complete mechanism for the chlorination of methane.

Answer

The answer to this problem is actually above in the initiation, propagation and termination descriptions.

? EXERCISE 10.2.2

Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.

Answer

Since the second step in propagation is energetically favorable and fast, it drives the equilibrium toward products, even though the first step is not favorable.

? EXERCISE 10.2.3

Which step of the radical chain mechanism requires outside energy? What can be used as this energy?

Answer

Initiation step requires energy which can be in the form of light or het.

EXERCISE 10.2.4

Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Answer

To calculate the enthalpy of reaction, you subtract the BDE of the bonds formed from the BDE of the bonds broken.

Bonds broken are C-H and Br-Br.

Bonds formed are H-Br adn C-Br.

Bonds broken - bonds formed = change in enthalpy

(101 kcal/mol + 46 kcal/mol) - (87 kcal/mol + 70 kcal/mol) = change in enthalpy

-10 kcal/mol = change in enthalpy for bromination of ethane.

EXERCISE 10.2.5

1) Predict the mono-substituted halogenated product(s) of chlorine gas reacting with 2-methylbutane.

2) Predict the relative amount of each mono-brominated product when 3-methylpentane is reacted with Br_2. Consider 1°, 2°, 3° hydrogen.

3) For the following compounds, give all possible monochlorinated derivatives.

a) 

b) 

c) 

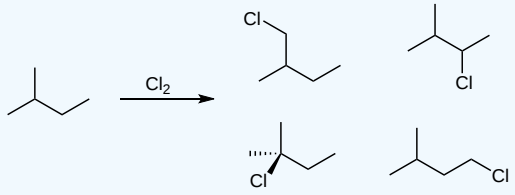
d) 

e) 

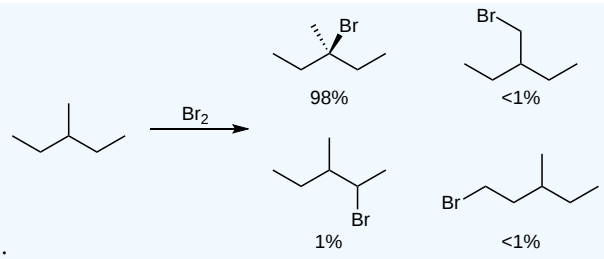
f) 

Answer

1)

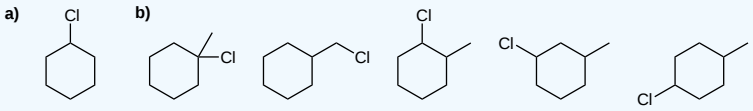


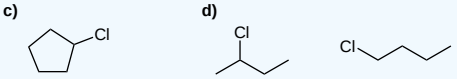
2)

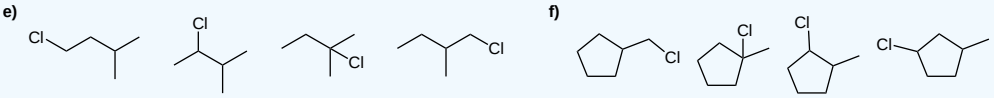


.

3)







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10.3: PREPARING ALKYL HALIDES FROM ALKENES - ALLYLIC BROMINATION

OBJECTIVES

After completing this section, you should be able to

1. write the equation for the bromination of a symmetrical alkene using N-bromosuccinimide.
2. predict the product formed when a given symmetrical alkene is treated with N-bromosuccinimide.
3. identify the reagent, the symmetrical alkene, or both, needed to produce a given allyl halide by allylic bromination.
4. list the following radicals in order of increasing or decreasing stability: allyl, vinyl, primary alkyl, secondary alkyl, tertiary alkyl, methyl.
5. explain the ease of forming an allyl radical, and the difficulty of forming a vinyl radical, in terms of relative $\ce{\sf{C–H}}$ bond dissociation energies.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

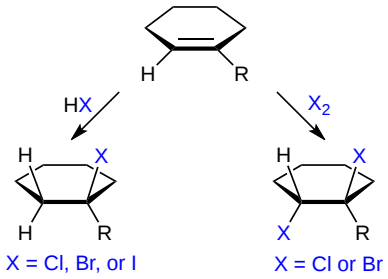
- allylic carbon

STUDY NOTES

We have discussed the electrophilic addition of X_2 and HX to alkenes as a route to forming alkyl halides (Sections 7.8 and 8.2). In this section we introduce bromination at the allyic position with N-bromosuccinimide (NBS). Notice that at the moment we are restricting our studies to the allylic bromination of symmetrical alkenes, such as cyclohexene. When we introduce an element of asymmetry, we find that more than one allyl radical can be formed; therefore, we must assess the relative stability of each radical when trying to predict which product will predominate. The method of doing this assessment is described in the next section.

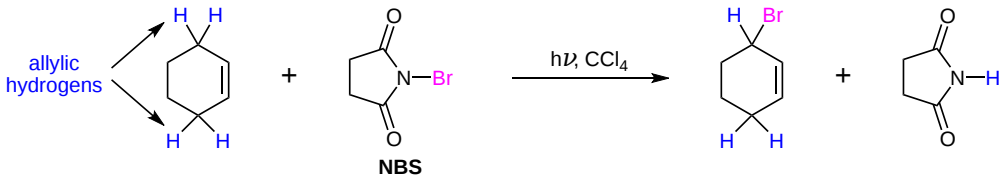
ALLYLIC BROMINATION

Previously, alkyl halides have been produced though reactions with alkenes. Hydrogen halides (HCl, HBr, and HI) react with alkenes in an electrophilic addition reaction discussed in **Section 7-8** to yield alkyl halides as products. Also, Bromine (Br_2) and chlorine (Cl_2) can react with alkenes to provide dihalogenated products as discussed in **Section 8-2**.



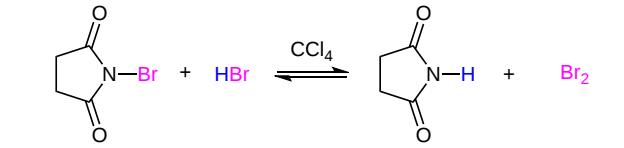
Another method for preparing alkyl halides from alkenes is with **N-bromosuccinimide (NBS)** in carbon tetrachloride (CCl_4) solution with the presence of light. The reaction specifically causes the substitution of bromine with a hydrogen attached to a carbon adjacent to the double bond - the allylic position.

GENERAL REACTION



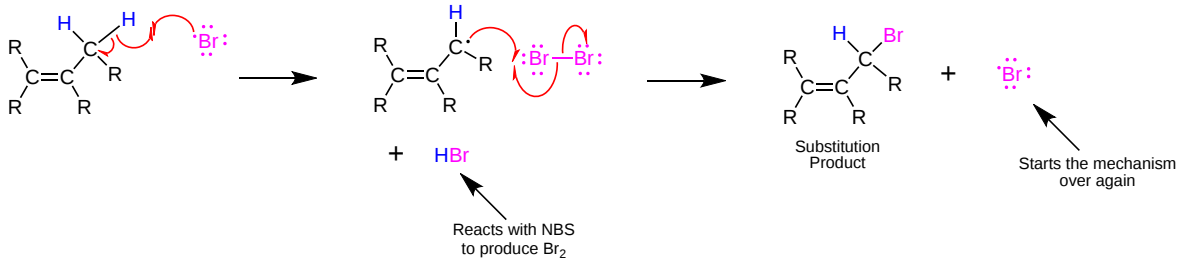
MECHANISM

The allylic bromination with NBS is analagous to the alkane halogenation reaction (Section 10.2) since it also occurs as a radical chain reaction. NBS is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts very rapidly with the HBr formed during the reaction mechanism to provide bromine (Br_2) which is required for the reaction to continue. Under the correct conditions, NBS provides a constant but very low concentration of Br_2 in the reaction mixture. The low concentration of Br_2 helps to prevent the formation of unwanted side-products.

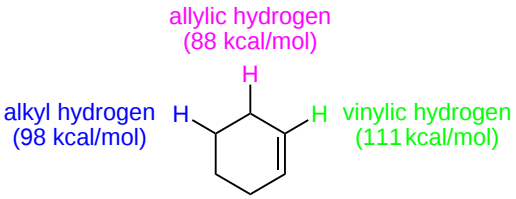


***N*-bromosuccinimide (NBS)** succinimide bromine

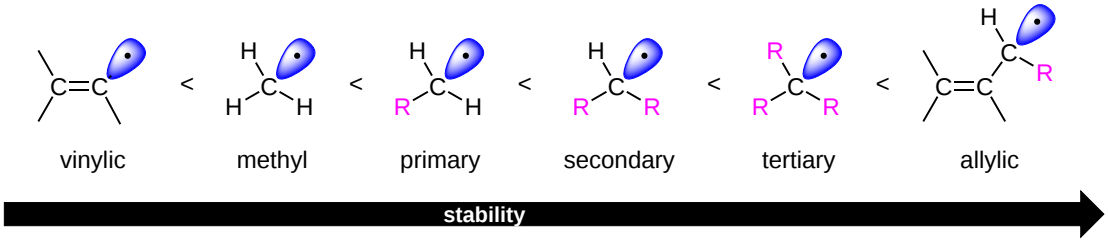
The mechanism starts with the formation of a small amount of bromine radical which then abstracts an allylic hydrogen to form an allylic radical and HBr. The HBr can then react with NBS to form the Br_2 required for the reaction. The allylic radical then abstracts a bromine atom from Br_2 to form the allyl halide product and a bromine radical. The bromine radical produced allows the reaction to continue.



The predominance of allylic substitution over other positions is based on bond dissociation energies. An allylic C-H bond has a strength of about 88 kcal/mol which is much weaker than a typical alkyl C-H bond (98 kcal/mol) or vinylic C-H bond (111 kcal/mol). Therefore, an allylic C-H bond is most likely to form a free radical and react.



Because a allylic C-H bond requires less energy to undergo homolytic cleavage than even a tertiary C-H bond, it can be inferred that a allylic radical is more stable than a tertiary radical. The ordering of stability in radicals can be expanded to include vinylic and allylic radicals. The enhanced stability of allyl radicals can be attributed to resonance stabilization which will be discussed in the next section.



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10.4: STABILITY OF THE ALLYL RADICAL - RESONANCE REVISITED

OBJECTIVES

After completing this section, you should be able to

1. explain the stability of the allyl radical in terms of resonance.
2. explain the difference between resonance and tautomerism.
3. write an equation for the reaction of an unsymmetrical alkene with N-bromosuccinimide.
4. draw the structure of each of the possible products that could be obtained from the reaction of a given unsymmetrical alkene with N-bromosuccinimide, and predict which product will predominate.
5. explain the formation of more than one product from the reaction of N-bromosuccinimide with a given unsymmetrical alkene.
6. explain the observed product ratio when a given unsymmetrical alkene is treated with N-bromosuccinimide.

KEY TERMS

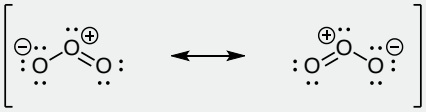
Make certain that you can define, and use in context, the key terms below.

- delocalized
- resonance forms
- resonance hybrid

STUDY NOTES

You will have encountered the concept of resonance if you have taken general first-year chemistry course. You should also briefly review Section 2.5.

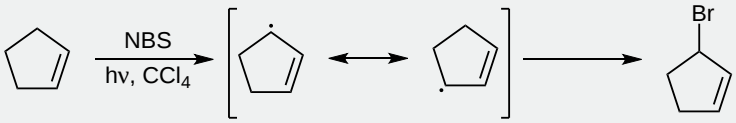
When we can represent a species by two or more different Lewis or Kekulé structures, neither of which represents the true structure of the species, these structures are referred to as *resonance forms*. A common example used in general chemistry courses to illustrate the concept of resonance is ozone, O_3. The two resonance forms of ozone may be represented as follows:



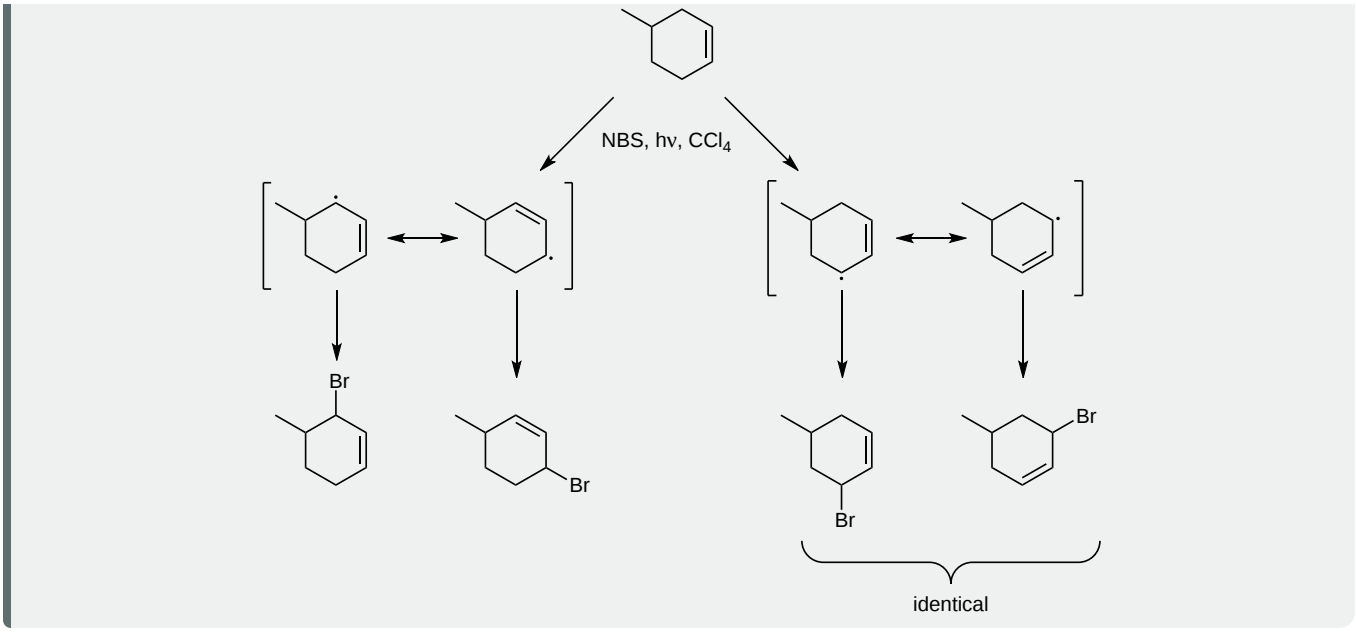
The concept of resonance is quite important, and will be used frequently throughout the remainder of this course. The guidelines below may assist you in drawing resonance contributors.

1. Resonance occurs whenever a molecule, radical or ion can be represented by two or more structures differing only in the arrangement of electrons (no atoms may be moved).
2. The true structure of a species is a hybrid of the resonance contributors and is more stable (i.e., lower in energy) than any of the contributors.
3. The most important contributors are those containing the most covalent bonds. Another way of saying the same thing is that the most important contributors have the least amount of charge separation.
4. Contributors in which all the atoms (except hydrogen) have a complete octet (i.e., are surrounded by eight electrons) are particularly important.

In the previous section we discussed the allylic bromination of a symmetrical alkene with NBS such as this cyclopentene, which affords one product.

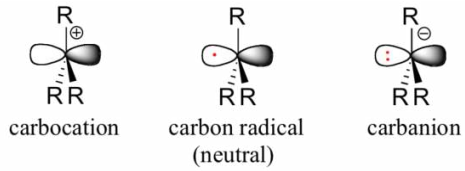


However, with an unsymmetrical alkene and the delocalized unpaired electron forming various allylic resonances, several products are possible. For example, the NBS bromination of 4-methyl-cyclohexene leads to three products.



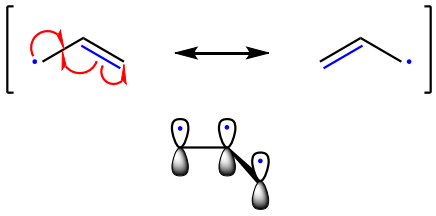
THE GEOMETRY AND RELATIVE STABILITY OF CARBON RADICALS

As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp^2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$orbital. Contrast this picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.

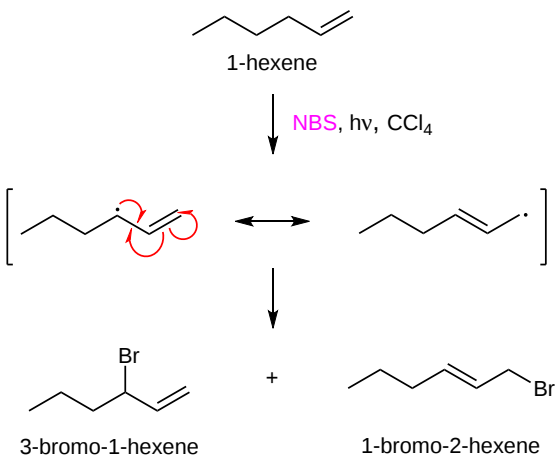


The trend in the stability of carbon radicals parallels that of carbocations (section 8.4B): tertiary radicals, for example, are more stable than secondary radicals, followed by primary and methyl radicals. This should make intuitive sense, because radicals, like carbocations, can be considered to be electron deficient, and thus are stabilized by the electron-donating effects of nearby alkyl groups.

Benzylic and allylic radicals are more stable than alkyl radicals due to resonance effects - an unpaired electron can be delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons. With two resonance forms, the allylic radical is electronically symmetrical. Due to resonance hybrid theory, neither structure is correct, but instead the structure lies somewhere between the two resonance forms. Another way to phrase this is that the unpaired electron is delocalized across all the carbon atoms through the pi system and not localized on one site. The more resonance structures, the more stable the molecule. This is why the allylic radical is more stable than the alkyl radical.

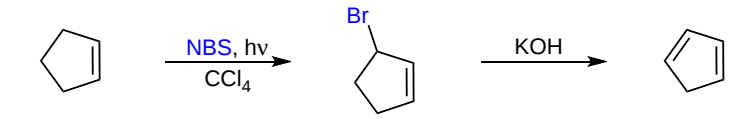


Because the allylic radical is symmetrical, a reaction can occur on either side. Therefore if reacting with bromine, the bromination could occur on either end of the allylic radical. When the allyl radical is symmetrical, this yields the same product. However, if you have an unsymmetrical allyl radical, it would lead to a mixture of products and not necessarily in equal amounts. This is because the intermediate radical is unsymmetrical. The reaction will occur at the less hindered site. An example would be 1-octene as a starting material in a bromination. The products the reaction would yield would be 3-bromo-1-octene and 1-bromo-2-octene.



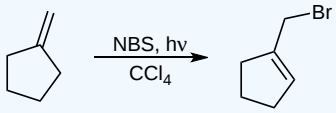
FURTHER REACTIONS

The products from allylic bromination reactions can easily be converted into dienes by elimination using a base. If the alkyl chain is long enough, alkenes can be converted to dienes through a two-step process: allylic bromination followed by elimination.

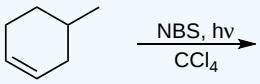


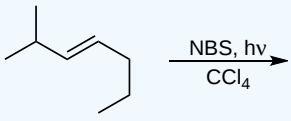
EXERCISE 10.4.1

1) The following reaction shows the major product. Explain why this would be the final product and why the 2° bromo product is not the major product.



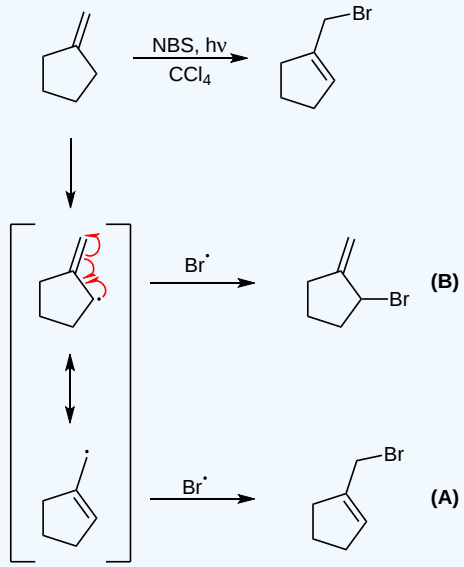
2) Predict the products of the following reactions:



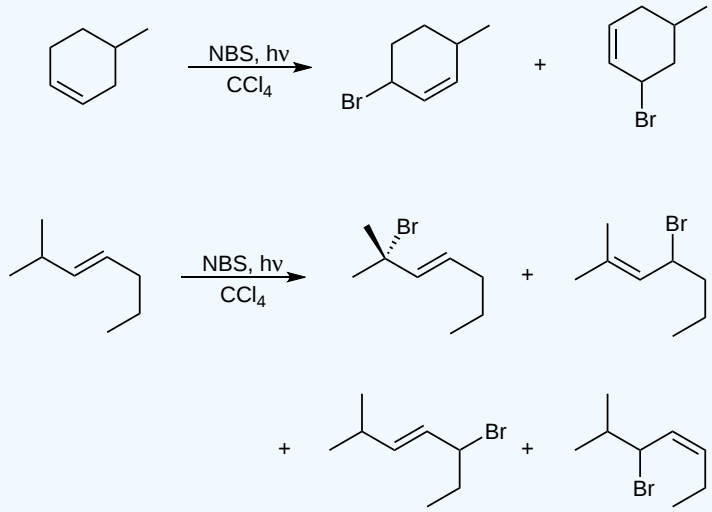


Answer

1) The product (A) is a 1° halogen which is more predominant product even though the (B) had a better transition state with a 2° radical. The 1° radical intermediate is not as sterically hindered.



2)



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10.5: PREPARING ALKYL HALIDES FROM ALCOHOLS

OBJECTIVES

After completing this section, you should be able to

1. write an equation for the conversion of an alcohol to an alkyl halide.
2. list a given series of alcohols in increasing or decreasing order of reactivity with hydrogen halides.
3. identify the alkyl halide formed when a given alcohol reacts with thionyl chloride, phosphorus tribromide, or a hydrogen halide.
4. identify the alcohol which should be used to prepare a given alkyl halide using one of the reagents specified in Objective 3.
5. select the most appropriate reagent for converting a given alcohol to a given alkyl halide.

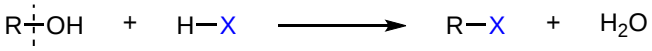
STUDY NOTES

The use of thionyl chloride for converting alcohols to alkyl chlorides has the added benefit that both of the by-products, sulfur dioxide and hydrogen chloride, are gases. This characteristic simplifies the isolation and purification of the reaction product.

In the laboratory, one can test for the presence of alcohols with Lucas reagent (a mixture of concentrated hydrochloric acid and zinc chloride). Lucas reagent converts alcohols to alkyl chlorides: tertiary alcohols fastest followed by secondary alcohols; primary alcohols do not react to any significant extent. Thus, Lucas reagent can help distinguish among primary, secondary and tertiary alcohols due to going through a substitution reaction.

GENERAL REACTION

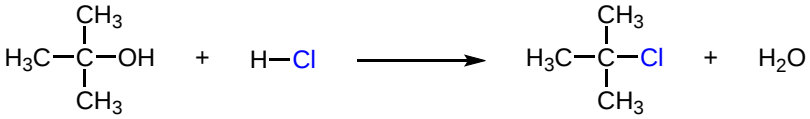
When alcohols react with an acid halide, a substitution takes place producing an alkyl halide and water:



- The order of reactivity of alcohols is 3° > 2° > 1° > Methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

Tertiary alcohols react reasonably rapidly HCl, HBr, or HI, but for primary or secondary alcohols the reaction rates are too slow for the reaction to be of much importance. For the reactions that do occur, bubbling HX into an alcohol solution yields a haloalkane or alkyl halide. Below the reaction shows, tert-butanol and hydrochloric acid reacting to yield *t*-butyl chloride and water.

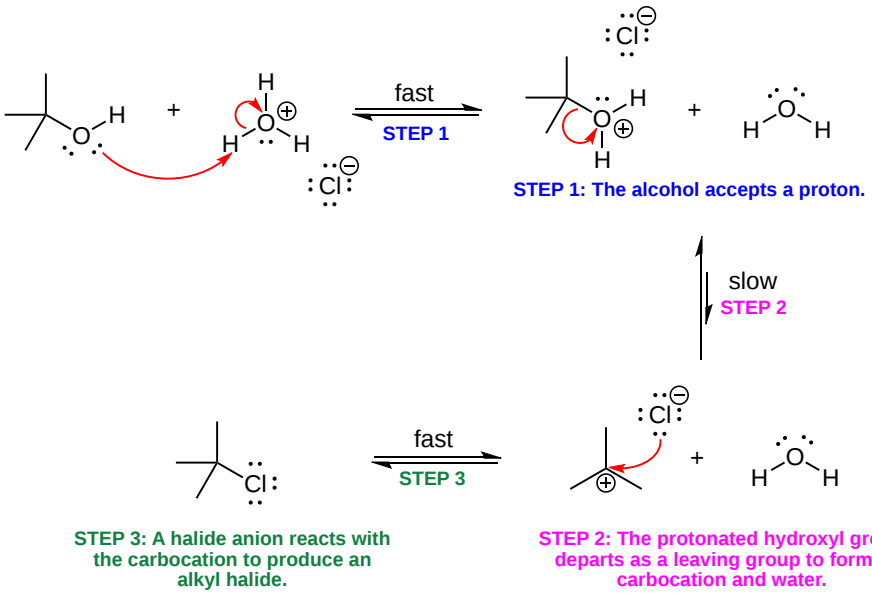
EXAMPLE



MECHANISM

Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as a leaving group.

The S_N1 mechanism is illustrated by the reaction of tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_N1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Protonation of the alcohol converts a poor leaving group (OH^-) to a good leaving group H_2O which makes the dissociation step of the S_N1 mechanism more favorable. In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

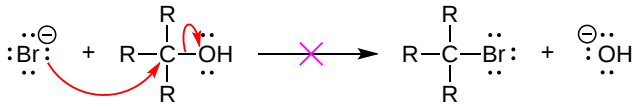


Carbocation rearrangements are extremely common in organic chemistry reactions are are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial molecule.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism. In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



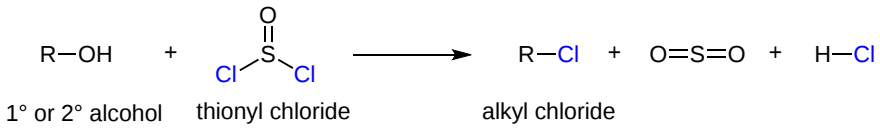
Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols that are not activated (converted to a better leaving group). Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion.

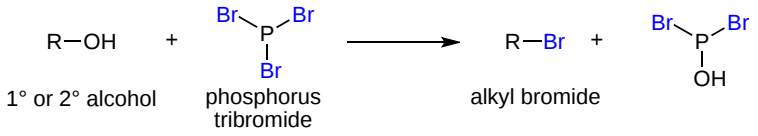


CONVERSION OF ALCOHOLS INTO ALKYL HALIDES USING $SOCL_2$ OR PBR_3

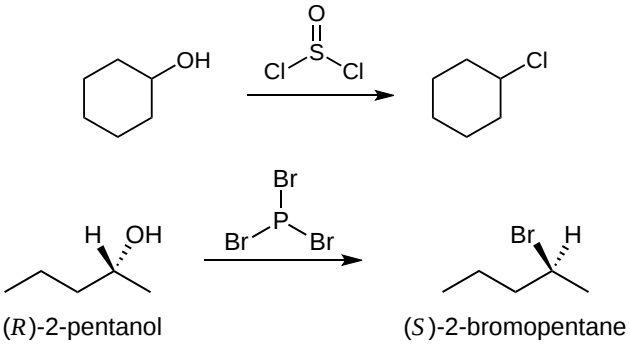
The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with **thionyl chloride ($SOCl_2$)** and **phosphorus tribromide (PBr_3)**, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

GENERAL REACTION





EXAMPLE

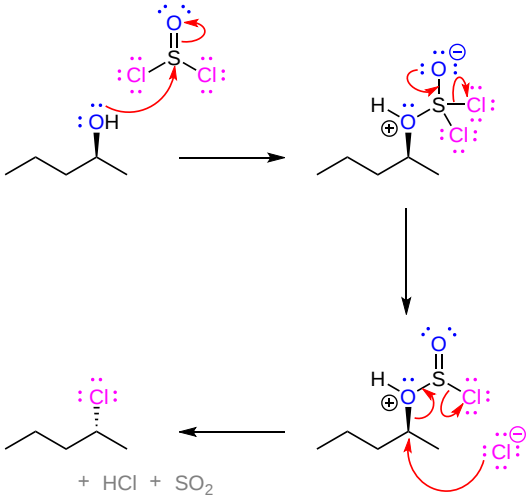


MECHANISMS

Both of these reagents form an alkyl halide through an S_N2 mechanism. The mechanism for both reactions starts by converting the hydroxide of the alcohol into a better leaving group through formation of an intermediate. Thionyl chloride creates an intermediate chlorosulfite (-$OSOCl_2$) compound and phosphorus tribromide makes an intermediate dibromophosphite (-$OPBr_2$) compound. These intermediate compounds can subsequently be eliminated as a leaving group during an S_N2 reaction with the corresponding nucleophilic halide ion. Since these reactions proceeds through a backside attack, there is inversion of configuration at the carbon

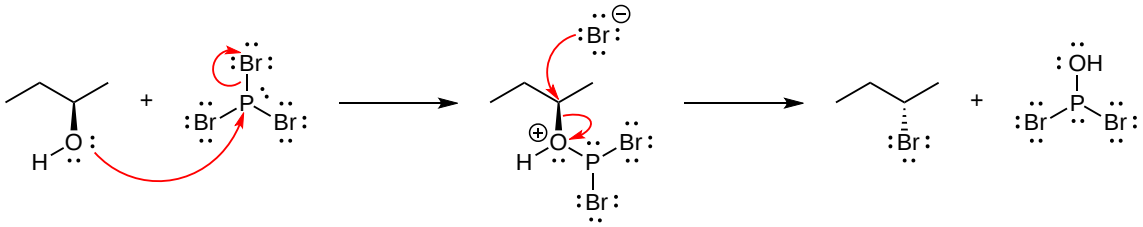
THIONYL CHLORIDE

Notice that during the reaction with thonyl chloride hydrochloric acid (HCl) and sulfur dioxide (SO_2) are produced as byproducts.



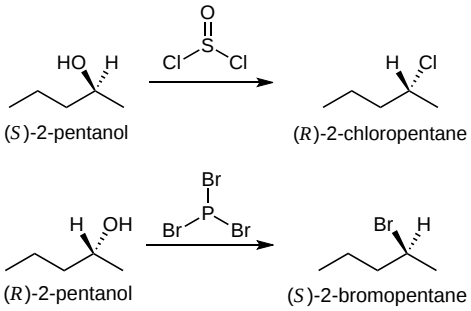
PHOSPHORUS TRIBROMIDE

During this reaction $HOPBr_2$ is made as a biproduct.



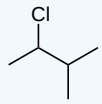
STEREOCHEMICAL CONSIDERATIONS

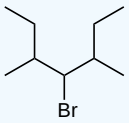
The S_N2 reaction with the corresponding nucleophilic halide ion contained in the mechanism of both reactions causes an inversion of configuration at the carbon atom.

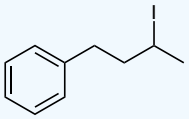


EXERCISE 10.5.1

1) Predict the alcohol required for the synthesis of the following halides:



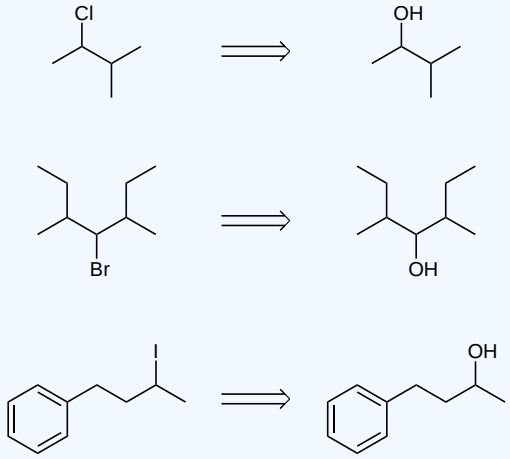




Answer

1)

https://chem.libretexts.org/@go/page/31498



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10.6: REACTIONS OF ALKYL HALIDES - GRIGNARD REAGENTS

OBJECTIVES

After completing this section, you should be able to

- write an equation to describe the formation of a Grignard reagent.
- give examples of Grignard reagents formed from aryl and vinyl halides as well as from alkyl halides.
- explain the reactivity of Grignard reagents in terms of the polarity of the carbon-magnesium bond.
- write an equation for the reaction of a Grignard reagent with a proton donor, such as water.
- predict the product formed from the reaction of a given organohalide with magnesium followed by a proton donor.
- identify the organohalide, the reagents, or both, needed to prepare a given alkane.
- describe how a deuterium atom may be introduced at a specific location in an organic molecule through use of a Grignard reagent.
- describe at least one limitation on the use of Grignard reagents in organic synthesis.
- write an equation for the direct conversion of an alkyl halide to an alkane using a hydride donor, such as lithium aluminum hydride.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

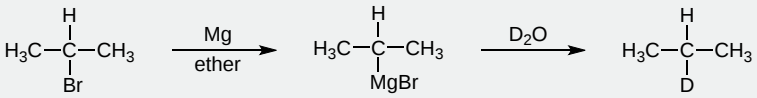
- carbanion
- Grignard reagent

STUDY NOTES

The organomagnesium compounds formed by the reaction of an alkyl or aryl halide with magnesium are called *Grignard reagents*. As you will see throughout the remainder of this course, Grignard reagents can be used to synthesize a wide range of organic compounds and are extremely useful to the organic chemist.

In the introductory section, we tried to stress that the chemistry of alkyl halides is quite different from that of aryl (or vinyl) halides. However, both alkyl and aryl halides react with magnesium to form Grignard reagents.

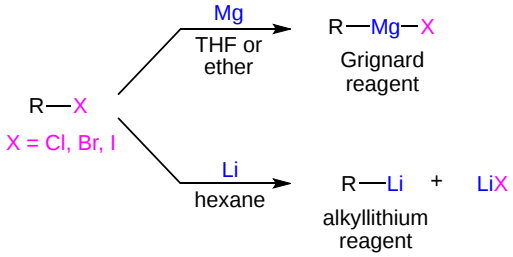
The reaction of a Grignard reagent with D_2O ("heavy water") provides a convenient method for introducing a deuterium atom (remember D is equivalent to ^2H) into a molecule at a specific location. For example:



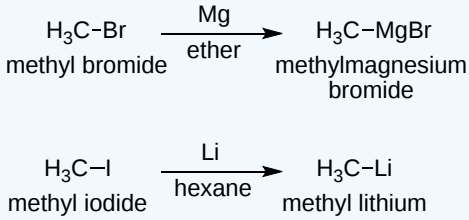
FORMATION OF ORGANOMETALLIC REAGENTS

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, of which the alkali metals are stronger. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal which has characteristics similar to a carbanion (R:-). Most alkyl halides can undergo this reaction including: 1°, 2°, 3°, vinyl, and aryl. Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used.

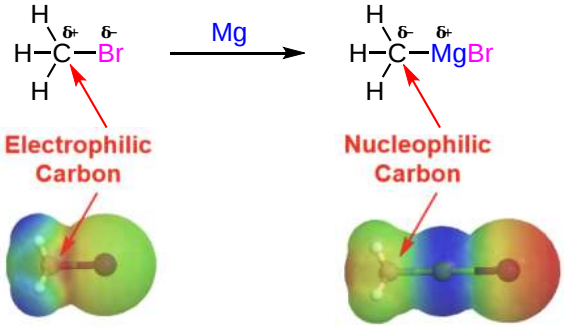
Many organometallic reagents are commercially available, however, it is often necessary to make then. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination). The alkyl magnesium halides described in the first reaction are called **Grignard Reagents** after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The products of the second reaction are called **Alkyllithium Reagents** The other metals mentioned above react in a similar manner, but Grignard and Alkylithium Reagents are most widely used. Although the formulae drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.



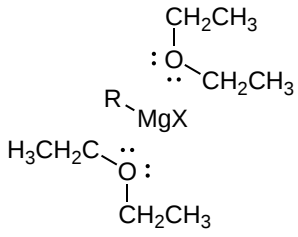
EXAMPLE 10.6.1



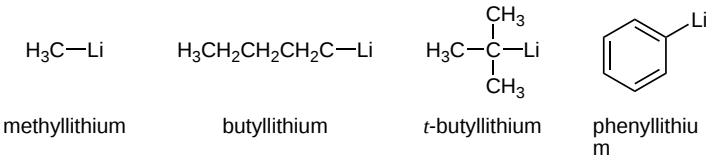
These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). The Polarity change is evident when looking at the electrostatic maps of the alkyl halide and the Grignard reagent. In the alkyl halide, the electronegative halogen atom holds much of the electron density which gives the carbon a slight positive charge (shown in blue in the electrostatic potential map below) making it electrophilic. In the Grignard reagent, the carbon has a slight negative charge making it nucleophilic (shown in yellow & red).



A suitable solvent must be used for reactions that form organometallic molecules. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Diethyl ether or tetrahydrofuran (THF) are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (as pictured below). This complex helps stabilize the organometallic and increases its ability to react.



COMMON ORGANOMETALLIC REAGENTS



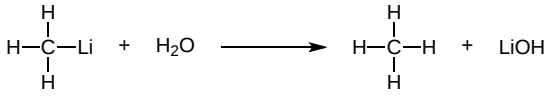
methyllithium butyllithium *t*-butyllithium phenyllithium



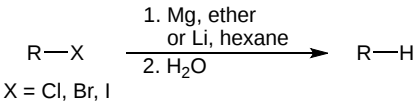
methylmagnesium bromide phenylmagnesium bromide

ORGANOMETALLIC REAGENTS AS BASES

These reagents are very strong bases (pKa's of saturated hydrocarbons range from 42 to 50). Although not usually done with Grignard reagents, organolithium reagents can be used as strong bases. Both Grignard reagents and organolithium reagents react with water to form the corresponding hydrocarbon. This is why so much care is needed to insure dry glassware and solvents when working with organometallic reagents.



In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



? EXERCISE 10.6.1

How strong of a base would you expect ethyl Grignard to be? Would the following reactions be able to take place?





Answer

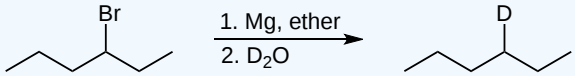
Because hydrocarbons like ethane are very weak acids (pKa = 50), then the corresponding carbanion ($CH_3CH_2^-$) is expected to be a strong base. Both reactions will occur.

? EXERCISE 10.6.2

How would you make a deuterated compound from an alkyl halide?

Answer

By first making a Grignard and then exposing it to heavy water.



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10.7: ORGANOMETALLIC COUPLING REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation for the formation of an alkyllithium from an alkyl halide.
2. write an equation for the formation of a lithium dialkylcopper (Gilman) reagent from an alkyllithium and copper(I) iodide.
3. write an equation for the coupling of a lithium dialkylcopper reagent with an alkyl halide (i.e., a Corey-House synthesis).
4. draw the structure of the product formed from a given Corey-House synthesis.
5. identify the reagents needed to convert two given organohalides to a specified hydrocarbon through a Corey-House synthesis.

KEY TERMS

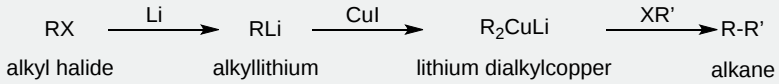
Make certain that you can define, and use in context, the key terms below.

- Corey-House synthesis
- pheromone

STUDY NOTES

A *pheromone* is a chemical released by members of one species to cause specific behavioural or physiological changes in other members of the same species. Examples include sex pheromones, alarm pheromones and trail pheromones.

The *Corey-House synthesis* provides us with a method of coupling together two alkyl groups through the formation of a new carbon-carbon bond. The product of such a reaction is an alkane, and this synthetic method gives us a route for the preparation of unsymmetrical alkanes. The method was developed during the late 1960s by E. J. Corey and Herbert House working independently at Harvard University and Massachusetts Institute of Technology, respectively. The overall synthetic route is shown on the next page. Note that R and R′ represent alkyl groups, which can be the same or different, and X represents a halogen (preferably bromine or iodine).

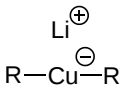


In order to obtain a good yield of alkane, both R′X and RX should be primary alkyl halides. However, the experimental procedure can be modified so that this synthesis can be carried out using a wide range of alkyl, aryl, vinyl, benzyl and allyl halides. A detailed discussion of these modifications is beyond the scope of this course, but you should be aware of possible limitations in the use of the Corey-House synthesis.

Note: In some textbooks, lithium diorganocoppers are referred to as lithium dialkylcoppers, or cuprates.

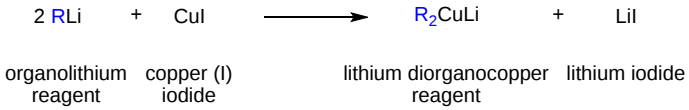
GILMAN REAGENTS

Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a **lithium diorganocopper reagent** (also called diorganocuprates), which often is referred to as a **Gilman reagent**. Remember that organolithium reagents are formed by a reaction of lithium metal with an organohalide. Lithium diorganocopper reagents are considered a source of carbanion-like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of lithium diorganocuprate reagents is slightly different and this difference will be exploited in specific situations. Diorganocuprate reagents are made from the reaction of two equivalents of an organolithium reagent and copper (I) iodide (CuI). The created lithium diorganocuprate reagent acts as a source of $R:^-$

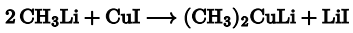


lithium diorganocopper (Gilman reagent)

GENERAL REACTION



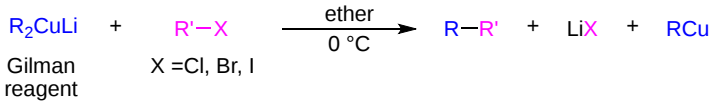
EXAMPLE



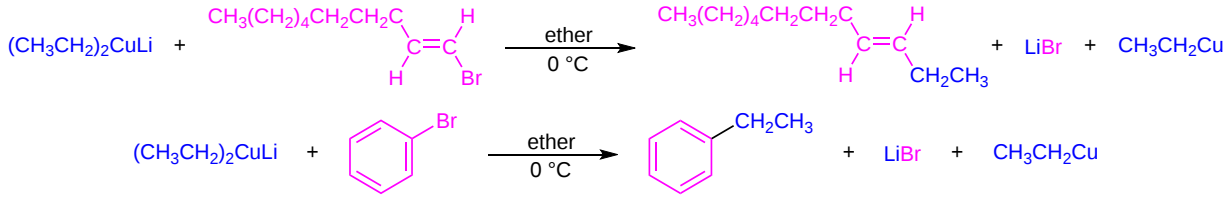
COUPLING REACTIONS WITH GILMAN REAGENTS

Gilman reagents undergo a coupling reaction with organochlorides, bromides, and iodides to form a carbon-carbon bond. During the reaction one of the alkyl groups from the Gilman reagent replaces the halogen atom in the organohalide. This reaction is useful in organic synthesis because it allows a larger molecule to be built from smaller fragments. Most alkyl halides, including aryl and vinyl halides, are capable of undergoing this reaction.

GENERAL REACTION

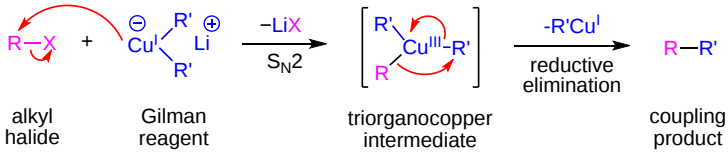


EXAMPLES



MECHANISM

The mechanism begins with copper in the Gilman reagent being oxidized from Cu^{+1} to Cu^{+3}. Losing electrons allows the copper atom to act as a nucleophile and undergo an S_N2 like substitution reaction with the alkyl halide. The resulting neutral tri-organocopper intermediate undergoes reductive elimination, reducing Cu^{+3} to Cu^{+1}, and creating the alkyl coupling product.

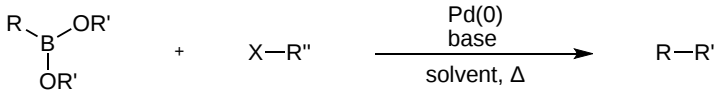


THE SUZUKI-MIYAURA REACTION

The reactions of diorganocopper reagents with organohalides are related to the processes that occur with other organometallic reagents such as organopalladiums. Suzuki-Miyaura coupling (or Suzuki coupling) is a metal-catalyzed reaction, typically with Pd, between an alkenyl (vinyl), aryl, or alkynyl organoborane (boronic acid or boronic ester, or special cases with aryl trifluoroborane) and halide or triflate under basic conditions. This reaction is used to create carbon-carbon bonds to produce conjugated systems of alkenes, styrenes, or biaryl compounds. Organopalladium reagents are often preferred over diorganocopper reagents, because only a catalytic amount of the organopalladium is necessary rather than a full equivalent which makes the reaction less toxic.

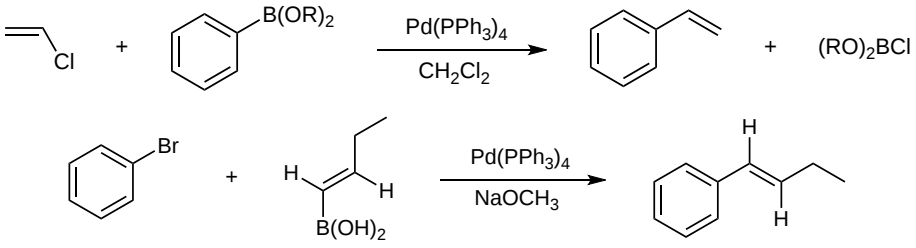


GENERAL REACTION



R = aryl, alkene (vinyl), alkyne; R' = H (boronic acid), alkyl (boronic ester);
R'' = aryl, alkene (vinyl), alkyne
X = halide (I, Br, Cl*), triflate (−OTf) *Cl requires special conditions for activation

EXAMPLES

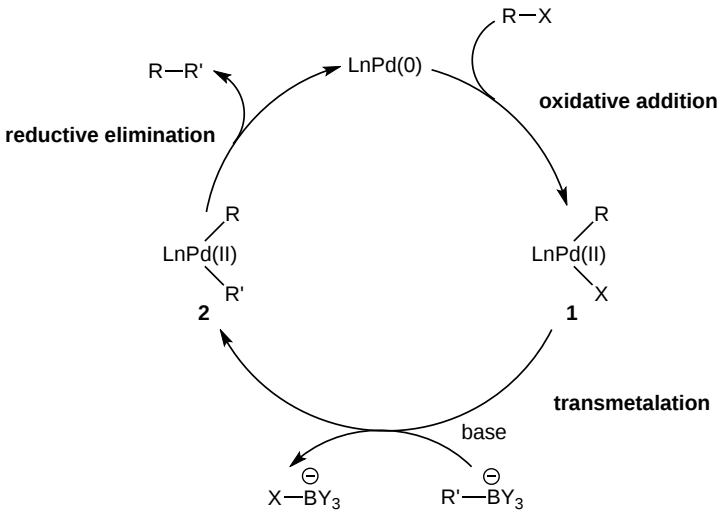


MECHANISM

The general catalytic cycle for Suzuki cross coupling involves three fundamental steps: *oxidative addition*, *transmetalation*, and *reductive elimination* as demonstrated in the figure below.

The *oxidative addition* of aryl halides to the Pd(0) complex gives an intermediate 1, a Pd(II) species. Under the participation of base, an organoborane compound reacts with intermediate 1 in a *transmetalation* step to afford intermediate 2.

This is followed by *reductive elimination* to give the desired coupling product and regenerate the original Pd(0) species. Depending on different catalytic systems with various catalysts, ligands, and solvents, there are additional processes in the catalytic cycle, including ligand or solvent association and dissociation.



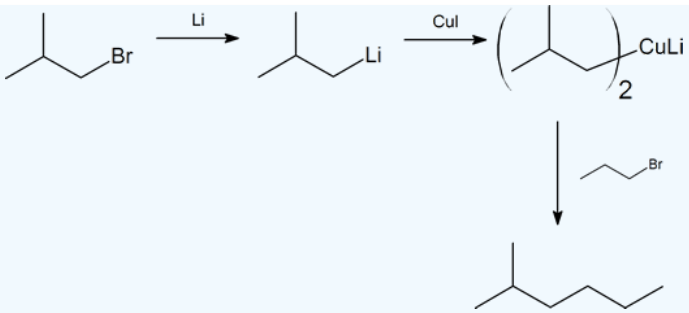
EXERCISE 10.7.1

Starting with alkyl halides containing no more than four carbon atoms, how would you synthesize each of the following alkanes?

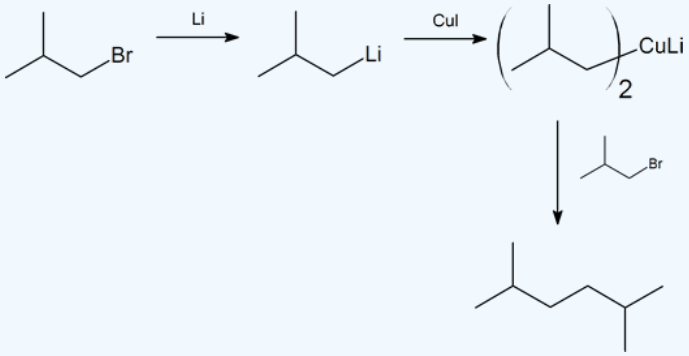
a. 2,5-dimethylhexane
b. 2-methylhexane

Answer

Notice that in (*a*), both the alkyl halides are primary. This fact should ensure a good yield of product.



In (*b*) we have the choice of using 2-bromopropane and 1-bromobutane, or 1-bromo-2-methylpropane and 1-bromopropane. We chose the latter as it enables us to use two primary alkyl halides, and hence a simpler procedure.



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10.8: OXIDATION AND REDUCTION IN ORGANIC CHEMISTRY

OBJECTIVES

After completing this section, you should be able to

- identify organic reactions as being oxidations, reductions, or neither.
- rank given compounds in order of their oxidation level.

KEY TERMS

Make certain that you can define, and use in context, the terms below.

- oxidation
- reduction
- heteroatom

GENERAL REDOX REACTIONS

General chemistry courses describe oxidation and reduction - when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. Also, oxidation and reduction half reactions occur in pairs: if one species is oxidized, another must be reduced at the same time. Thus, the combination of an oxidation and a reduction half reaction is termed a 'redox reaction.' Most of the redox reactions you have seen previously in general chemistry typically involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

$$Cu^{+2}(aq) + Zn(s) \longrightarrow Cu(s) + Zn^{+2}(aq)$$

$$Cu^{+2}(aq) + 2e^- \longrightarrow Cu(s)$$

Reduction

$$Zn(s) \longrightarrow Zn^{+2}(aq) + 2e^-$$

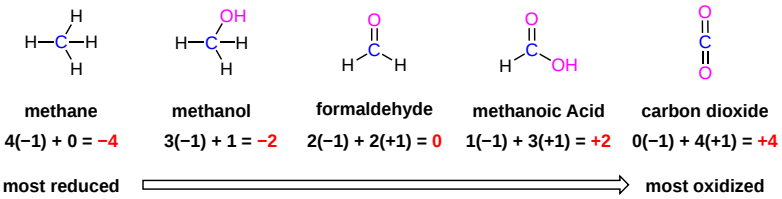
Oxidation

In order, to keep track of electrons in organic molecules an oxidation state formalism is used. Oxidation states do not represent the actual charge on an atom, but it will allow the number of electrons being gained or lost by a particular atom to be determined during a reaction.

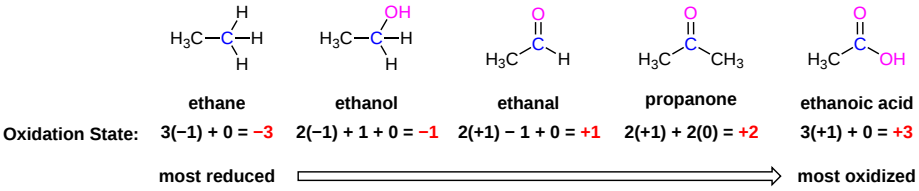
To calculate the oxidation state of a carbon atom the following rules are used:

1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative atom, such as nitrogen, oxygen, sulfur, or a halogen.

When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized. We'll take a series of single carbon compounds as an example. Methane (CH_4) is at the lowest oxidation level of carbon because is has the maximum possible number of bonds to hydrogen. Carbon dioxide (CO_2) is at the highest oxidation level because it has the maximum number of bonds to an electronegative atom.



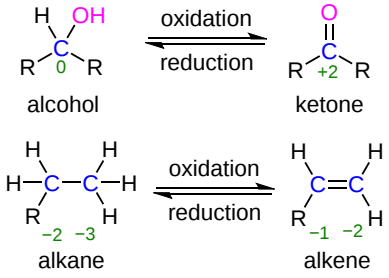
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



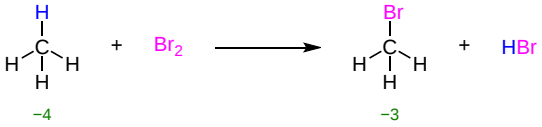
ORGANIC REDOX REACTIONS

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized. If a reaction converts a compound to a higher oxidation level that is an oxidation. If it converts a compound to a lower oxidation level it is a reduction. If the oxidation level of the reactant does not change it is not a redox reaction.

Two examples of organic redox reactions are shown below. The conversion of an alcohol to a ketone is considered an oxidation because the oxidation level of the carbon increases from 0 to +2. This implies that the reaction would require an oxidizing agent. Likewise, the conversion of a ketone to an alcohol is a reduction and would require a reducing agent. The conversion of an alkane to alkene is an oxidation because the oxidation state on both carbons is increasing while the reverse reaction would be a reduction.

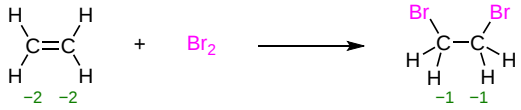


Now reaction previously discussed in this textbook can be considered to determine if they are in fact redox reaction. The free radical bromination of methane to bromomethane would be an oxidation because the oxidation level of carbon is raised from -4 to -3.

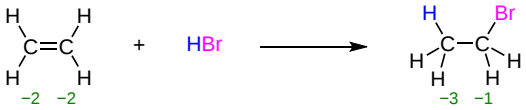


free radical halogenation: **oxidation**

The electrophilic addition of Br_2 to an alkene to provide a 1,2-dibromide is an oxidation because both carbons increase their oxidation level from -2 to -1. However, the electrophilic addion of HBr to an alkene to provide an alkyl halide is not a redox reaction because the overall oxidation state of carbons involved are not changed. One carbon has its oxidation level decreased from -2 to -3 while the other carbon's oxidation level is increased from -2 to -1. Overall, the change in oxidation level cancels out to leave an overall change of oxidcation level in the compound of 0.

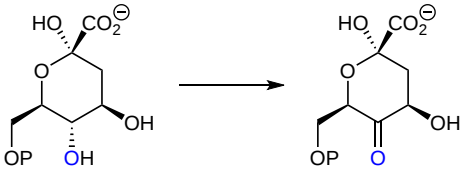


electrophilic addition of Br_2: **oxidation**

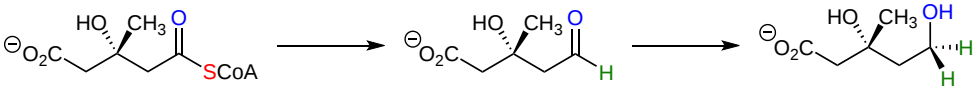


electrophilic addition of HBr: **not redox**

You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant . Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up on the oxidation ladder.

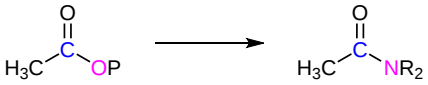


Likewise, this next reaction involves the transformation of a carboxylic acid derivative (a thioester) first to an aldehyde, then to an alcohol: this is a *double* reduction, as the substrate loses two bonds to heteroatoms and gains two bonds to hydrogens.



thioester aldehyde alcohol

An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



carbon is in same oxidation state: **not redox**

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized- remember, oxidation and reduction always occur in tandem! We will soon learn in detail about the most important biochemical and laboratory redox agents.

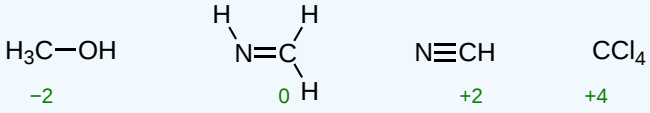
Worked Example 10.8.1

Rank the following compounds in order of increasing oxidation level:



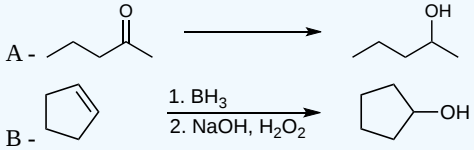
Answer

The easiest way to solve this problem is to calculate the oxidation level of the carbon in each compound. Remembering that hydrogens decrease the oxidation level by one, electronegative elements increase the oxidation level by one, and carbons do not change the oxidation level, the oxidation level of each carbon can be calculate. The carbon in CH_3OH has three bonds to hydrogens and one bond to oxygen so it oxidation level is 3(-1) + 1(+1) = -2. The carbon in HCN has one bond to hydrogens and three bonds to nitrogen so it oxidation level is 1(-1) + 3(+1) = +2. The carbon in CH_2NH has two bonds to hydrogens and two bond to nitrogen so it oxidation level is 2(-1) + 2(+1) = 0. The carbon in CCl_4 has zero bonds to hydrogens and four bonds to chlorine so it oxidation level is o(-1) + 4(+1) = +4. The compounds now can be listing in the following order of increasing oxidation level.



? EXERCISE 10.8.2

In each case state whether the reaction is an oxidation or reduction of the organic compound.



Answer

A – Reduction

B – Oxidation

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10.S: ORGANOHALIDES (SUMMARY)

CONCEPTS & VOCABULARY

10.1 Introduction to Organohalides

- Alkyl halides (and allyl and benzyl halides) are more reactive than vinyl and aryl halides.

10.2 Names and Properties of Alkyl Halides

- Reactivity of alkyl halides is often related to the substitution of the carbon atom the halogen is attached to.
- Alkyl halides are categorized by the number of bonds to other alkyl groups (**primary**, **secondary**, and **tertiary**).
- Carbon-halogen bonds are polarized with partial positive charges on carbon and partial negative charges on the halogen.
- Fluorine is the most electronegative of the halogens while iodine is the least electronegative.
- Iodine is the largest of the halogens yielding the longest/weakest bonds to carbon of the halogens.
- Since haloalkanes have dipole-dipole interactions, they have greater intermolecular forces than similar sized alkanes and therefore higher boiling points.
- Alkyl halides are either slightly soluble or insoluble in water, but are soluble in organic solvents.

10.3 Preparing Alkyl Halides from Alkanes - Radical Halogenation

- Halogenation of alkanes is exothermic, so it is energetically favorable.
- Radical chain mechanisms consist of three steps: **initiation**, **propagation** and **termination**.
- Hydrogens on more substituted carbon atoms are more reactive to radical halogenation.

10.4 Preparing Alkyl Halides from Alkenes - Allylic Bromination

- More substituted radicals and radicals with resonance structures are more stable than other radicals.
- Radical substitution can be carried out at the allylic or benzylic carbon by reacting with NBS.

10.5 Stability of the Allyl Radical - Resonance Revisited

- Allyl cations, anions and radicals have resonance structures. To draw these resonance structures non-bonded and pi-bond electrons can be moved.
- Resonance hybrids are used to show the combination of all resonance structures for a molecule or ion.

10.6 Preparing Alkyl Halides form Alcohols

- Alcohols can be reacted with hydrohalogen acids or a mixture of halogen salts and a stronger acid (to form hydrohalogen acids *in situ*).
- Alcohols will also react with thionyl chloride or with phosphorus halides to from haloalkanes.

10.7 Reactions of Alkyl Halides - Grignard Reactions

- Organometallic reagents can be formed from alkyl halides and reactive metals (such as lithium and magnesium).
- Alkyl magnesium halide compounds are callled Grignard reagents.
- Grignard reagents react as bases where the alkyl group gets protonated and the metal complexes to the conjugate base of the reacting acid.

10.8 Organometallic Coupling Reactions

- Lithium dialkyl copper compounds are called Gilman reagents.
- Gilman reagents have different reactivity from the other organometallics (lithium and Grignard reagents).
- Organometallics can be reacted with alkyl halides to join to alkyl groups (coupling reactions).

10.9 Oxidation and Reduction in Organic Chemistry

- Gaining bonds to hydrogen for organic molecules is reduction.
- Losing bonds to hydrogen for organic molecules is oxidation.

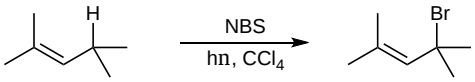
SKILLS TO MASTER

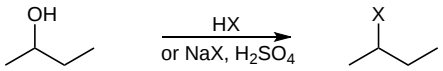
- Skill 10.1 Differentiate between types of halides (alkyl, allyl, aryl, benzyl, and vinyl).
- Skill 10.2 Differentiate between substitution of alkyl halides (primary, secondary, and tertiary).
- Skill 10.3 Identify relative reactivity of carbon-hydrogen bonds to radical halogenation.
- Skill 10.4 Draw resonance structures for radical compounds.

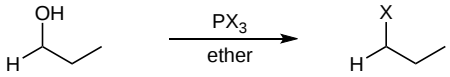
- Skill 10.5 Draw mechanisms for radical halogenation of alkanes (initiation, propagation and termination).
- Skill 10.6 Calculate the enthalpy change of a reaction using bond dissociation energies of reactants and products.
- Skill 10.7 Determine products for allylic bromination reactions.
- Skill 10.8 Draw resonance structures for allylic and other similar compounds and ions.
- Skill 10.9 Draw products of reactions of alcohols to form alkyl halides.
- Skill 10.10 Write equations to form Grignard reagents from alkyl halides.
- Skill 10.11 Draw reaction products for Grignard reagents acting as bases.
- Skill 10.12 Write equations for the formation of Gilman reagents.
- Skill 10.13 Draw reaction products of organometallic coupling reactions.
- Skill 10.14 Explain oxidation and reduction in organic molecules.

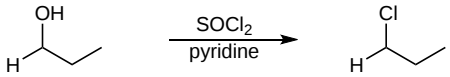
SUMMARY OF REACTIONS

Preparation of Alkyl Halides

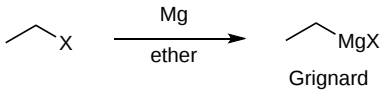


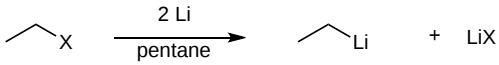


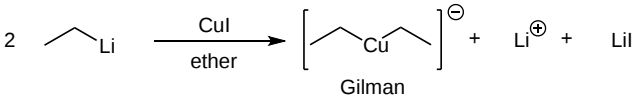


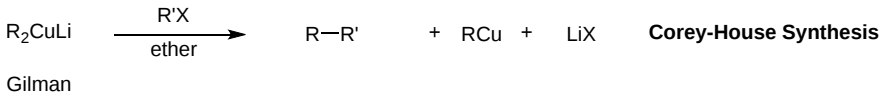


Reactions Alkyl Halides









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CHAPTER OVERVIEW

11: REACTIONS OF ALKYL HALIDES- NUCLEOPHILIC SUBSTITUTIONS AND ELIMINATIONS

LEARNING OBJECTIVES

After you have completed Chapter 11, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use the reactions studied in this chapter with those from earlier ones when designing multistep syntheses.
- use the reactions and concepts discussed in this chapter to solve road map problems.
- define, and use in context, the key terms introduced.

In this course, you have already seen several examples of nucleophilic substitution reactions; now you will see that these reactions can occur by two different mechanisms. You will study the factors that determine which mechanism will be in operation in a given situation, and examine possible ways for increasing or decreasing the rates at which such reactions occur. The stereochemical consequences of both mechanisms will also be discussed. Elimination reactions often accompany nucleophilic substitution; so these reactions are also examined in this chapter. Again you will see that two different mechanisms are possible, and, as in the case of nucleophilic substitution reactions, chemists have learned a great deal about the factors that determine which mechanism will be observed when a given alkyl halide undergoes such a reaction.

11.0: Introduction
11.1: The Discovery of Nucleophilic Substitution Reactions
11.2: The SN2 Reaction
11.3: Characteristics of the SN2 Reaction
11.4: The SN1 Reaction
11.5: Characteristics of the SN1 Reaction
11.6: Biological Substitution Reactions
11.7: Elimination Reactions- Zaitsev's Rule
11.8: The E2 Reaction and the Deuterium Isotope Effect
11.9: The E2 Reaction and Cyclohexane Conformation
11.10: The E1 and E1cB Reactions
11.11: Biological Elimination Reactions
11.12: A Summary of Reactivity - SN1, SN2, E1, E1cB, and E2
11.S: Reactions of Alkyl Halides - Nucleophilic Substitutions and Eliminations (Summary)

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11.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to identify substitution and elimination as being the two most important reactions of alkyl halides.

STUDY NOTES

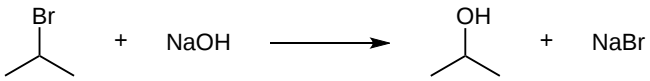
Alkyl halides are electrophiles, which means they can undergo nucleophilic substitution and base-induced elimination reactions. These reaction types offer a large and useful range of reactions for organic synthesis in the laboratory.

THE REACTIONS

Two reactions are shown her with both involving heating a halogenoalkane under reflux with sodium or potassium hydroxide solution. Two different reactions can occur.

NUCLEOPHILIC SUBSTITUTION

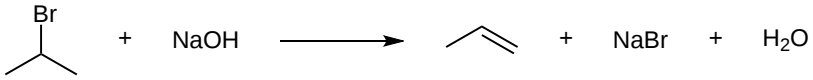
The hydroxide ions present are good nucleophiles, and one possibility is a replacement of the halogen atom by an -OH group to give an alcohol via a nucleophilic substitution reaction.



In the example, 2-bromopropane is converted into propan-2-ol.

ELIMINATION

Hydroxide ions are also strong bases, therefore halogenoalkanes also undergo elimination reactions in the presence of sodium or potassium hydroxide.



In this reaction, the 2-bromopropane has reacted to form an alkene - propene.

Notice that a hydrogen atom has been removed from one of the end carbon atoms together with the bromine from the centre one. In all simple elimination reactions the things being removed are on adjacent carbon atoms, and a double bond is set up between those carbons.

WHAT DECIDES WHETHER YOU GET SUBSTITUTION OR ELIMINATION?

The reagents you are using are the same for both substitution or elimination - the halogenoalkane and either sodium or potassium hydroxide solution. In all cases, you will get a mixture of both reactions happening - some substitution and some elimination. What you get most of depends on a number of factors.

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11.1: THE DISCOVERY OF NUCLEOPHILIC SUBSTITUTION REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the Walden inversion.
2. write a short paragraph describing the Walden inversion.
3. describe, using equations, a series of reactions interconverting two enantiomers of 1-phenyl-2-propanol which led to the conclusion that nucleophilic substitution of primary and secondary alkyl halides proceeds with inversion of configuration.

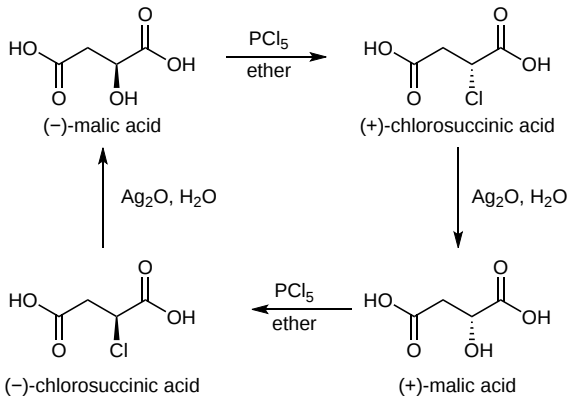
STUDY NOTES

The IUPAC name for malic acid is 2-hydroxybutanedioic acid. This acid is produced by apples, a fact which seems to have been appreciated by the British novelist Thomas Hardy in *The Woodlanders*:

Up, upward they crept, a stray beam of the sun alighting every now and then like a star on the blades of the pomace-shovels, which had been converted to steel mirrors by the action of the malic acid.

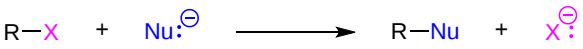
In 1896, the German chemist Paul Walden discovered that he could interconvert pure enantiomeric (+) and (-) malic acids through a series of reactions. This conversion meant that there was some kind of change in the stereochemistry made during the series of reactions. First, (−)-malic acid was reacted with **phosphorus pentachloride (PCl_5)** to provide (+)-chlorosuccinic acid.

This was reacted with **silver(I)oxide (Ag_2O)** to provide (+)-malic acid. These two combined steps caused an inversion of stereochemistry of (−)-malic acid to (+)-malic acid. The reaction series was then continued to convert (+)-malic acid back into (−)-malic acid by further reaction with PCl_5 and Ag_2O.

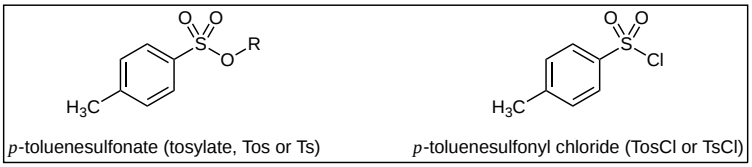


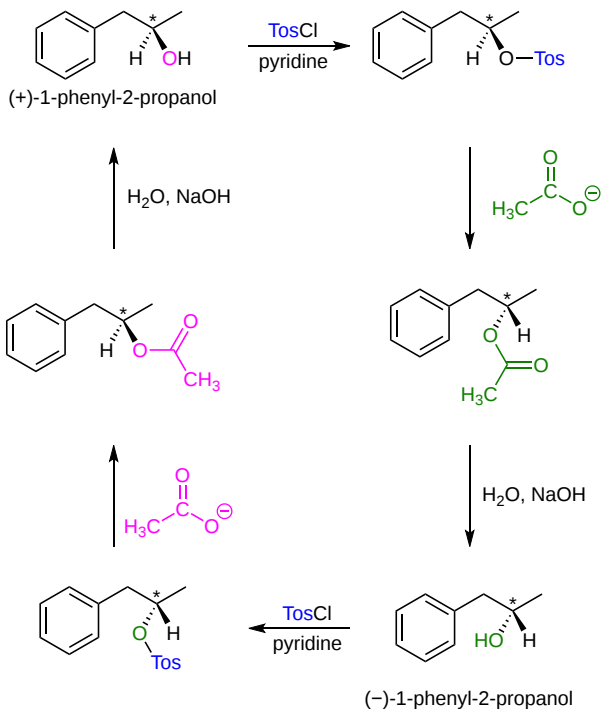
These results were considered astonishing. The fact that (−)-malic acid was converted into (+)-malic acid meant that the configuration of the chiral center has somehow been changed during the reaction series.

These reactions are currently referred to as nucleophilic substitution reactions because each step involves the substitution of one nucleophile by another. These are among the most common and versatile reaction types in organic chemistry.

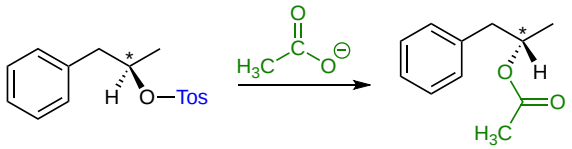


Further investigations into these reaction were undertaken during the 1920's and 1930's to clarify the mechanism and clarify how the inversion of configurations occur. These reactions involved nucleophilic substitution of an alkyl p-toluenesulfonate (called a tosylate group). For this purpose the tosylate groups act similarly to a halogen substituent. In the series of reactions (+)-1-phenyl-2-propanol is interconverted with (-)-1-phenyl-2-propanol.





Somewhere in this three-step series of reactions the configuration at a chiral center is being inverted. In the first step the tosylate is formed without breaking the C-O bond of the chiral center, which means the configuration is unchanged. Similarly, the cleavage of the ester in step three occurs without breaking the C-O bond of the chiral center, which also means the configuration of the chiral carbon is unaffected. It was determined that the second step where acetate nucleophile undergoes a substitution with tosylate was causing the stereochemical configuration to be inverted.



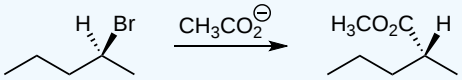
inversion of configuration

? EXERCISE 11.1.1

1) Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

Answer

1)



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11.2: THE SN2 REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an expression relating reaction rate to the concentration of reagents for a second-order reaction.
2. determine the order of a chemical reaction from experimentally obtained rate data.
3. describe the essential features of the S_N2 mechanism, and draw a generalized **transition state** for such a reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- bimolecular
- kinetics
- rate coefficient
- rate equation
- reaction rate
- second-order reaction
- S_N2

STUDY NOTES

Most of the key terms introduced in this section should already be familiar to you from your previous general chemistry course.

Reaction rate refers to the change in concentration of a reactant or product per unit of time. Using strict SI units, reaction rates are expressed in mol · L^{-1} · s^{-1}, but in some textbooks you will find this value written as M/s. In general, the reaction rate of a given reaction changes with time, as it is dependent on the concentration of one or more of the reactants.

An equation which shows the relationship between the reaction rate and the concentrations of the reactants is known as the rate equation. All rate equations contain a proportionality constant, usually given the symbol *k*, which is known as the rate coefficient. Some textbooks refer to this value as the "rate constant," but this name is a little misleading as it is not a true constant. The rate coefficient of a given reaction depends on such factors as temperature and the nature of the solvent.

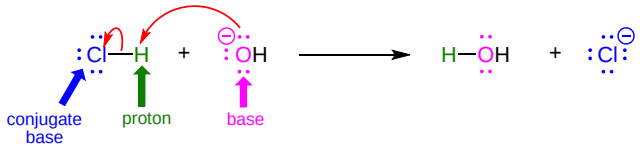
S_N2 is short for "bimolecular nucleophilic substitution." You will encounter abbreviations for other types of reactions later in this chapter.

If you are unclear on the point about the inversion of configuration during an S_N2 reaction, construct a molecular model of a chiral alkyl halide, the **transition state** formed when this substance reacts with a nucleophile in an S_N2 process, and the product obtained from this reaction.

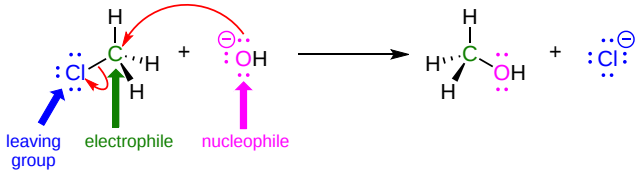
BRØNSTED-LOWRY ACID-BASE REACTIONS

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.

Acid-base reaction:

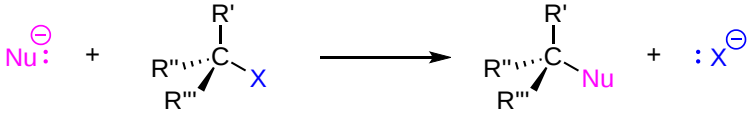


Nucleophilic substitution:



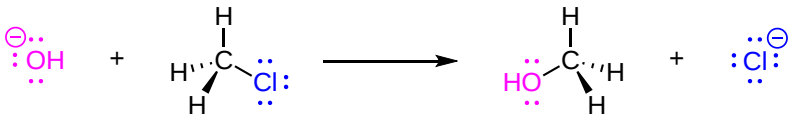
In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base. Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. In a similar fashion, we will call the leaving group 'X'. We will see as we study actual reactions that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture we will not include a charge designation on the 'X' or 'Nu' species. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction.

GENERAL S_N2 REACTION



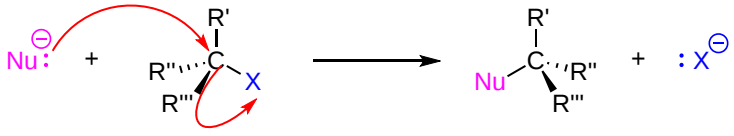
R = alkyl or H

EXAMPLE



THE S_N2 MECHANISM

Bimolecular nucleophilic substitution (S_N2) reactions are **concerted**, meaning they are a **one step process**. This means that the process whereby the nucleophile attacks and the leaving group leaves is simultaneous. Hence, the bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electrophilic carbon and the halogen. This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that this is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. The mechanism starts when lone pair electrons from the nucleophile attacks the electrophilic carbon of the alkyl halide to form a C-Nu sigma bond. Simultaneously, X-C bond is broken when the electrons are pushed onto the leaving group. Overall during this mechanism, a set of lone pair electrons are transferred from the nucleophile to the leaving groups.



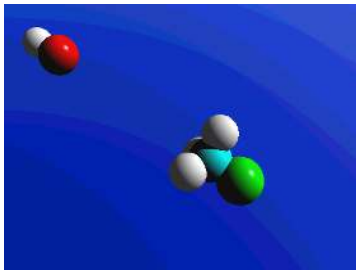
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must attack the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the leaving group - which is also an electron-rich group - blocks the way.



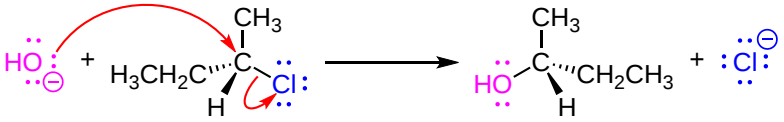
Nucleophilic attack is blocked from the front side… *…so attack occurs from the back side.*

The result of this backside attack is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, showing the S_N2 reaction between hydroxide ion and methyl iodide. Notice how backside attack by the hydroxide nucleophile results in inversion at the tetrahedral carbon electrophile.



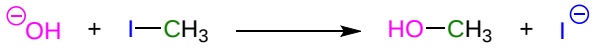
EXAMPLE



(*S*)-2-chlorobutane (*R*)-2-butanol

BIMOLECULAR NUCLEOPHILIC SUBSTITUTION REACTIONS AND KINETICS

In the term S_N2, (as previously stated) the number two stands for bimolecular, meaning there are two molecules involved in the rate determining step. The rate of bimolecular nucleophilic substitution reactions depends on the concentration of both the haloalkane and the nucleophile. To understand how the rate depends on the concentrations of both the haloalkane and the nucleophile, let us look at the following example. The hydroxide ion is the nucleophile and methyl iodide is the haloalkane.



$$\text{Rate} = k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$

If we were to double the concentration of either the haloalkane or the nucleophile, we can see that the rate of the reaction would proceed twice as fast as the initial rate.

$$\text{Rate}_1 = k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 2k\,[CH_3{-}I]\,[{}^{\ominus}OH]$$
$$\text{Rate}_2 = 2\text{Rate}_1$$

If we were to double the concentration of both the haloalkane and the nucleophile, we can see that the rate of the reaction would proceed four times as fast as the initial rate.

$$Rate_1 = k\,[CH_3{-}I]\,[^{\ominus}OH]$$
$$Rate_2 = 4k\,[CH_3{-}I]\,[^{\ominus}OH]$$
$$Rate_2 = 4Rate_1$$

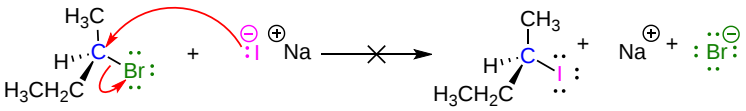
The bimolecular nucleophilic substitution reaction follows second-order kinetics; that is, the rate of the reaction depends on the concentration of two first-order reactants. In the case of bimolecular nucleophilic substitution, these two reactants are the haloalkane and the nucleophile. For further clarification on reaction kinetics, the following links may facilitate your understanding of rate laws, rate constants, and second-order kinetics:

- Definition of a Reaction Rate
- Rate Laws and Rate Constants
- The Determination of the Rate Law
- Second-Order Reactions

S_N2 REACTIONS ARE STEREOSPECIFIC

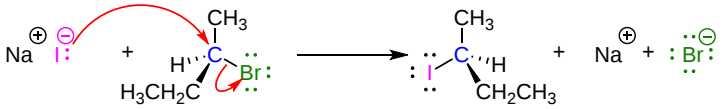
The S_N2 reaction is stereospecific. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an (*R*) enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the (*R*) enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the (*S*) enantiomer.

Frontside attack with retention of configuration:



(*R*)-2-bromobutane (*R*)-2-iodobutane

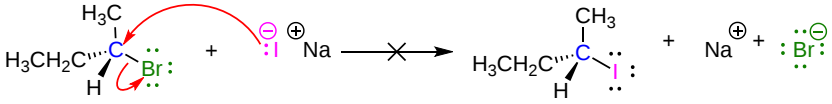
Backside attack with inversion of configuration:



(*R*)-2-bromobutane (*S*)-2-iodobutane

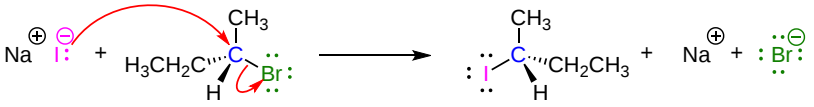
Conversely, if the substrate is an (*S*) enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the (*S*) enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the (*R*) enantiomer.

Frontside attack with retention of configuration:



(*S*)-2-bromobutane (*S*)-2-iodobutane

Backside attack with inversion of configuration:

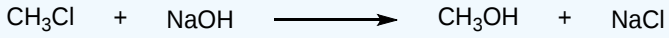


(*S*)-2-bromobutane (*R*)-2-iodobutane

In conclusion, S_N2 reactions that begin with the (*R*) enantiomer as the substrate will form the (*S*) enantiomer as the product. Those that begin with the (*S*) enantiomer as the substrate will form the (*R*) enantiomer as the product. This concept also applies to substrates that are *cis* and substrates that are *trans*. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

EXERCISE 11.2.1

1) The reaction below follows the S_N2 mechanism.



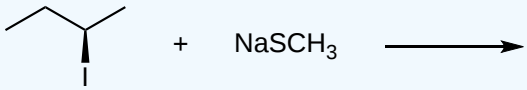
a) Write the rate law for this reaction.

b) Determine the value of the rate coefficient, k, if the initial concentrations are 0.01 M CH_3Cl, 0.01 M NaOH, and the initial reaction rate is 6 x 10^{-10} M/s.

c) Calculate the initial reaction rate if the initial reactant concentrations are changed to 0.02 M CH_3Cl and 0.0005 M NaOH.

2) Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

3) Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



4) Since everything is relative in chemistry, one reaction's nucleophile can be another reaction's leaving group. Some functional groups can only react as a nucleophile or electrophile, while other functional groups can react as either a nucleophile or electrophile depending on the reaction conditions. Classify the following compounds as nucleophile, electrophile, or leaving groups. More than one answer may be possible.

a) bromoethane

b) hydroxide

c) water

d) chlorocyclohexane

e) ethanol

f) bromide

Answer

1) a) rate = k [CH_3Cl] [OH^-]

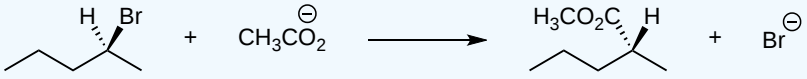
b) substitute the data into the rate expression above and apply algebra to solve for k

k = 6 x 10^{-6} $Lmol^{-1}s^{-1}$

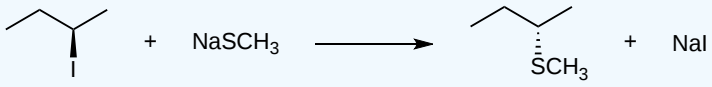
c) Using the rate law above, substitute the value for k from the previous question along with the new concentrations to determine the new initial rate.

rate = 6 x 10^{-10} M/s

2)



3)



4)

a) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

b) strong nucleophile

c) weak nucleophile and good leaving group

d) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

e) weak nucleophile, a poor electrophile without clever chemistry (stay tuned for future chapters), good leaving group

f) good nucleophile and a good leaving group

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11.3: CHARACTERISTICS OF THE SN2 REACTION

OBJECTIVES

After completing this section, you should be able to

1. discuss the role of steric effects in S_N2 reactions.
2. arrange a given series of alkyl halides in order of increasing or decreasing reactivity towards nucleophilic substitution through the S_N2 mechanism.
3. suggest a reason why vinyl halides and aryl halides do not undergo S_N2 reactions.
4. discuss how the nature of the nucleophile affects the rate of an S_N2 reaction.
5. arrange a given series of common nucleophiles (e.g., CN^-, I^-, Br^- Cl^-, H_2O) in order of increasing or decreasing nucleophilicity.
6. discuss how the nature of the leaving group affects the rate of an S_N2 reaction.
7. arrange a given series of leaving groups in order of increasing or decreasing ability to leave during an S_N2 reaction.
8. discuss the role played by the solvent in an S_N2 reaction.
9. give examples of the solvents which are commonly used for S_N2 reactions, and identify those that promote a high reaction rate.
10. predict which of two given S_N2 reactions will proceed faster, by taking into account the structure of the substrates, the nucleophiles involved, leaving-group ability, solvent effects, or any combination of these factors.

KEY TERMS

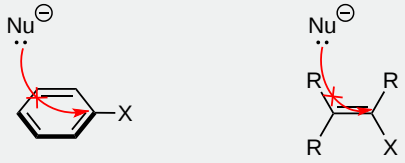
Make certain that you can define, and use in context, the key terms below.

- leaving group
- polar aprotic solvent
- solvation

STUDY NOTES

You may wish to review the discussion of acid-base theory given in Sections 2.7-2.11.

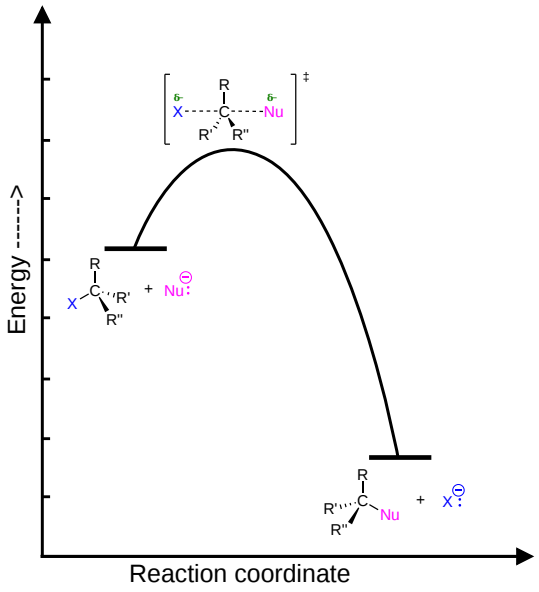
Both aryl and vinylic halides are relatively unreactive in S_N2 displacement mechanisms, mostly because during the backside attack of the molecule the incoming nucleophile is sterically hindered by both substituents and electron density from any double bonds present. Also, leaving groups on sp^2-hybridized carbons tend to be held tighter than sp^3-hybridized carbons.



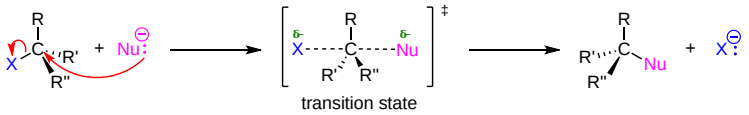
Solvation may be defined as the interaction between molecules of solvent and particles of solute. The result of solvation is to stabilize (i.e., lower the energy of) the solute particles. Solvents with lone pairs of electrons are good at solvating cations. Protic (i.e., hydroxylic) solvents are able to solvate anions through hydrogen bonding. As water has two lone pairs of electrons and is also protic, it is good at solvating both anions and cations.

POTENTIAL ENERGY DIAGRAM FOR AN S_N2 REACTION

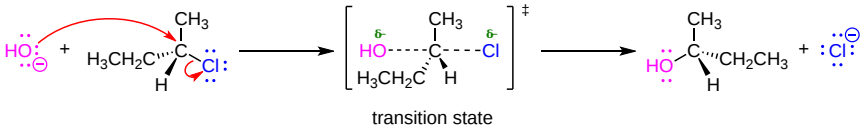
The potential energy diagram for an S_N2 reaction is shown below. This is a single-step, concerted process so a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. For an S_N2 reaction the transition state directly determines the energy of activation which must be overcome for the reaction to occur. Factors which affect the stability of the transition state affect the rate of the S_N2 reaction.



For an S_N2 reaction, the transition state represents the half way point of the reaction. The C-Nu bond is in the process of forming and is represented by a dashed bond. The X-C bond is in the process of breaking and is also represented by a dash bond. The negative charge of the nucleophile is in the process of being transfered to the leaving groups. This is represented by both the nucleophile and the leaving group having a partial negative charge. The electrophilic carbon and the three 'R' substituents all lie on the same plane. Brackets and a double-dagger are placed around the structure to represent that it is a transition state.

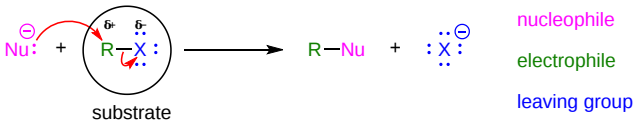


EXAMPLE

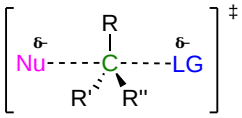


STERICALLY HINDERED SUBSTRATES WILL REDUCE THE S_N2 REACTION RATE

Steric hindrance about the electrophilic carbon, is one of the most important factors Determining the rate of S_N2 reactions. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below we are most interested in the electrophilic carbon that bears the leaving group.



The S_N2 **transition state** is very crowded. Recall that there are a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.

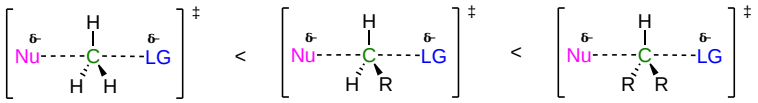


S_N2 Transition State

If each of the three substituents were hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion created in the planar portion of the transition state thereby increasing the ease at which the nucleophilic substitution reaction occurs. If one of the

hydrogens, however, were replaced with an R group, such as a methyl or ethyl group, there would be an increase in steric repulsion created in the planar portion of the transition state. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion in the transition state.

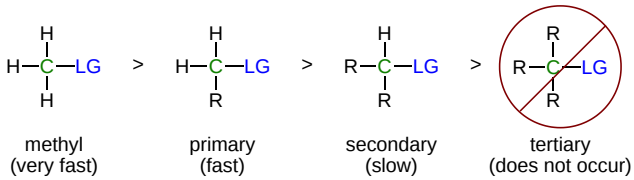
Steric repulsion of S_N2 Transition States



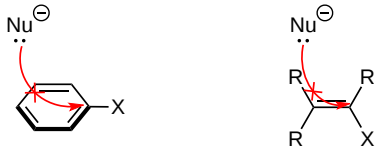
How does steric hindrance affect the rate at which an S_N2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. The increases steric hindrance destabilizes the transition state causing it to become higher in energy. This in turn increases the energy of activation and decreases the reaction rate.

The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms results in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.

S_N2 Displacement Reactivity of Haloalkanes



Vinyl and aryl halides are unreactive toward S_N2 displacement due to extreme steric factors. To perform an S_N2 reaction, the incoming nucleophile would have to enter the plane of the C-C double bond and move through the molecule to achieve the backside displacement required.



In addition to alkyl groups being added to the electrophilic carbon, it turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 1-bromo-2-methylpropane differs from 1-bromopropane in that it has a methyl group attached to the carbon that neighbors the electrophilic carbon. The addition of this methyl group results in a significant decrease in the rate of a nucleophilic substitution reaction.



1-bromo-2-methylpropane 1-bromopropane

If R groups were added to carbons farther away from the electrophilic carbon, we would still see a decrease in the reaction rate. However, branching at carbons farther away from the electrophilic carbon would have a much smaller effect.

THE NUCLEOPHILE

Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. In both laboratory and biological organic chemistry, the most relevant nucleophilic atoms are oxygen, nitrogen, and sulfur, and the most common nucleophilic functional groups are water, alcohols, phenols, amines, thiols, and occasionally carboxylates.

When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes a something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

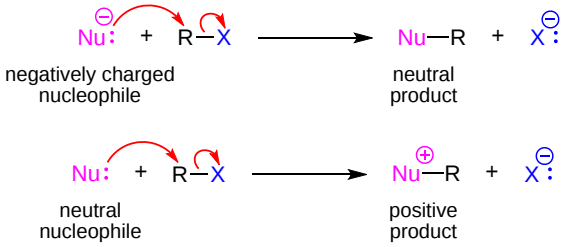
Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the

pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and vice versa. The range of basicities included in the following table is remarkable, covering over fifty powers of ten! In general, as the pKa of the conjugate acid increases the base becomes a stronger nuclophile. This, however, is not always the case.

Base	$I^{(-)}$	$Cl^{(-)}$	H_2O	$CH_3CO_2^{(-)}$	$RS^{(-)}$	$CN^{(-)}$	$RO^{(-)}$	$NH_2^{(-)}$	$CH_3^{(-)}$
Conj. Acid	HI	HCl	$H_3O^{(+)}$	CH_3CO_2H	RSH	HCN	ROH	NH_3	CH_4
pK_a	-9	-7	0.0	4.8	8	9.1	16	33	48

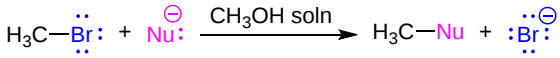
increasing base strength

Nucleophilicity is a more complex property. Any compound, neutral or charged, which has lone pair electrons can act a neuclophile. After a S_N2 reaction neutral nucleophiles make a positively charges products and negatively charged nucleophiles make neutral products. In general, negatively charges compound tend to make better nucleophilies.



Specifically, nucleophilicity refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH_3-Br. The nucleophilicity of the $Nu:^{(-)}$ reactant in the following substitution reaction varies as shown in the chart below:

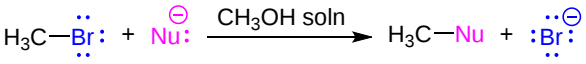
Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH_3-Br. Thus the nucleophilicity of the $Nu:^{(-)}$ reactant in the following substitution reaction varies as shown in the chart below:



NUCLEOPHILICITY: $H_2O < CH_3CO_2^{(-)} < NH_3 < CL^{(-)} < BR^{(-)} < HO^{(-)} < CH_3O^{(-)} < I^{(-)} < CN^{(-)} < CH_3S^{(-)}$

increasing nucleophile strength

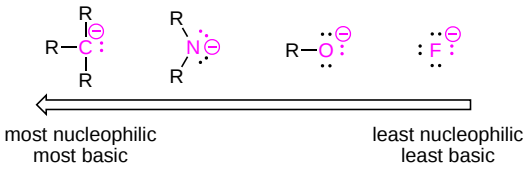
The versatility of the S_N2 reaction is shown by the wide variety of functional groups which can be formed.



Nucleophile		Products		
Formula	**Name**	**Formula**	**Name**	**Functional Group**
$CH_3S^{(-)}$	Methanethiolate	CH_3SCH_3	Dimethylsulfide	Sulfide
$CN^{(-)}$	Cyanide	CH_3CN	Acetonitrile	Nitrile
$I^{(-)}$	Iodide	CH_3I	Iodomethane	Alkyl Halide
$CH_3O^{(-)}$	Methoxide	CH_3OCH_3	Diethylether	Ether
$HO^{(-)}$	Hydroxide	CH_3OH	Methanol	Alcohol
$Br^{(-)}$	Bromide	CH_3Br	Bromomethane	Alkyl Halide
$Cl^{(-)}$	Chloride	CH_3Cl	Chloromethane	Alkyl Halide
NH_3	Ammonia	$CH_3NH_3^{(+)}$	Methylammonium ion	Ammonium
$CH_3CO_2^{(-)}$	Acetate	$CH_3O_2CH_3$	Methyl acetate	Ester
H_2O	Water	$CH_3OH_2^{(+)}$	Methylhydronium ion	Protonated Alcohol

PERIODIC TRENDS IN NUCLEOPHILICITY

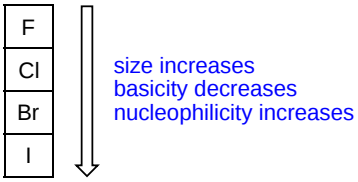
There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:



The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

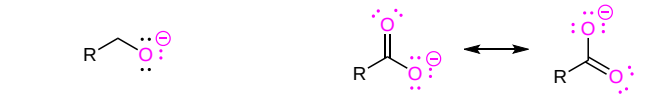
Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons and act as a nucleophile.



RESONANCE EFFECTS ON NUCLEOPHILICITY

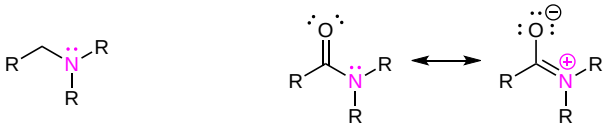
Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.



alkoxide ion
charge is localized on oxygen
more nucleophilic

carboxylate ion
charge is delocalized over both oxygens
less nucleophilic

The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



amine
more nucleophilic

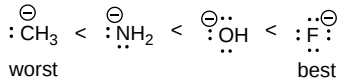
amide
less nucleophilic

THE LEAVING GROUP

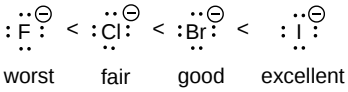
As Electronegativity Increases, The Ability of the Leaving Group to Leave Increases

As mentioned previously, if we move from left to right on the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing -

CH_3 to be the worst leaving group and F^- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that S_N2 reactions of fluoroalkanes are rarely observed.

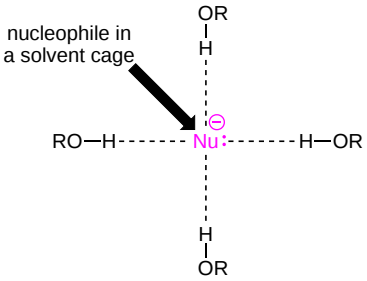


As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.



INFLUENCE OF THE SOLVENT IN AN S_N2 REACTION

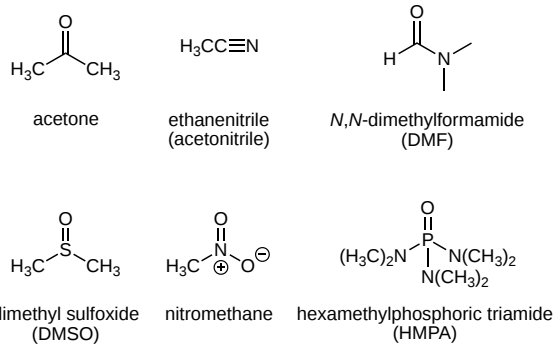
The rate of an S_N2 reaction is significantly influenced by the solvent in which the reaction takes place. The use of **protic solvents** (those, such as water or alcohols, with hydrogen-bond donating capability) decreases the power of the nucleophile, because of strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile. In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. A less powerful nucleophile in turn means a slower S_N2 reaction. S_N2 reactions are faster in **polar, aprotic solvents:** those that lack hydrogen-bond donating capability.



Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate an a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).

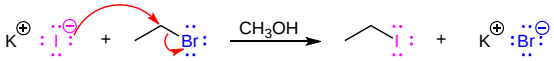
Below are several polar aprotic solvents that are commonly used in the laboratory:

Polar Aprotic Solvents

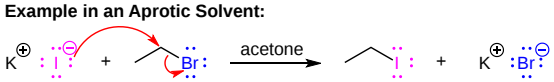


These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic effects on the rate at which a nucleophilic substitution reaction can occur. For example, if we consider the reaction between bromoethane and potassium iodide, the reaction occurs 500 times faster in acetone than in methanol.

Example in a Protic Solvent:



Example in an Aprotic Solvent:



500 times faster!

SUMMARY OF FACTORS IN AFFECTING S_N2 REACTIONS

There are four main factors which affect S_N2 reaction:

1) The structure of the alkyl portion of the substrate: S_N2 reactions are affected by steric hindrance around the electrophilic carbon. As steric hindrance increases the rate of S_N2 reactions decrease. Methyl and primary substrates work well for S_N2 reactions, secondary substrates react slowly, and teritary substrates do not undergo S_N2 reactions at all.

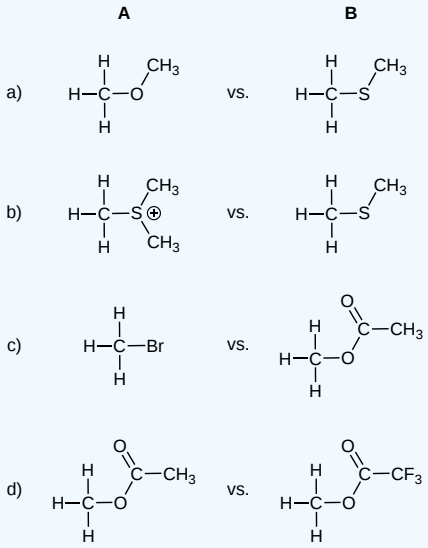
2) The reactivity of the nucleophile: The rate of S_N2 reaction is increased when strong nucleophiles are used. Strong nucleophiles tend to be negatively charged and good bases. Also, being of an increases size tends to increase the nucleopihlicity of an atom.

3) The nature of the leaving group: The rate of S_N2 reaction is increased when leaving groups are used in the substrate. Good leaving groups tend to stabilize the electrons gained during an S_N2 reaction. High electronegativity, resonance, and an increases size all can stabilize electrons.

4) The solvent: S_N2 reaction are severely hindered when a polar protic solvent is used for the reaction. Instead, polar aprotic solvents tend to be used for S_N2 reaction.

EXAMPLE 11.3.1

In each pair (A and B) below, which electrophile would be expected to react more rapidly in an S_N2 reaction with the thiol group of cysteine as the common nucleophile?



Solution (8.13)

? EXERCISE 11.3.1

1) What product(s) do you expect from the reaction of 1-bromopentane with each of the following reagents in an S_N2 reaction?

a) KI

b) NaOH

c) $CH_3C{\equiv}C\text{-}Li$

d) NH_3

2)

Which in the following pairs is a better nuceophile?

a) $(CH_3CH_2)_2N^-$ or $(CH_3CH_2)_2NH$

https://chem.libretexts.org/@go/page/31507

b) $(CH_3CH_2)_3N$ or $(CH_3CH_2)_3B$

c) H_2O or H_2S

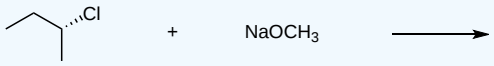
3) Order the following in increasing reactivity for an S_N2 reaction.

CH_3CH_2Br CH_3CH_2OTos $(CH_3CH_2)_3CCl$ $(CH_3CH_2)_2CHCl$

4) Solvents benzene, ether, chloroform are non-polar and not strongly polar solvents. What effects do these solvents have on an S_N2 reaction?

5) Predict the products of these nucleophilic substitution reactions, including stereochemistry when appropriate.

a)



b)



d)

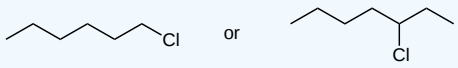


d)

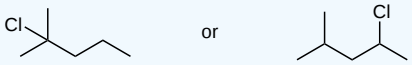
(*S*)-2-bromopentane + sodium hydroxide →

6) Predict which compound in each pair would undergo the S_N2 reaction faster.

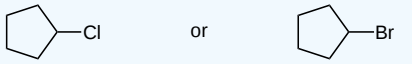
a)



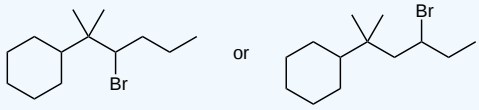
b)



c)

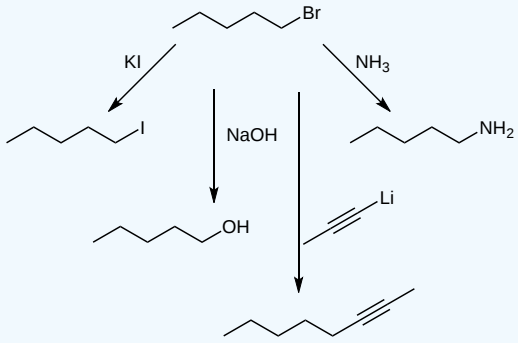


d)



Answer

1)



2)

a) $(CH_3CH_2)_2N^-$ as there is a charge present on the nitrogen.

b) $(CH_3CH_2)_3N$ because a lone pair of electrons is present.

c) H_2O as oxygen is more electronegative.

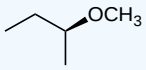
3)

$(CH_3CH_2)_3CCl$ OR $(CH_3CH_2)_2CHCl$ < CH_3CH_2Br < CH_3CH_2OTos

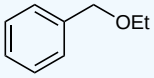
4) They will decrease the reactivity of the reaction.

5)

a)

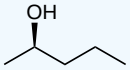


b)



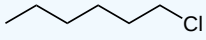
c) No reaction

d)

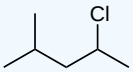


6)

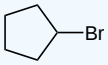
a)



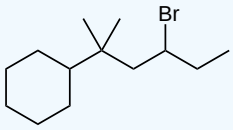
b)



c)



d)



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11.4: THE SN1 REACTION

OBJECTIVES

After completing this section, you should be able to

- write an expression relating reaction rate and reactant concentration for a first-order reaction.
- compare the kinetics of S_N1 and S_N2 reactions.
- identify the rate-limiting step for a reaction, given the reaction energy diagram.
- sketch a reaction energy diagram for a reaction, given the mechanism and sufficient information to identify the rate-limiting step.
- write the mechanism of a typical S_N1 reaction, and discuss the important features of the mechanism.
- discuss the stereochemistry of an S_N1 reaction, and explain why a racemic mixture is expected when substitution takes place at the chiral carbon atom of an optically pure substrate.
- explain why unimolecular nucleophilic substitution at the chiral carbon atom of an optically pure substrate does not result in complete racemization.
- compare the stereochemical consequences of the S_N1 mechanism with those of the S_N2 mechanism.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- first-order reaction
- rate-limiting step
- S_N1

STUDY NOTES

You should recognize that certain compounds (notably tertiary alkyl halides) which react very slowly by the S_N2 mechanism can undergo rapid nucleophilic substitution by an alternative mechanism.

The abbreviation S_N1 refers to "unimolecular nucleophilic substitution." In a *first-order reaction*, the rate of the reaction depends on the concentration of only one of the reactants. Thus, when an alkyl halide reacts by an S_N1 mechanism, the rate of reaction is dependent on the concentration of the alkyl halide, but is independent of the concentration of the attacking nucleophile.

Note: In many textbooks the "rate-limiting step" is called the "rate-determining step."

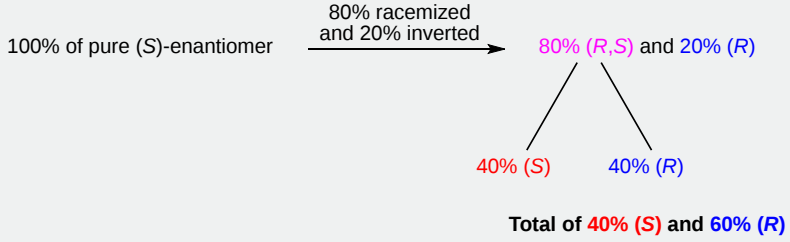
Racemization problems can be a potential source of confusion. Most students entering an introductory organic chemistry course have a reasonable background in mathematics, and feel comfortable if they have a formula or equation they can use in this type of situation. Thus, we recommend that you consider the following approach.

1. In a given mixture of enantiomers, let x = the fraction of the (+)-enantiomer, and $1 - x$ = the fraction of the (−)-enantiomer. [Remember that the fraction can be obtained by dividing the percentage by 100%.]
2. The observed $[\alpha]_D$ of the mixture is then given by:

   Observed $[\alpha]_D = x$ ($[\alpha]_D$ of the (+)-enantiomer)

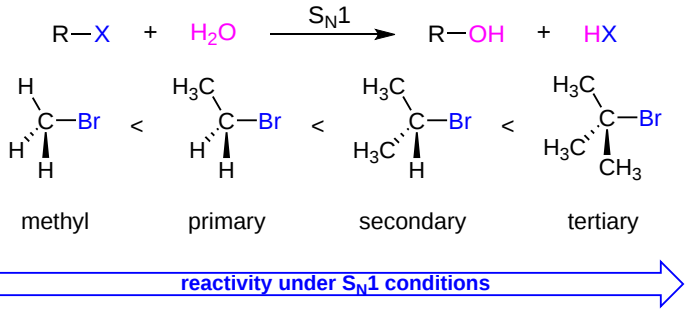
   + $(1 - x)$($[\alpha]_D$ of the (−)-enantiomer)

Another source of confusion is the way in which the terms "percentage racemization" and "percentage inversion" are used. To illustrate this idea, consider a given reaction that is said to be 80% racemized and 20% inverted. You must be clear in your mind that 80% racemized means that we have 40% of the original configuration and 60% (40% + 20%) of the inverted configuration. This point is illustrated in the diagram below.



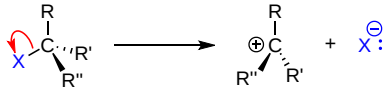
GENERAL S_N1 REACTION

When looking at the following substitution reaction it would be expected to be extremely slow. The reaction represents a worst case scenario based off the rules of an S_N2 reaction. The substrate is sterically hindered, the nucleophile is relatively weak, and the solvent is polar protic. However, the reaction proceeds quickly and prefers tertiary substrates over methyl, which is opposite to the trend seen in S_N2 reactions. It makes sense that this substitution reaction occurs using a different mechanism than S_N2.

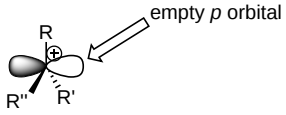


THE S_N1 MECHANISM

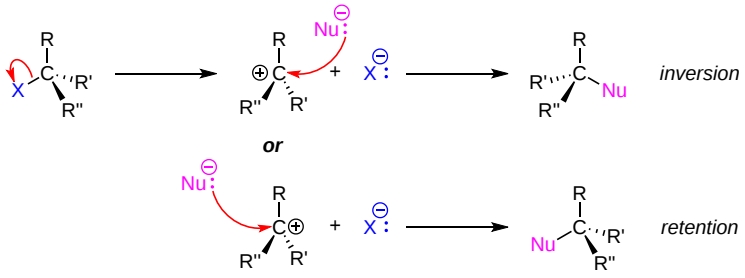
A second model for a nucleophilic substitution reaction is called the '**dissociative**', or '**S_N1**' mechanism. In the S_N1 reaction, the bond between the substrate and the leaving group is broken when the leaving group departs with the pair of electrons that formerly composed the bond.



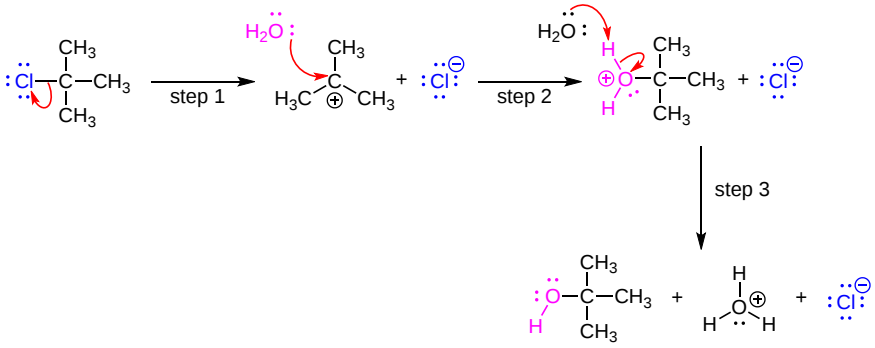
This results in the formation of a **carbocation** (from "carbon" and "cation") the word for a positively charged carbon atom. Because the carbocation has only three bonds, it bears a formal charge of +1. Recall that a carbocation is sp^2 hybridized, with trigonal planar geometry. The positive charge is contained in an empty, unhybridized *p* orbital perpendicular to the plane formed by the three sigma bonds. The formation of a carbocation is not energetically favored, so this step in the reaction is the slowest step and determines the overall rate of the reaction. The step which controls the overall rate of a reaction is called the **rate-determining step**.



In the second step of this two-step reaction, the nucleophile attacks the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry. Since the nucleophile attacks the carbocation only after the leaving group has departed, there is no need for back-side attack. The carbocation and its substituents are all in the same plane, meaning that the nucleophile can attack from either side. As a result, both enantiomers are formed in an the S_N1 reaction, leading to a **racemic mixture** of both enantiomers.

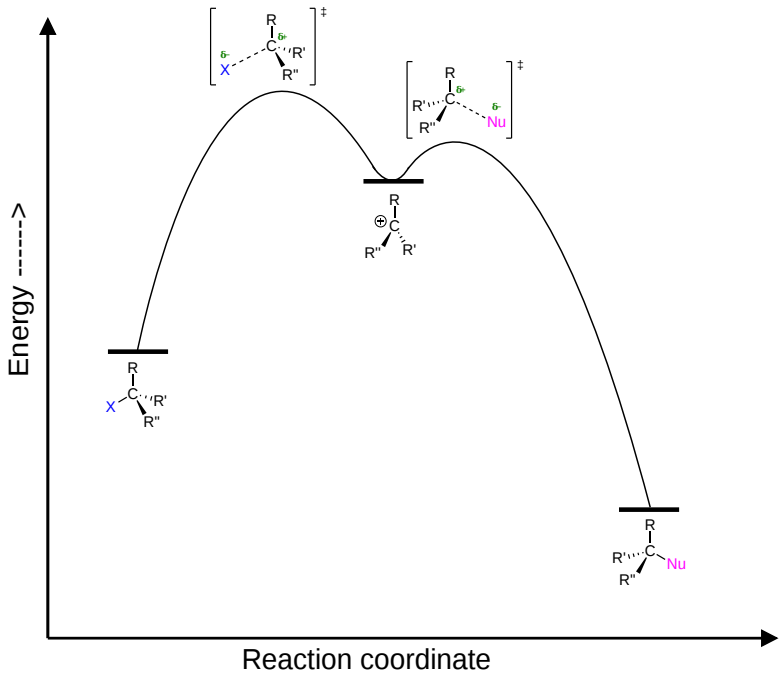


Because S_N1 reactions almost exclusively involve neutral nucleophile the product of this second step of the mechanism is often positively charged. The neutral substitution product is usually formed after a third, deprotonation step.



REACTION COORDINATE DIAGRAMS AND S_N1 MECHANISM

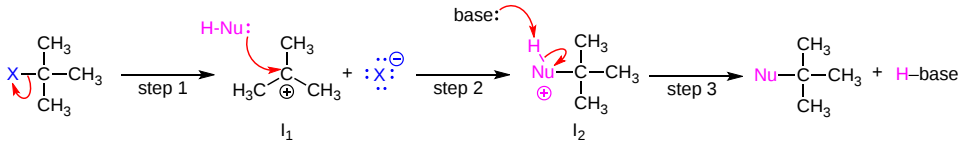
During the S_N1 reaction we see an example of a reaction intermediate, a very important concept in the study of organic reaction mechanisms that was introduced earlier in the module on organic reactivity Recall that many important organic reactions do not occur in a single step; rather, they are the sum of two or more discreet bond-forming / bond-breaking steps, and involve transient intermediate species that go on to react very quickly. In the S_N1 reaction, the carbocation species is a reaction intermediate. A potential energy diagram for an S_N1 reaction shows that the carbocation intermediate can be visualized as a kind of valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the two transition states. The following reaction coordinate diagram shows an example of a an S_N1 reaction with a negatively charged nucleophile.



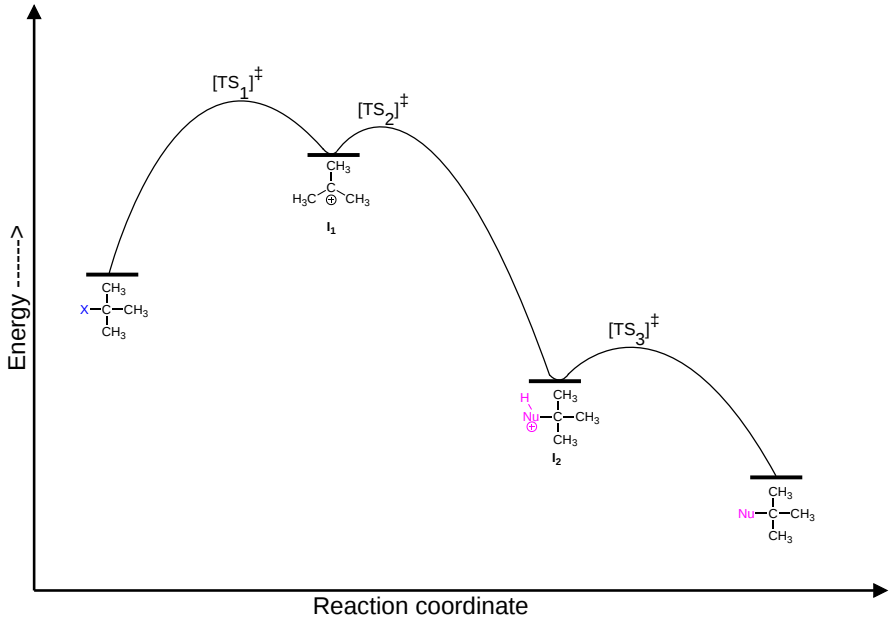
There are several important consequences to the **unimolecular** nature of the rate-determining step in the the S_N1 reaction. The first step (dissociation) is the rate determining step, so the rate is controlled only by the loss of the leaving group and does not involve any participation of the nucleophile. Therefore, the rate of the reaction is dependent only on the concentration of the substrate, not on the concentration of the nucleophile.

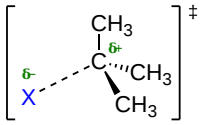
This can also be shown for the reactions with a neutral nucleophile which includes an extra step of deprotonation. A potential energy diagram for this mechanism shows that each of the two positively-charged intermediates (I_1 and I_2) can be visualized as a valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the transition states. The first, bond-breaking step is the slowest, rate-determining step - notice it has the highest activation energy and leads to the highest-energy species, I_1, the

carbocation intermediate. Step 2 is rapid: a new covalent bond forms between a carbocation and a water nucleophile, and no covalent bonds are broken. The third step represents a Bronsted-Lowry proton transfer which is rapid, with low activation energy.



Because the first step of the mechanism is the rate determining step, the first transition state will be the most important. During the first step, a carbon-leaving group bond in a neutral substrate is broken to form a carbocation intermediate and a leaving group anion. The breaking bond is represented as a dashed-partial bond in the transition state. A partial positive charge is shown on the carbon to represent the formation of a carbocation and a partial negative charge is shown on the leaving group to represent the formation of an anion.





Transition State 1 ([TS_1]‡)

S_N1 REACTION KINETICS

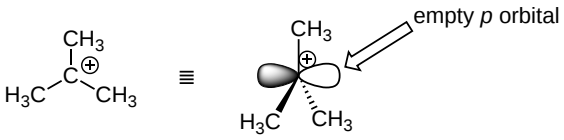
In the first step of an S_N1 mechanism, two charged species are formed from a neutral molecule. This step is much the slower of the three steps, and is therefore rate-determining. In the reaction energy diagram, the activation energy for the first step is higher than that for the second step indicating that the S_N1 reaction has *first order*, *unimolecular* kinetics because the rate determining step involves one molecule splitting apart, not two molecules colliding. It is important to remember that first order refers to the rate law expression where the generic term substrate is used to describe the alkyl halide.

$$\text{rate} = k\,[\text{substrate}]$$

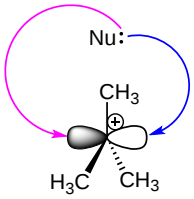
Because an S_N1 reaction is first order overall the concentration of the nucleophile does not affect the rate. Since the nucleophile is not involved in the rate-limiting first step, the nature of the nucleophile does not affect the rate of an S_N1 reaction.

STEREOCHEMICAL CONSIDERATIONS

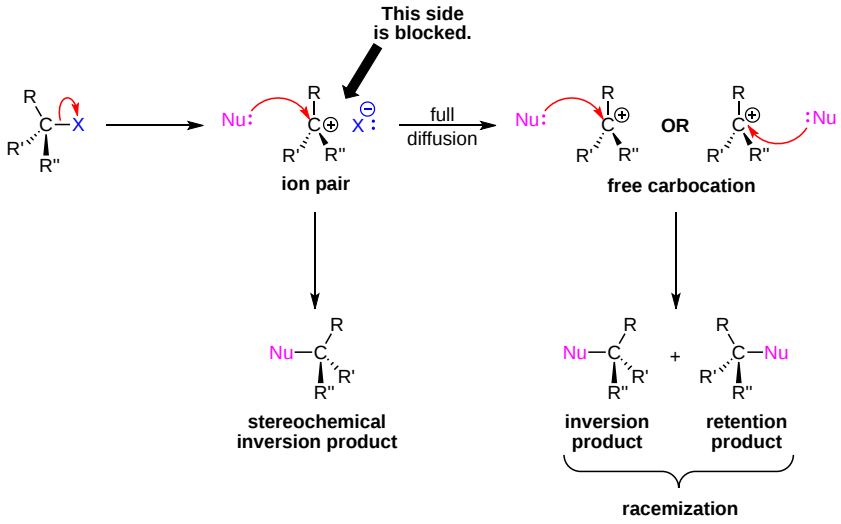
We saw that S_N2 reactions result in inversion of stereochemical configuration at the carbon center. The difference in mechanisms means the stereochemical outcome of S_N1 can be different than S_N2. Recall that a carbocation intermediate produced during an S_N1 reaction is sp^2-hybridized, with an empty p orbital perpendicular to the plane formed by the three sigma bonds:



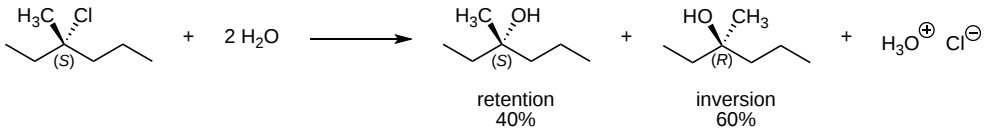
Because the nucleophile is free to attack from either side of the carbocation electrophile, the reaction leads to a 50:50 mixture of two stereoisomeric products. In other words: the S_N1 reaction occurs with both retention or inversion of configuration at the electrophilic carbon, leading to racemization if the carbon is chiral after the substitution.



However, often chemical reactions are more complicated than the mechanisms that represent limiting cases like S_N1 and S_N2. Experimental data has shown that the inversion product is favored over racemization due to the formation of **ion pairs**. After dissociation during the rate determining step the carbocation and the leaving group are still electrostatically associated. The leaving group anion is temporarily held in place which provides a shield to one side of the carbocation. If substitution occurs before the leaving group anion fully diffuses away the stereochemical inversion substitution product is created. Only after the leaving group fully diffuses away can racemization occur. Overall, the product of an S_N1 reaction shows an excess of the stereochemical inversion product.



For an example, consider the hydrolysis of (*S*)-3-chloro-3-methylhexane.



EXERCISE 11.4.1

Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

a) $CH_3I + CH_3S^{\ominus} \xrightarrow{S_N2}$

b) $(CH_3)_3CBr + CH_3SH \xrightarrow{S_N1}$

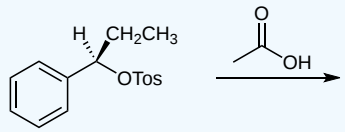
Answer

For Reaction A, the rate law is rate = k[CH_3I][CH_3S^-]. Therefore, if the concentration of the nucleophile, CH_3S^-, is doubled and the concentration of the alkyl halide remains the same, then the reaction rate will double.

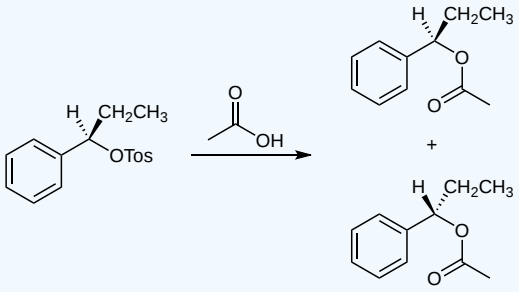
For Reaction B, the rate law is rate = k[$(CH_3)_3Br$]. Therefore, if the concentration of the nucleophile, CH_3SH, is doubled and the concentration of the alkyl halide remains the same, then reaction rate stays the same.

EXERCISE 11.4.2

Give the products of the following S_N1 reaction. Show stereochemistry.



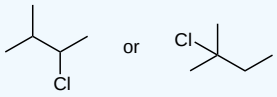
Answer



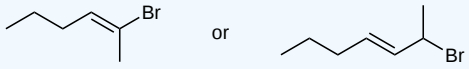
EXERCISE 11.4.3

Predict with compound in each pair will undergo an S_N1 reaction more quickly.

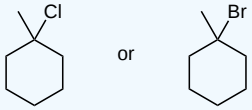
a)



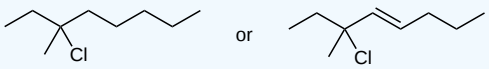
b)



c)

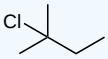


d)

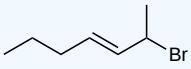


Answer

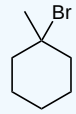
a)

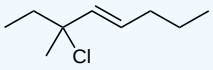


b)



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c) 

d) 

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11.5: CHARACTERISTICS OF THE SN1 REACTION

OBJECTIVES

After completing this section, you should be able to

1. discuss how the structure of the substrate affects the rate of a reaction occurring by the S_N1 mechanism.
2. arrange a given list of carbocations (including benzyl and allyl) in order of increasing or decreasing stability.
3. explain the high stability of the allyl and benzyl carbocations.
4. arrange a given series of compounds in order of increasing or decreasing reactivity in S_N1 reactions, and discuss this order in terms of the Hammond postulate.
5. discuss how the nature of the leaving group affects the rate of an S_N1 reaction, and in particular, explain why S_N1 reactions involving alcohols are carried out under acidic conditions.
6. explain why the nature of the nucleophile does not affect the rate of an S_N1 reaction.
7. discuss the role played by the solvent in an S_N1 reaction, and hence determine whether a given solvent will promote reaction by this mechanism.
8. compare the roles played by the solvent in S_N1 and in S_N2 reactions.
9. determine which of two S_N1 reactions will occur faster, by taking into account factors such as the structure of the substrate and the polarity of the solvent.
10. determine whether a given reaction is most likely to occur by an S_N1 or S_N2 mechanism, based on factors such as the structure of the substrate, the solvent used, etc.

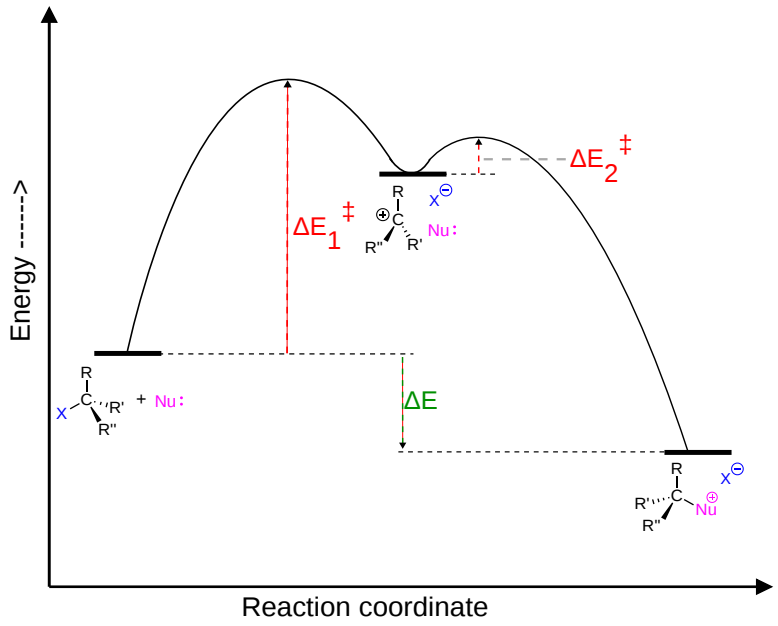
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

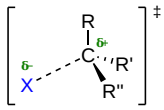
- benzylic
- dielectric constant
- polarity

THE SUBSTRATE IN S_N1REACTIONS

As discussed in the previous section S_N1 reactions follow first order kinetics due to a multi-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide to form a carbocation.



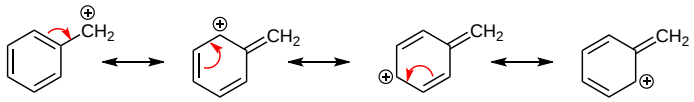
The transition state for the rate determining step shows the transition of an alkyl halide to a carbocation. Because the rate determining step is endothermic, the Hammond postulate says that the transition state more closely resembles the carbocation intermediate. Factors which stabilize this intermediate will lower the energy of activation for the rate determining step and cause the rate of reaction to increase. In general, a more stable carbocation intermediate formed during the reaction allows for a faster the S_N1 reaction rate.



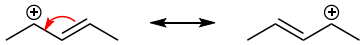
Transition State 1

($TS_1^{\ddagger}$)

In Section 7-9, the stability of alky carbocations was shown to be $3^o > 2^o > 1^o >$ methyl. Two special cases of resonance-stabilized carbocations, allyl and benzyl, must be considered and added to the list. The delocalization of the positive charge over an extended p orbital system allows for allyl and benzyl carbocations to be exceptionally stable. The resonance hybrid of an allyic cation is made up of two resonance forms while the resonance hybrid of the benzylic carbocation is made up of five.

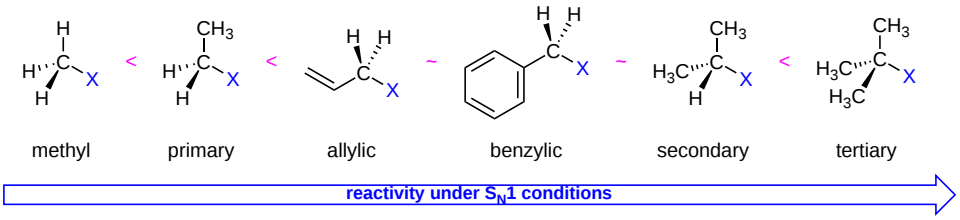


Resonance Structures for a Benzyl Carbocation



Resonance Structures for an Allylic Carbocation

Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	$CH_2{=}CH\text{-}CH_2^{(+)}$	≈	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

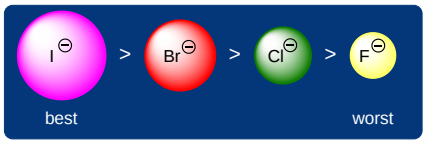


EFFECTS OF LEAVING GROUP

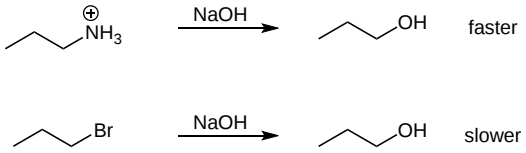
Since leaving group removal is involved in the rate-determining step of the S_N1 mechanism, reaction rates increase with a good leaving group. A good leaving group can stabilize the electron pair it obtains after the breaking of the C-Leaving Group bond faster. Once the bond breaks, the carbocation is formed and the faster the carbocation is formed, the faster the nucleophile can come in and the faster the reaction will be completed.

Because weak bases tend to strongly hold onto their electrons, they are lower energy molecules and they tend to make good leaving groups. Strong bases, on the other hand, donate electrons readily because they are high energy, reactive molecules. Therefore, they are not typically good leaving groups. As you go from left to right on the periodic table, electron donating ability decreases and thus ability to be a good leaving group increases. Halides are an example of a good leaving group whose leaving-group ability increases as you go down the halogen column of the periodic table.

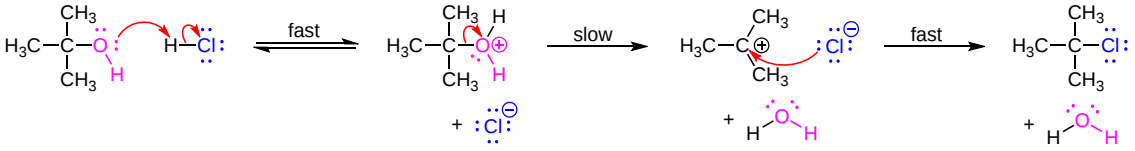




The two reactions below only vary by the different leaving groups in each reaction. The reaction with a more stable leaving group is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.

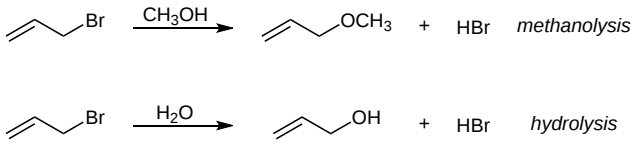


Under acidic conditions, the -OH group of an alcohol can be converted into a neutral water leaving group through protonation. As discussed in **Section 10-5**, this occurs during the conversion of a tertiary alcohol to an alkyl halide through reaction with HCl or HBr. Because the -OH group itself is a poor nucleophile, the mechanism starts with protonation to form a hydronium ion. Neutral water is then lost as a leaving group to create the carbocation intermediate which then reacts with the halide ion nucleophile to provide the alkyl halide product. This reaction works best when a tertiary alcohol is used because it produces a stable carbocation intermediate.



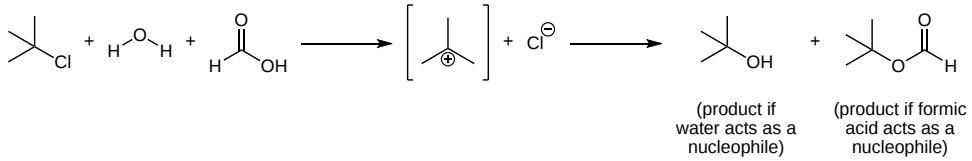
THE NUCLEOPHILE

Since nucleophiles only participate in the fast second step, their relative molar concentrations rather than their nucleophilicities should be the primary product-determining factor. If a nucleophilic solvent such as water is used, its high concentration will assure that alcohols are the major product. While recombination of the halide anion with the carbocation intermediate can occur, it simply reforms the starting compound. Also this is less likely since there are less molecules of the leaving group in solution than there are of the solvent. Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The S_N1 reaction of allyl bromide in methanol is an example of what we would call **methanolysis**, while if water is the solvent the reaction would be called **hydrolysis**:



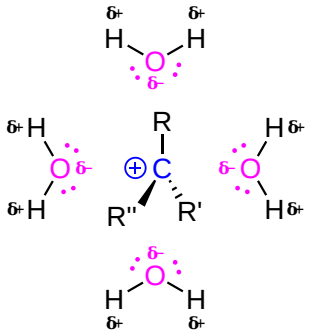
The strength of the nucleophile does not affect the reaction rate of S_N1 because, as described previously, the nucleophile is not involved in the rate-determining step. However, if you have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affects the distribution of products that you will get. For example, if you have $(CH_3)_3CCl$ reacting in

water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.



SOLVENT EFFECTS ON THE S_N1 REACTION

Since the hydrogen atom in a polar protic solvent is highly positively charged, it can interact with the anionic nucleophile which would negatively affect an S_N2 reaction which depends on nucleophilic attack during the rate-determining step of the reaction. However, this does not affect an S_N1 reaction because the nucleophile is not a part of the rate-determining step. Polar protic solvents actually speed up the rate of the unimolecular substitution reaction because the large dipole moment of the solvent helps to stabilize the carbocation-like transition state. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction.



The polarity and the ability of the solvent to stabilize the intermediate carbocation is very important as shown by the relative rate data for a solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant the more polar the substance and in the case of S_N1 reactions, the faster the rate.

Solvent	Dielectric Constant	Relative Rate
CH_3CO_2H	6	1
CH_3OH	33	4
H_2O	78	150,000

(note that even though acetic acid is a highly polar molecule, it tends to make a dimer with itself greatly reducing its dielectric constant)

PREDICTING S_N1 VS. S_N2 MECHANISMS

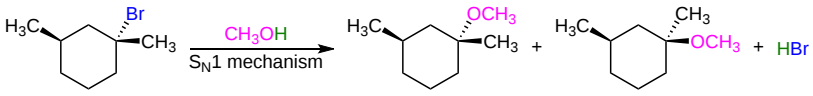
When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.

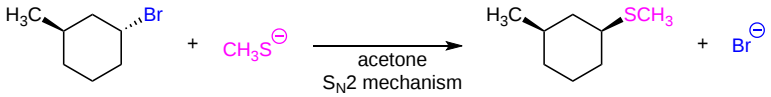
2) **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.

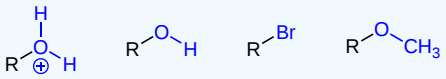


In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar aprotic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.

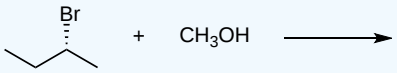


? EXERCISE 11.5.1

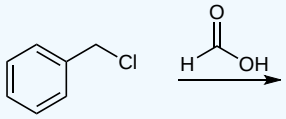
1. Put the following leaving groups highlighted in blue in order of decreasing leaving group ability



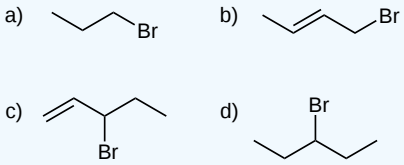
2. Which solvent would an S_N1 reaction occur faster in? H_2O or CH_3CN
3. What kind of conditions disfavor S_N1 reactions?
4. What are the products of the following reaction and does it proceed via S_N1 or S_N2?



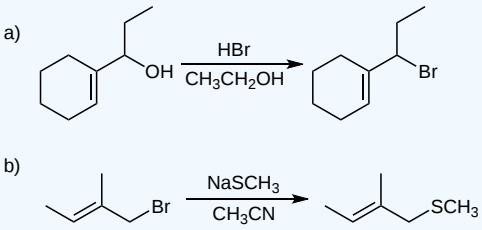
5. How could you change the reactants in the problem 4 to favor the other substitution reaction?
6. Indicate the expected product and list why it occurs through S_N1 instead of S_N2?



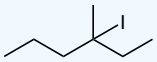
7. Rank the following by increasing reactivity in an S_N1 reaction.

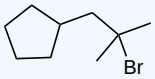


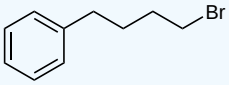
8. 3-bromo-1-pentene and 1-bromo-2-pentene undergo S_N1 reaction at almost the same rate, but one is a secondary halide while the other is a primary halide. Explain why this is.
9. Label the following reactions as most likely occuring by an S_N1 or S_N2 mechanism. Suggest why.

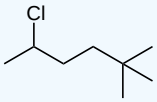


10. Give the solvolysis product expected when the compound is heated in methanol.

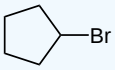
a) 

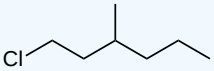
b) 

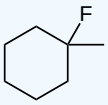
c) 

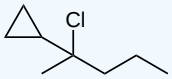
d) 

11. Predict whether each compound below would be more likely to undergo a S_N2 or S_N1 reaction.

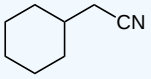
a) 

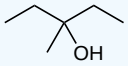
b) 

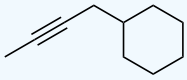
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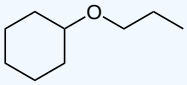
d) 

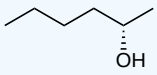
12. Show how each compound may be synthesized using nucleophilic substitution reactions.

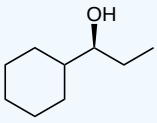
a) 

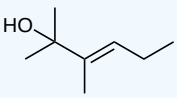
b) 

c) 

d) 

e) 

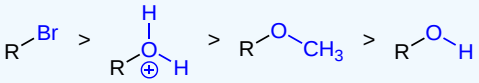
f) 

g) 

Answers

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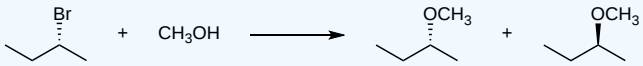
1.



2. An S_N1 reaction would occur faster in H_2O because it's polar protic and would stabilize the carbocation and CH_3CN is polar aprotic.

3. Polar aprotic solvents, a weak leaving group and primary substrates disfavor S_N1 reactions.

4.

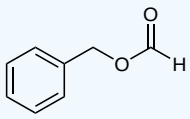


racemic mixture

Reaction proceeds via S_N1 because a secondary carbocation was formed, the solvent is polar protic and Br^- is a good leaving group.

5. You could change the solvent to something polar aprotic like CH_3CN or DMSO, and you could use a stronger nucleophile such as $NaOCH_3$. Note that this would give only the inverted product, and not a racemic mixture.

6.

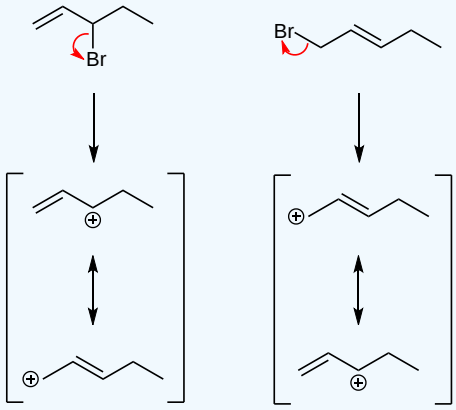


This reaction occurs via S_N1 because Cl^- is a good leaving group, the intermediate carbocation is a stable benzylic cation, and the solvent is polar protic. This is an example of a solvolysis reaction because the nucleophile is also the solvent.

7. Consider the stability of the intermediate, the carbocation.

A < D < B < C (most reactive)

8. They have the same intermediates when you look at the resonance forms.

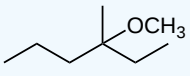


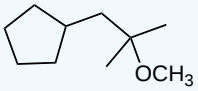
9.

A – S_N1 *poor leaving group, protic solvent, secondary cation intermediate

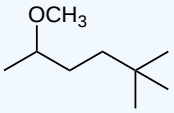
B – S_N2 *good leaving group, polar solvent, primary position.

10.

a) 

b) 

c) no reaction

d) 

11.

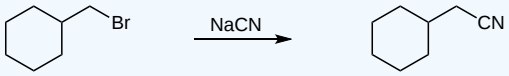
a) Can undergo S_N1 or S_N2, depending on reaction conditions

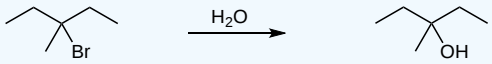
b) S_N2

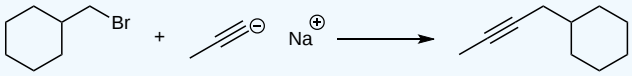
c) S_N1

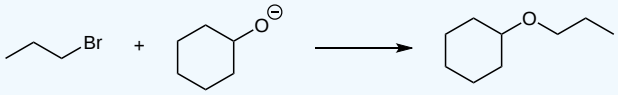
d) S_N1

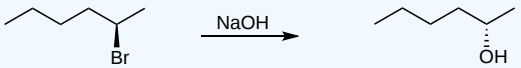
12.

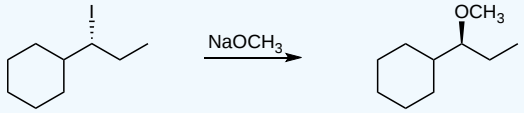
a) 

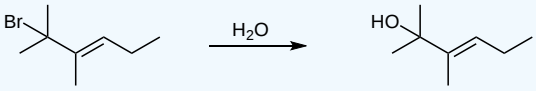
b) 

c) 

d) 

e) 

f) 

g) 

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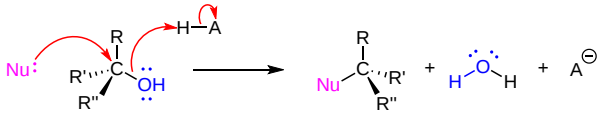
11.6: BIOLOGICAL SUBSTITUTION REACTIONS

OBJECTIVE

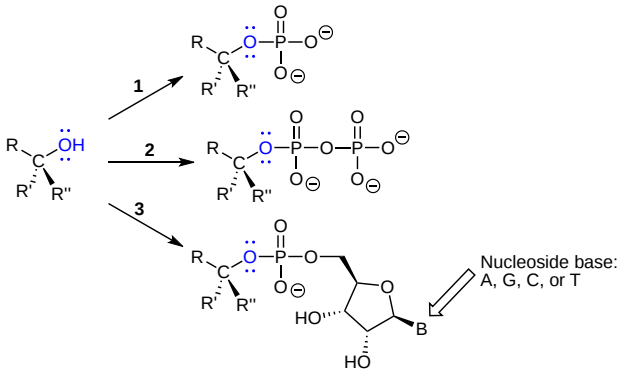
After completing this section, you should have an appreciation that S_N1 and S_N2 mechanisms exist and are well-known in biological chemistry.

LEAVING GROUPS IN BIOCHEMICAL REACTIONS

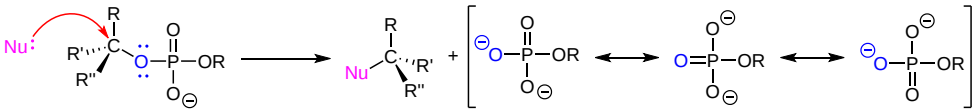
In biological reactions, we do not often see halides serving as leaving groups (in fact, outside of some marine organisms, halogens are fairly unusual in biological molecules). More common leaving groups in biochemical reactions are phosphates, water, alcohols, and thiols. In many cases, the leaving group is protonated by an acidic group on the enzyme as bond-breaking occurs. For example, hydroxide ion itself seldom acts as a leaving group – it is simply too high in energy (too basic). Rather, the hydroxide oxygen is generally protonated by an enzymatic acid before or during the bond-breaking event, resulting in a (very stable) water leaving group.



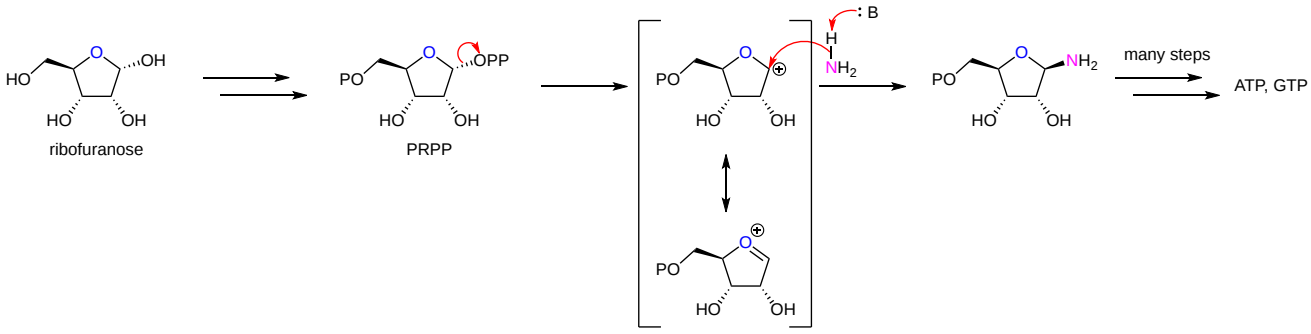
More often, however, the hydroxyl group of an alcohol is first converted enzymatically to a phosphate ester in order to create a better leaving group. This phosphate ester can take the form of a simple monophosphate (arrow 1 in the figure below), a diphosphate (arrow 2), or a nucleotide monophosphate (arrow 3).



Due to resonance delocalization of the developing negative charge, phosphates are excellent leaving groups.



Here's a specific example (from DNA nucleotide biosynthesis) that we will encounter in more detail in this section:

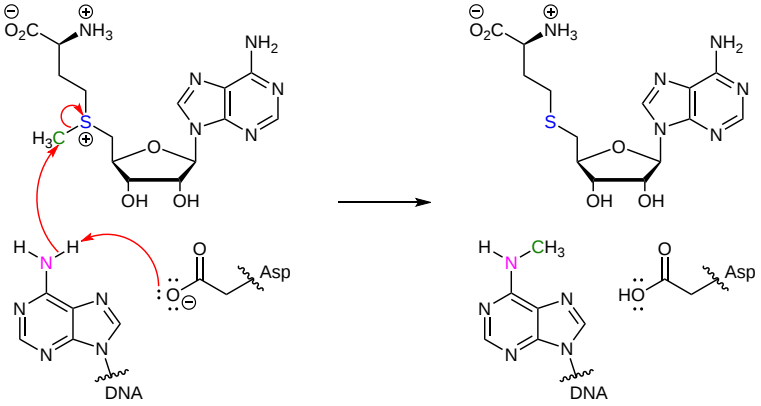


Here, the OH group on ribofuranose is converted to a diphosphate, a much better leaving group. Ammonia is the nucleophile in the second step of this S_N1-like reaction.

We will learn much more about phosphates in this section. What is important for now is that in each case, an alcohol has been converted into a much better leaving group, and is now primed for a nucleophilic substitution reaction.

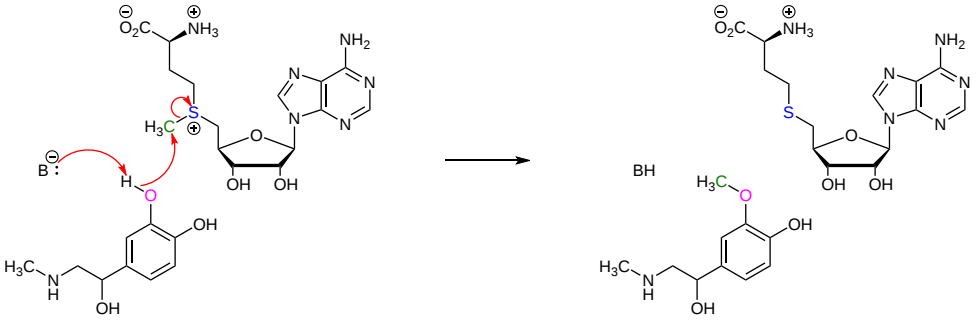
SAM METHYLTRANSFERASES

Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent methyltransferase enzymes. We have already seen, in chapter 6 and again in chapter 8, how a methyl group is transferred in an S_N2 reaction from SAM to the amine group on the nucleotide base adenosine:



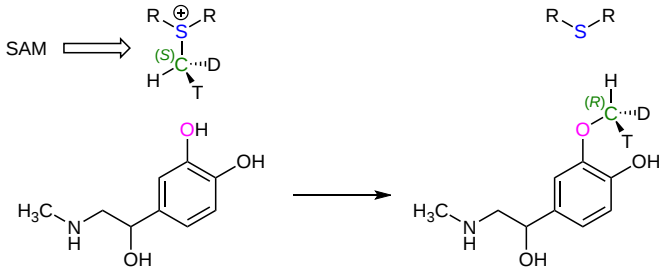
(*Nucleic Acids Res*. **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it attacks, increasing its nucleophilicity. The electrophile in both reactions is a methyl carbon, so there is little steric hindrance to slow down the nucleophilic attack. The methyl carbon is electrophilic because it is bonded to a positively-charged sulfur, which is a powerful electron withdrawing group. The positive charge on the sulfur also makes it an excellent leaving group, as the resulting product will be a neutral and very stable sulfide. All in all, in both reactions we have a reasonably good nucleophile, an electron-poor, unhindered electrophile, and an excellent leaving group.

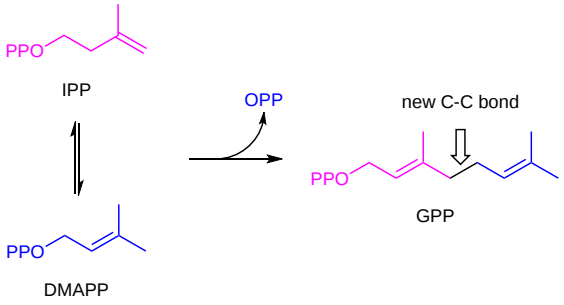
Because the electrophilic carbon in these reactions is a methyl carbon, a stepwise S_N1-like mechanism is extremely unlikely: a methyl carbocation is very high in energy and thus is not a reasonable intermediate to propose. We can confidently predict that this reaction is S_N2. Does this S_N2 reaction occur, as expected, with inversion of stereochemistry? Of course, the electrophilic methyl carbon in these reactions is achiral, so inversion is not apparent. To demonstrate inversion, the following experiment has been carried out with catechol-O-methyltransferase:



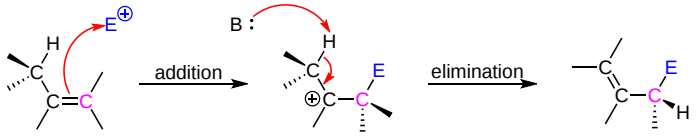
Here, the methyl group of SAM was made to be chiral by incorporating hydrogen isotopes tritium (^{3}H, T) and deuterium (^{2}H, D). The researchers determined that the reaction occurred with inversion of configuration, as expected for an S_N2 displacement (*J. Biol. Chem.* **1980,** *255,* 9124).

SUBSTITUTION BY ELECTROPHILIC ADDITION/ELIMINATION

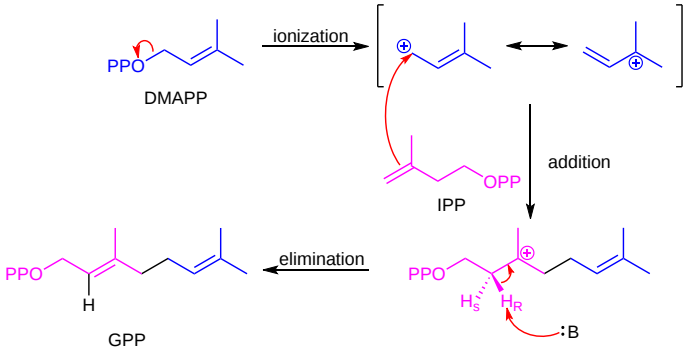
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism, which we saw in general form in this section:

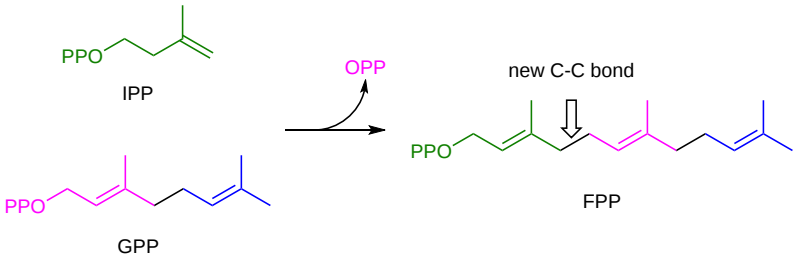


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

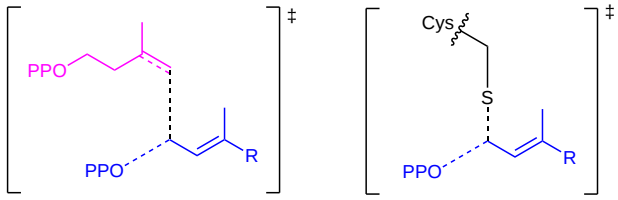


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

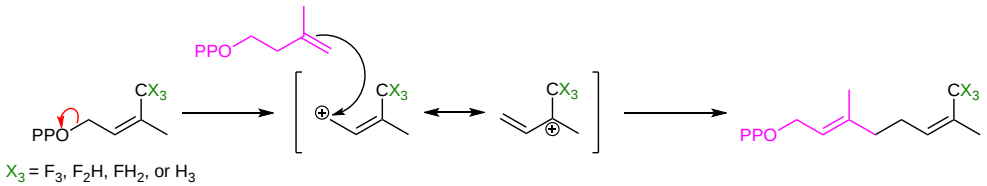


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction (section 9.3). The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down (see section 9.3B).



If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

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11.7: ELIMINATION REACTIONS- ZAITSEV'S RULE

OBJECTIVE

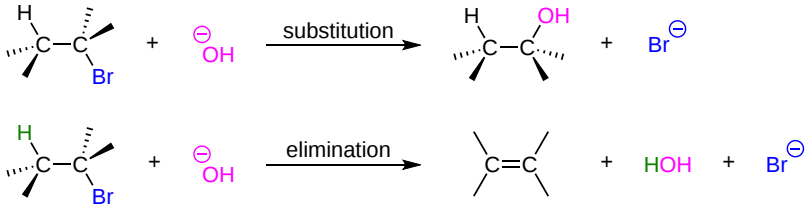
After completing this section, you should be able to apply Zaitsev's rule to predict the major product in a base-induced elimination of an unsymmetrical halide.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

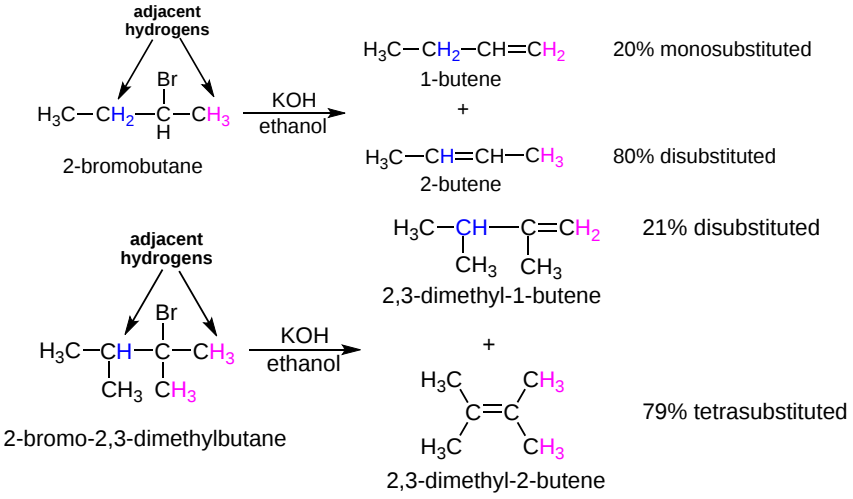
- Zaitsev's rule

When an alkyl halide is reacted with a nucleophile/Lewis base two major types of reaction can occur. Thus far in this chapter, we have discussed substitution reactions where a nucleophile displaces a leaving group at the electrophilic carbon of a substrate. Alternatively, the nucleophile could act as a Lewis base and cause an elimination reaction by removing a hydrogen adjacent to the leaving group. These reaction are similar and are often in competition with each other.



INTRODUCTION

The prefix "regio" indicates the interaction of reactants during bond making and/or bond breaking occurs preferentially by one orientation. If two or more structurally distinct groups of adjacent hydrogens are present in a given reactant, then multiple constitutionally isomeric alkenes may be formed by an elimination. **Zaitsev's rule** is an empirical rule used to predict the major products of elimination reactions. It states that in an elimination reaction the major product is the more stable alkene with the more highly substituted double bond. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.



By using the strong base hydroxide, we direct these reactions toward elimination (rather than substitution). In both cases there are two different sets of adjacent hydrogens available to the elimination reaction (these are colored blue and magenta). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1°-hydrogens (magenta) and two 2°-hydrogens (blue) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six adjacent

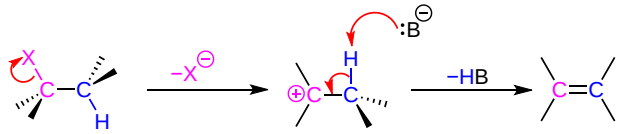
1° hydrogens (magenta) compared with one 3°-hydrogen (blue). These results point to a strong favoring the more highly substituted product double bond predicted by **Zaitsev's Rule**.

THE E1, E2, AND E1CB REACTIONS

Elimination reaction take place by three common mechanism, E1, E2, and E1cB, all of which break the H-C and X-C bonds at different points of their mechanism. In addition, the different mechanisms will have subtle effects on the reaction products which will be discussed later in this chapter.

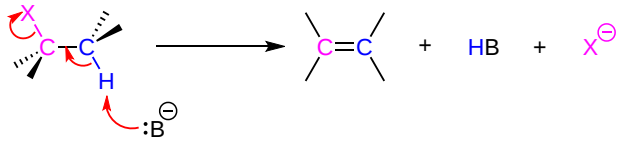
E1 MECHANISM

This mechanism starts the breaking of the C-X to provide a carbocation intermediate. A base removes a hydrogen adjacent to the original electrophilic carbon. The electrons from the broken H-C bond move to form the pi bond of the alkene. In much the same fashion as the S_N1 mechanism, the first step of the mechanism is slow making it the rate determining step. This means that the reaction kinetics are unimolecular and first-order with respect to the substrate.



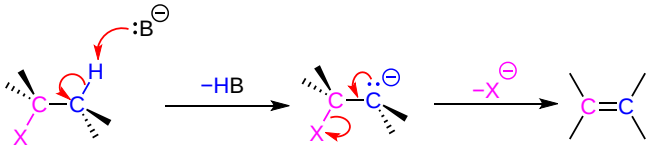
E2 MECHANISM

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the leaving group. The electrons of the broken H-C move to form the pi bond of the alkene. In doing this the C-X bond is broken causing the removal of the leaving group.



E1CB MECHANISM

The E1cB mechanism starts with the base deprotonating a hydrogen adjacent to the leaving to form a carbanion. In the second step of the mechanism the lone pair electrons of the carbanion move to become the pi bond of the alkene. This causes the C-X bond to break and the leaving group to be removed.



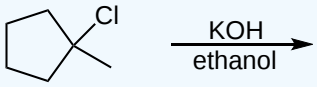
PREDICTING THE PRODUCTS OF AN ELIMINATION REACTION

For most elimination reactions, the formation of the product involves the breaking of a C-X bond from the electrophilic carbon, the breaking of a C-H bond from a carbon adjacent to the electrophilic carbon, and the formation of a pi bond between these two carbons. Which elimination mechanism is being followed has little effect on these steps. The limitations of each elimination mechanism will be discussed later in this chapter.

To determining the possible products, it is vital to first identify the electrophilic carbon in the substrate. Next identify all hydrogens on carbons directly adjacent to the electrophilic carbon. Each unique adjacent hydrogen has the possibility of forming a unique elimination product. Break a C-H bond from each unique group of adjacent hydrogens then break the C-X bond. Finally connect the adjacent carbon and the electrophilic carbon with a double bond. Repeat this process for each unique group of adjacent hydrogens. Finally, compare all of the possible elimination products. The product whose double bond has the most alkyl substituents will most likely be the preferred product.

WORKED EXAMPLE 11.7.1

What would be the expected products of the following reaction? Which would be expected to be the major product?



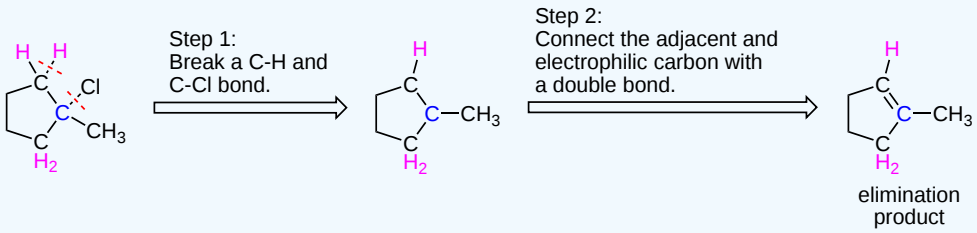
Solution

To solve this problem, first find the electrophilic carbon in the starting compound. This carbon is directly attached to the chlorine leaving groups and is shown in blue in the structure below. Next, identify all unique groups of hydrogens on carbons directly adjacent to the electrophilic carbon. In the starting compound, there are two distinct groups of hydrogens which can create a unique elimination product if removed. They are shown as magenta and green in the structure below.

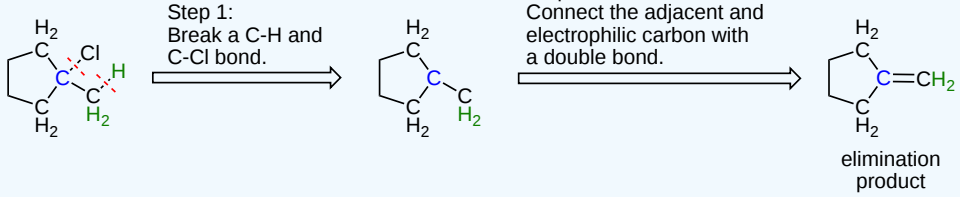


Create the possible elimination product by breaking a C-H bond from each unique group of adjacent hydrogens then breaking the C-C*l* bond. Then connect the adjacent carbon and the electrophilic carbon with a double bond to create an alkene elimination product. Repeat this process for each unique group of adjacent hydrogens. Because the starting compound in this example has two unique groups of adjacent hydrogens, two elimination products can possibly be made.

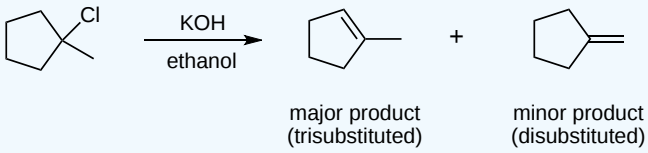
Product 1



Product 2

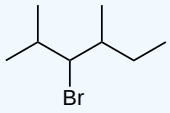


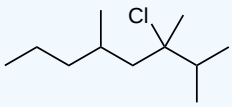
Finally, compare the possible elimination products to determine which has the most alkyl substituents. This product will most likely be the preferred. For this example product 1 has three alkyl substituents and product 2 has only two. This means product 1 will likely be the preferred product of the reaction.

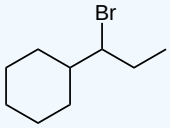


EXERCISE 11.7.1

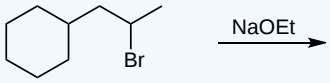
1) Ignoring the alkene stereochemistry show the elimination product(s) of the following compounds:

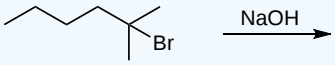
a) 

b) 

c) 

2) Predict the major products of the following reactions.

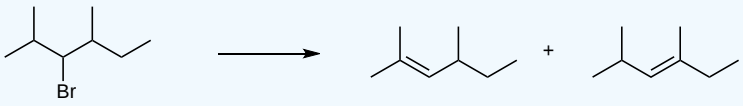
a) 

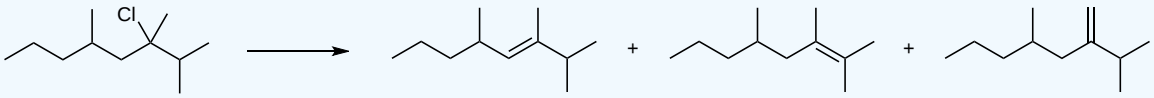
b) 

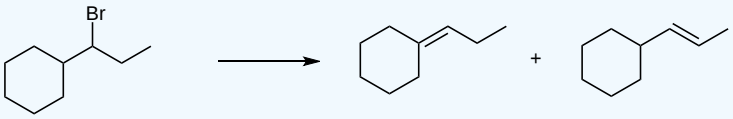
c) 

Answer

1)

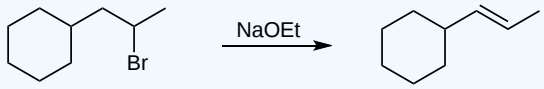
a) 

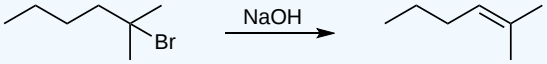
b) 

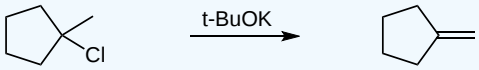
c) 

2)

https://chem.libretexts.org/@go/page/31511

a) 

b) 

c) 

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11.8: THE E2 REACTION AND THE DEUTERIUM ISOTOPE EFFECT

OBJECTIVES

After completing this section, you should be able to

1. write the mechanism of a typical E2 reaction.
2. sketch the transition state of a typical E2 reaction.
3. discuss the kinetic evidence that supports the proposed E2 mechanism.
4. discuss the stereochemistry of an E2 reaction, and explain why the anti periplanar geometry is preferred.
5. determine the structure of the alkene produced from the E2 reaction of a substrate containing two chiral carbon atoms.
6. describe the deuterium isotope effect, and discuss how it can be used to provide evidence in support of the E2 mechanism.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

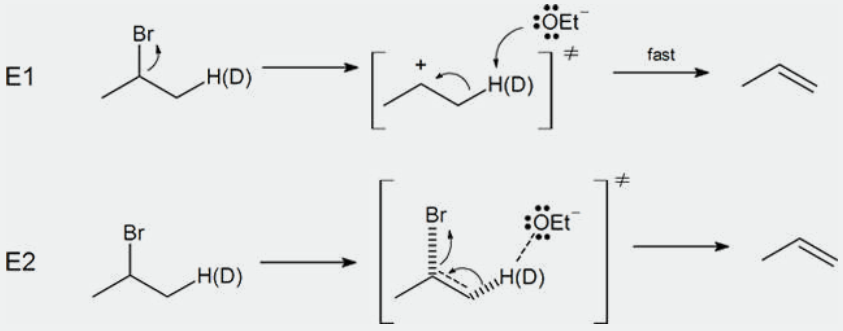
- anti periplanar
- deuterium isotope effect
- E2 reaction
- periplanar
- syn periplanar

STUDY NOTES

An *E2 reaction* is a bimolecular elimination reaction; thus, two molecules are involved in the rate-limiting step. In this section, we are concerned with E2 reactions involving an alkyl halide and a base.

Use molecular models to assist you to understand the difference between syn periplanar and anti periplanar, and to appreciate why E2 eliminations are stereospecific.

Note that when deuterium is used the kinetic isotope effect (KIE) is referred to as the deuterium isotope effect. A C–H bond is about 5 kJ/mol weaker than a C–D bond. So if the rate-limiting step involves a breaking of this bond as it does at the E2 transition state there will be a substantial difference in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence consistent with an E2 mechanism.

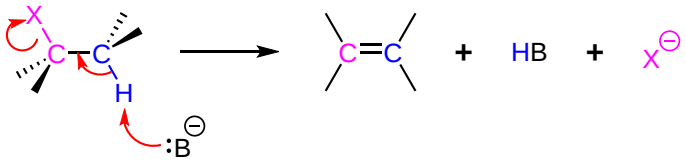


INTRODUCTION

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. E2 reactions are typically seen with secondary and tertiary alkyl halides, in the presence of a base (OH-, RO-, R_2N-). For a primary halide to undergo an E2 reaction a strong sterically hindered base is usually required. The products of an E2 reaction follow Zaitsev's rule, the most substituted alkene is usually the major product.

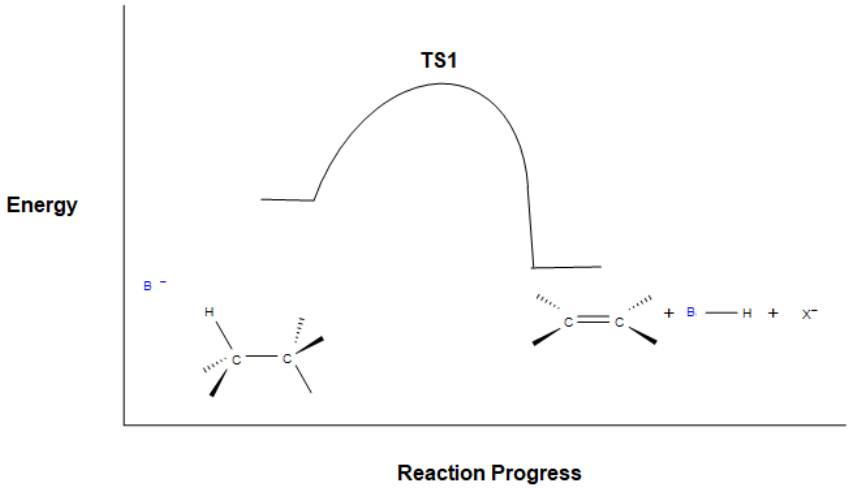
E2 MECHANISM

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the carbon with the leaving group. The electrons of the broken H-C bond move to form the pi bond of the neutral product alkene. In doing this, the C-X bond is broken causing the removal of the leaving group. Overall during this reaction an electron pair is transferred from the base to the leaving group.

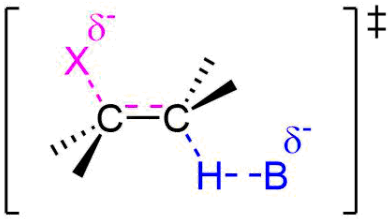


E2 REACTION TRANSITION STATE

Because the E2 reaction is predicted to follow a concerted mechanism only one transition state is expected in its energy coordinate diagram.



As the base begins to remove a hydrogen adjacent to the leaving group an H-B is starting to form and an H-C bond is in the process of breaking. Simultaneously, a C=C pi bond forms and the C-X bond breaks. During this reaction a set of electrons and a negative charge are transferred from the base to the leaving group. This is represented by a partial negative charge being present on both the base and the leaving group in the transition state.

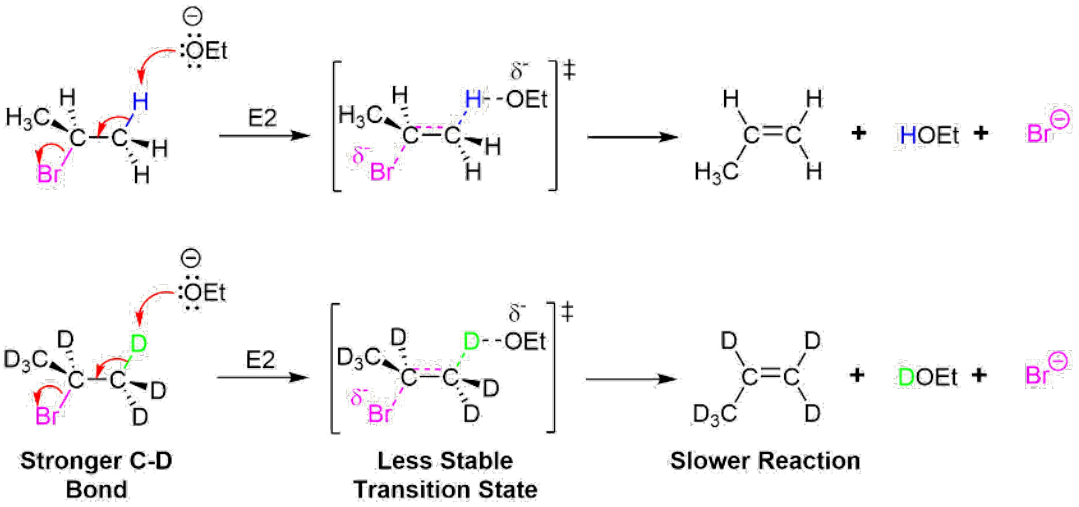


EVIDENCE FOR THE E2 MECHANISM AND TRANSITION STATE

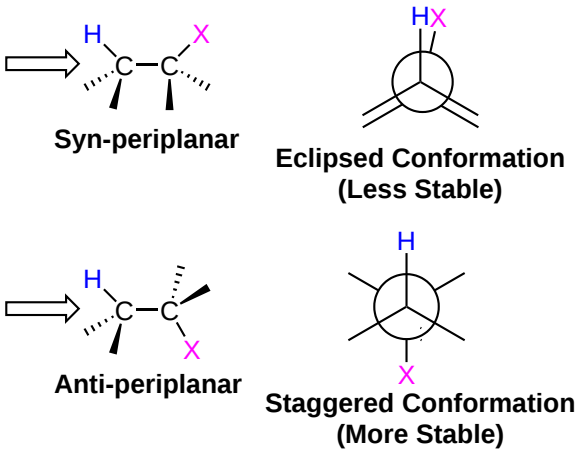
Kinetic studies of E2 reactions show that they are second order overall and follow the rate law: rate = k[RX][Base]. This data is consistent with the predicted bimolecular E2 mechanism that includes both the alkyl halide and the base participating in the mechanism's rate-determining step.

Further evidence for the predicted mechanism for the E2 reaction was provided by experiments involving the **deuterium isotope effect** (DIE). The **deuterium isotope effect** (DIE) is a phenomenon associated with molecules which have had hydrogen (H) atoms isotopically substituted with deuterium (D) atoms, exhibiting different reaction rates. The bond dissociation energy for C-D bonds is about 5 kJ/mol

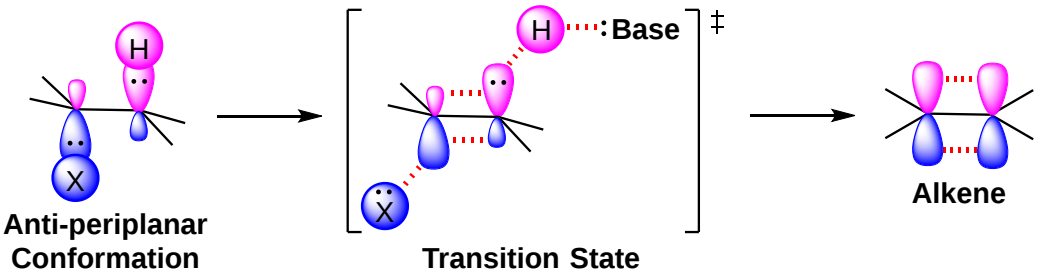
stronger than the bond dissociation energy of C-H bonds. This difference in energy results in a reduction in the rate of reaction, if the deuterium replacement occurs at a site of bond breaking in the rate determining step of a reaction. So if the rate-limiting step involves a breaking of this bond, as it does at the E2 transition state, there will be a substantial decrease in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence that the C-H bond is broken during the rate determining step of the E2 mechanism. This is consistent with the predicted mechanism of the E2 reaction consisting of a single concerted step. If the rate-determining step was the leaving group bond breaking first (as in an E1 reaction) the deuterium substitution would not have caused an observable change in reaction rate.



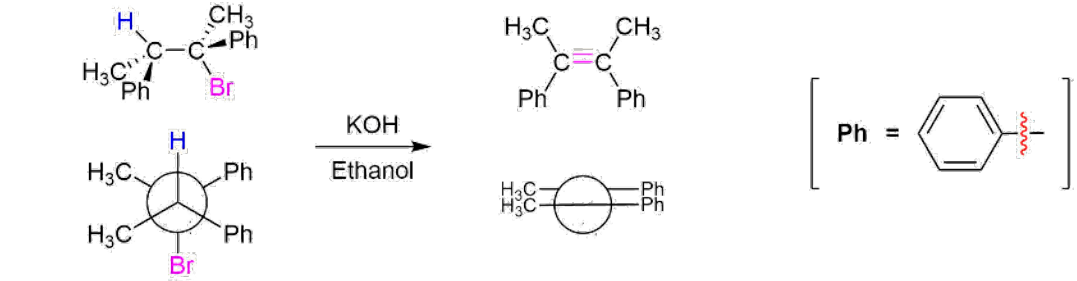
Yet another piece of evidence which supports the E2 mechanism comes when considering the stereochemistry of the elimination products. In the transition state of the E2 mechanism there are two carbons rehybridization from sp^3 to sp^2 while forming a π-bond. For good orbital overlap to occur during this change all the atoms involved in the reaction, the two carbons, the hydrogen, and the leaving group need to all lie in the same plane or **periplanar**. There are two possible ways this geometry can be achieved: **syn-periplanar** where the hydrogen and the leaving group are on the same side of the C-C bond and **anti-periplanar** where the hydrogen and the leaving group are on opposite sides of the C-C bond. To obtain a syn-periplanar geometry the substituents attached to the C-C bond must adopt an energetically unfavorable eclipsed conformation. The energy barrier to syn-orientation is such that syn-elimination is rarely observed in E2 reactions. E2 eliminations typically take place from the anti-periplanar conformation, as this is the most stable conformation due to the substituents attached to the C-C bond being staggered.



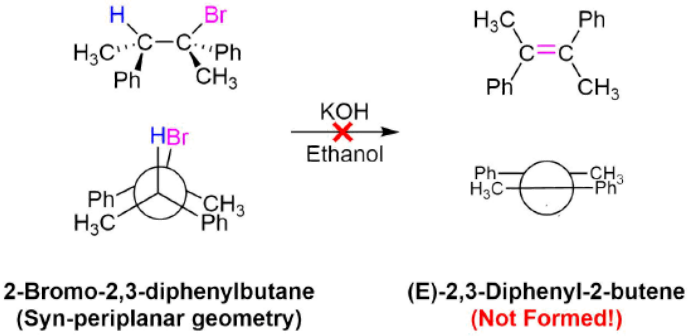
When viewing the transition state of the E2 mechanism when in the anti-periplanar conformation, the two sp^3 hybridized orbitals making up the C-H and C-X sigma bonds are in the same plane. When these two carbons rehybridization from sp^3 to sp^2, the p orbitals forming the π-bond will also have good overlap.



The stereochemical consequences of reactant molecules obtaining anti-periplanar geometry prior to E2 reactions has been observed in numerous experiments and provides further evidence of the proposed mechanism. For example, (2S, 3R)-2-bromo-2,3-diphenylbutane only forms (Z)-2,3-diphenyl-2-butene as a product of E2 elimination. To form the Z alkene isomer, the starting material must obtain the anti-periplanar geometry preferred for E2 reactions.



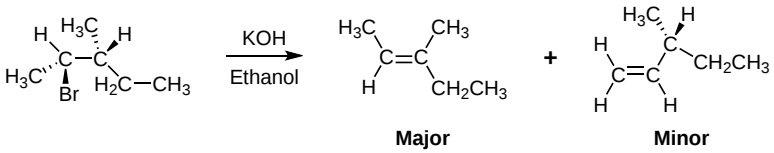
No isomeric E alkene product is formed because the starting materials would need to obtain a staggard, syn-periplanar geometry. The syn-periplanar geometry would be transferred to the transition state making it higher in energy and harder to form. The fact that only the Z alkene isomer forms provides further evidence that the E2 mechanism takes place by a single bimolecular step.



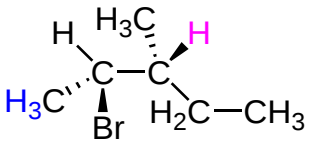
PREDICTING THE STEREOCHEMICAL PRODUCT OF E2 REACTIONS

E2 reactions have the requirements of a leaving group and a hydrogen on a carbon adjacent to the leaving group carbon. For non-ringed compounds, the C-C can usually undergo free rotation to place the C-X and C-H bonds anti-periplaner to each other. Stereochemical considerations usually come into play when both of the carbons in the C-C bond are chiral. When these carbons are achiral but contain the other requirements for an E2 reaction, products lacking stereochemistry are usually produced.

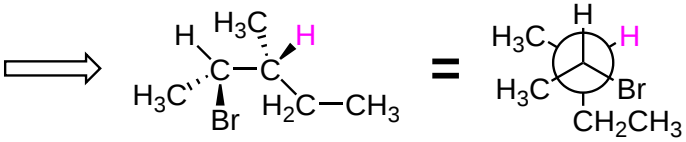
When both of the carbons in the C-C bond are chiral, one carbon will have a leaving group and the other carbon will have a single hydrogen. To consider the stereochemistry of an E2 product, start by creating a Newman projection looking down the C-C bond. Then rotate the C-C bond until the C-X and C-H bonds are in the anti position. The Newman projection now shows the relative positioning of the substituents on the C-C bond as they will appear in the double bond formed. It should be noted that if syn elimination was possible, a positional isomer of the double bond will be created. Consider the elimination products for (2R, 3R)-2-bromo-3-methylpentane.



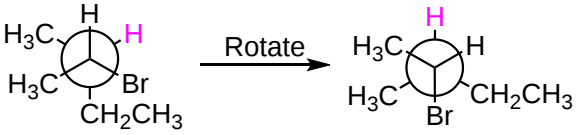
First, locate hydrogens on carbons adjacent to the leaving group. The compound used in this example has two unique sets of hydrogens.



Because the adjacent hydrogen colored fuchsia is attached to a chiral carbon it require special consideration. Convert the structure into a Newman projection along the C-C bond that will for the alkene elimination product. The C-C bond can be view down either direction and still product the correct product.

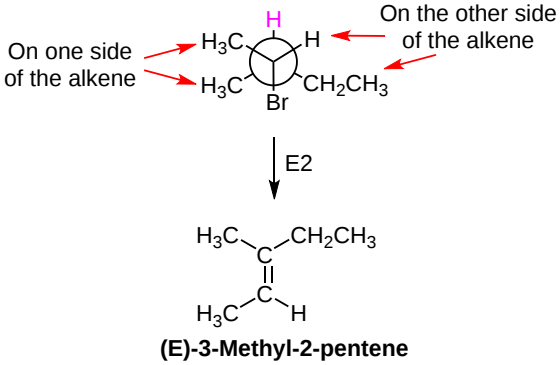


Then rotate such the the adjacent H and the leaving group are in the anti position.



Anti Position

This Newman projection shows the relative positioning of the substituents on the double bond formed. Note, none of the Z isomer is formed because it would require syn orientation of the H and Br.



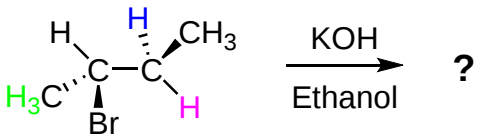
(E)-3-Methyl-2-pentene

Lastly, consider the products made by other adjacent hydrogens and apply Zaitsev's rule to predict the preferred product.

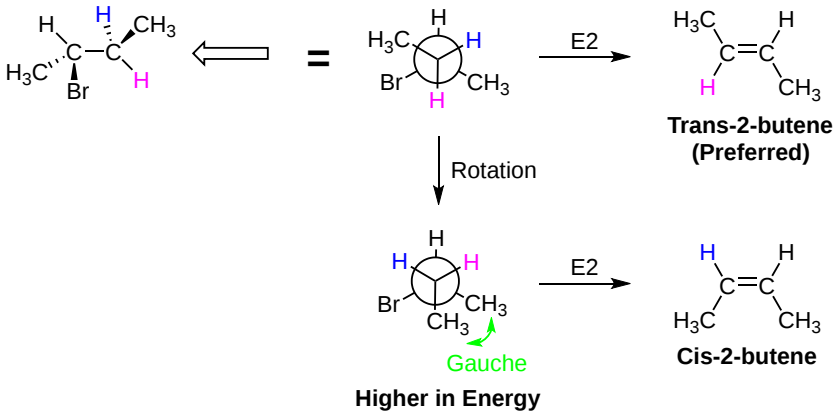
Example 1.svg

DETERMINING *CIS* AND *TRANS* PRODUCTS IN ELIMINATION REACTION

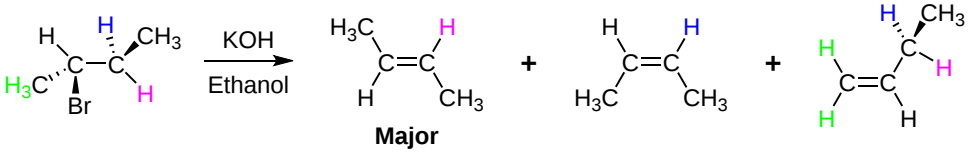
Understanding that E2 reactions require an anti-periplanar geometry can explain cis and trans alkene isomers can form as products. This occurs as an important exception to the rule that stereoisomers only form as elimination products when both of the carbons in the C-C bond forming the alkene are chiral. When considering the E2 reaction products of (R)-2-butane, there are two groups of hydrogens on carbons adjacent to the leaving group a CH_3 and a CH_2.



The carbon in the CH_2 group is achiral so both the H's appear to be equivalent. However, when the anti-periplanar geometry requirement is applied each hydrogen will produce its own unique product. Once the reactant is converted into a Newman projection it can be seen that the Br leaving group and the hydrogen colored blue are in the anti orientation and are ready to be eliminated. It should also be noted that the two CH_3 groups are also in the anti position which gives them the least amount of steric interaction possible. Because the CH_3 groups are on opposite sides of the Newman projection the CH_3 groups will be on opposite sides of the alkene thus creating the product *trans*-2-butene. When the Newman projection is rotated such that the fuchsia colored hydrogen is anti to the Br leaving group, the two CH_3 groups are now on the same. This orientation creates the isomer *cis*-2-butene. However, to obtain this orientation the two CH_3 groups must overcome the steric strain associated with a gauche conformation. This makes the transition state leading the cis isomer higher in energy and more difficult to form. Because of this, the trans isomer will be the major product. It is clear that the two hydrogens of the CH_2 group are not equivalent despite their not being attached to a chiral carbon.

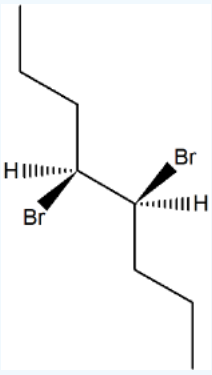


After considering all the products made during this E2 reaction the preferred product can be determined. The *cis* and *trans* isomer both have two alkene substituents while the third product only has one. Of the *cis* and *trans* isomer, the *trans* isomer is expected to be easier to form. Zaitsev's rule says that trans-2-butene will be the major product of this reaction.



? EXERCISE 11.8.1

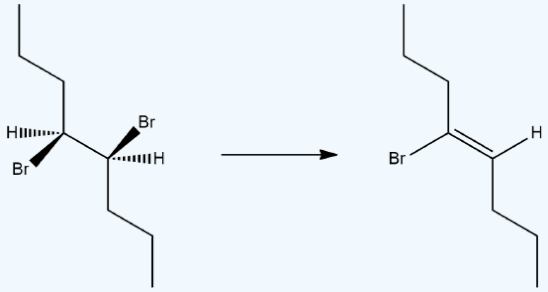
1) What is the product of the following molecule in an E2 reaction? What is the stereochemistry?



Answer

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The stereochemistry is (*Z*) for the reaction.



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11.9: THE E2 REACTION AND CYCLOHEXANE CONFORMATION

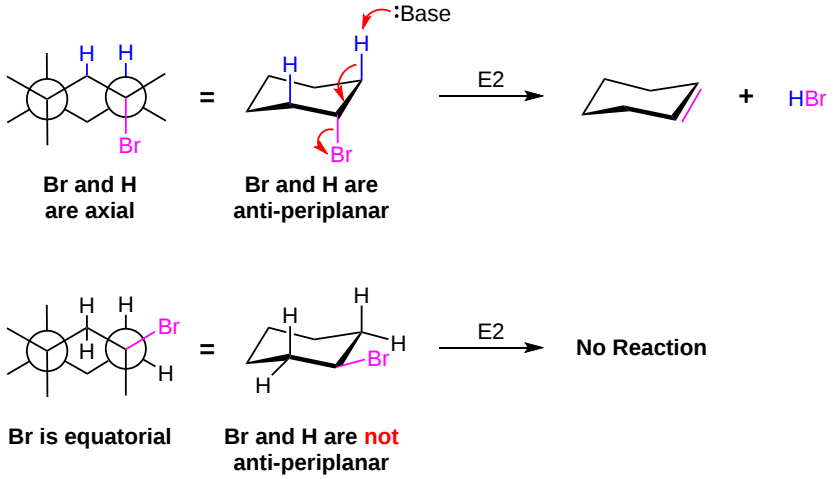
OBJECTIVES

After completing this section, you should be able to

1. identify anti periplanar arrangements of atoms in substituted cyclohexanes.
2. determine which cyclohexane conformation will generate a specific anti periplanar arrangement.

STEREOCHEMICAL REQUIREMENTS OF THE E2 REACTION

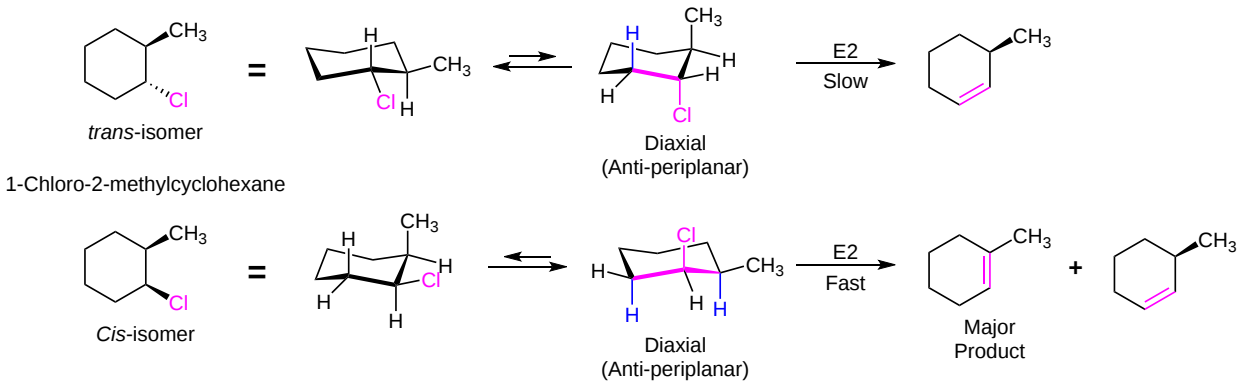
E2 elimination reactions of certain isomeric cycloalkyl halides show unusual rates and regioselectivity which can provide important supporting evidence that anti-periplanar is the preferred orientation of reactant species in the E2 transition state. Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. The compounds used here all have six-membered rings, so to achieve the anti-periplanar orientation required for the E2 reaction both the halogen and the adjacent hydrogen much assume an axial conformation.



For the compound, 2-methyl-1-chlorocyclohexane, the *cis* to the *trans* isomers have distinctly different reaction rates and form different preferred products. For example, *trans*-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its *cis*-isomer. For trans-methyl-1-chlorocyclohexane, to obtains a chair conformation which places the chlorine substituent in the axial orientation required for E2 elimination, the methyl substituents is also forced into an axial position. Having both substituents in the axial position makes this chair conformer of the *trans*-isomer much less stable and presents an energy barrier that must be overcome for an E2 reaction to occur. When *cis*-2-methyl-1-chlorocyclohexane obtains a chair conformation which places its chlorine substituent in an axial orientation, the methyl substituent is forced into an equatorial orientation. Having one substituent axial and one equatorial makes this chair conformation of the cis-isomer lower in energy and thus easier to form. Consequently, the E2 reaction rates with the *trans*-isomer are slower than with the *cis*-isomer.

Furthermore, the product from E2 elimination of the *trans*-isomer is 3-methylcyclohexene (not predicted by Zaitsev's rule), whereas the *cis*-isomer gives the 1-methylcyclohexene as the preferred product (as predicted by Zaitsev's rule). The trans-isomer only has one adjacent hydrogen which can obtain an axial orientation along with the chlorine. The adjacent hydrogen which would lead to a 1-methylcyclohexene product cannot obtain the diaxial, anti-periplanar orientation with chlorine so an E2 reaction cannot occur. This makes 3-methylcyclohexene the preferred E2 elimination product of the *trans*-isomer showing that the anti-periplanar orientation requirement of E2 reactions is more important in determining products for this reaction than Zaitsev's rule.

In the *cis*-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two adjacent axial hydrogens. Removing one hydrogen forms the product, 3-methylcyclohexene, while removing the other hydrogen forms 1-methylcyclohexene. Here Zaitsev's rule determines that the more substituted alkene, 1-methylcyclohexene, is the preferred product.

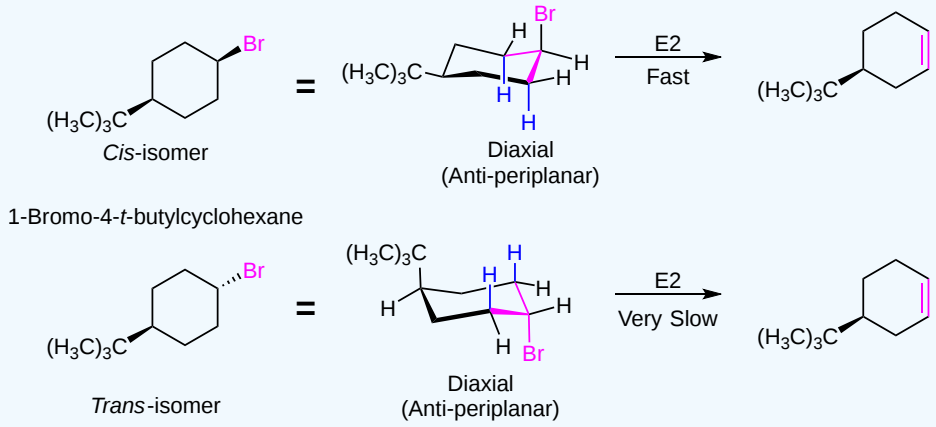


WORKED EXERCISE 11.9.1

Which isomer would be expected to undergo E2 elimination quicker cis or trans-1-bromo-4-tert-butylcyclohexane? Explain your answer.

Answer

In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that it will always assume an equatorial orientation, leaving the bromine to be axial in the *cis*-isomer and equatorial in the *trans*-isomer. Because of symmetry, the two axial adjacent hydrogens in the *cis*-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the bromine atom. To assume a conformation having an axial bromine, the *trans*-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, substitution by hydroxide anion predominates in this situation.



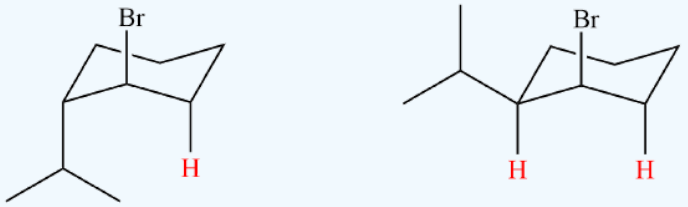
EXERCISE 11.9.1

Which of the following compounds will react faster in an E2 reaction; *trans*-1-bromo-2-isopropylcyclohexane or *cis*-1-bromo-2-isopropylcyclohexane?

Answer

The *cis* isomer will react faster than the *trans*. The *cis* isomer has two possible perpendicular hydrogen in which it can eliminate from.

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trans cis

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11.10: THE E1 AND E1CB REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write the mechanism for a typical E1 reaction.
2. explain why E1 elimination often accompanies S_N1 substitution.
3. write an equation to describe the kinetics of an E1 reaction.
4. discuss the stereochemistry of E1 reactions.
5. account for the lack of a deuterium isotope effect in E1 reactions.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- E1 reaction
- E1cB reaction

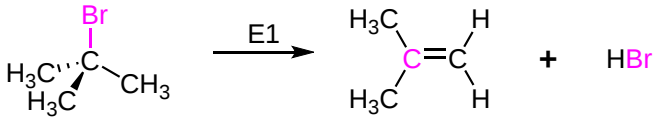
STUDY NOTES

The abbreviation E1 stands for "unimolecular elimination"; that is, an E1 reaction is an elimination reaction in which only one species is involved in the rate-limiting step.

Unimolecular Elimination (E1) is a reaction in which the removal of an HX substituent results in the formation of a double bond. It is similar to a unimolecular nucleophilic substitution reaction (S_N1) in various ways. One being the formation of a carbocation intermediate. Also, the only rate determining (slow) step is the dissociation of the leaving group to form a carbocation, hence the name unimolecular. Thus, since these two reactions behave similarly, they compete against each other. Many times, both these reactions will occur simultaneously to form different products from a single reaction. However, one can be favored over another through thermodynamic control. Although Elimination entails two types of reactions, E1 and E2, we will focus mainly on E1 reactions with some reference to E2.

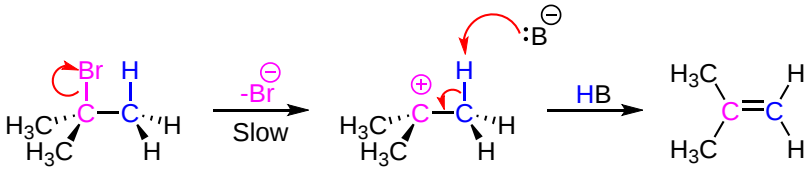
GENERAL E1 REACTION

An E1 reaction involves the removal of the halogen leaving group followed by the deprotonation of an adjacent hydrogen to produce an alkene product. In order to accomplish this, a Lewis base is required.



MECHANISM

This mechanism starts with the spontaneous removal of the leaving group. The leaving group also removes the electrons from the C-Br bond, making the attached carbon a carbocation. In much the same fashion as the S_N1 mechanism, the first step of the E1 mechanism is slow thus making it the rate determining step. This makes E1 reaction kinetics unimolecular and first-order with respect to the substrate. Next, a Lewis Base (B^-) deprotonates an adjacent hydrogen from the carbocation. The electrons of the C-H bond are donated to the adjacent C-C bond, forming a double bond. Unlike E2 reactions, which require the adjacent proton to be *anti* to the leaving group, E1 reactions only require a neighboring hydrogen. This is due to the fact that the leaving group has left the molecule to form an achiral, trigonal planar carbocation.

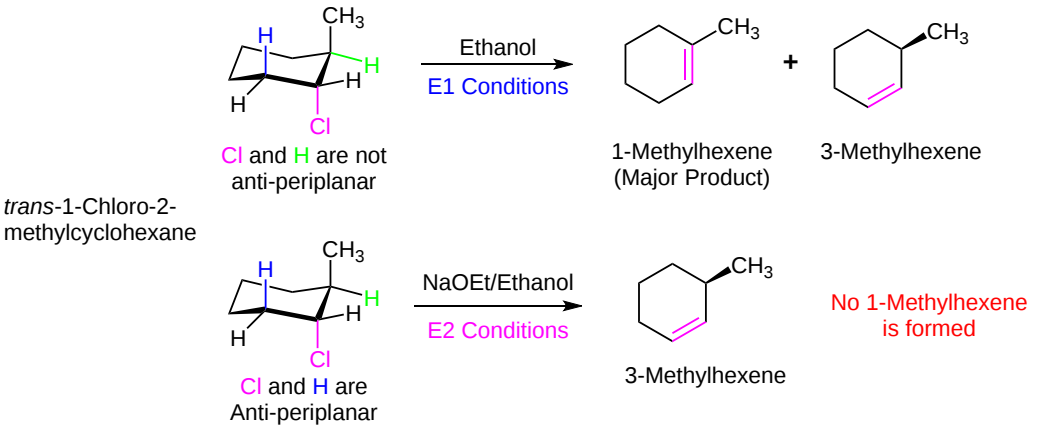


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EVIDENCE FOR THE E1 MECHANISM

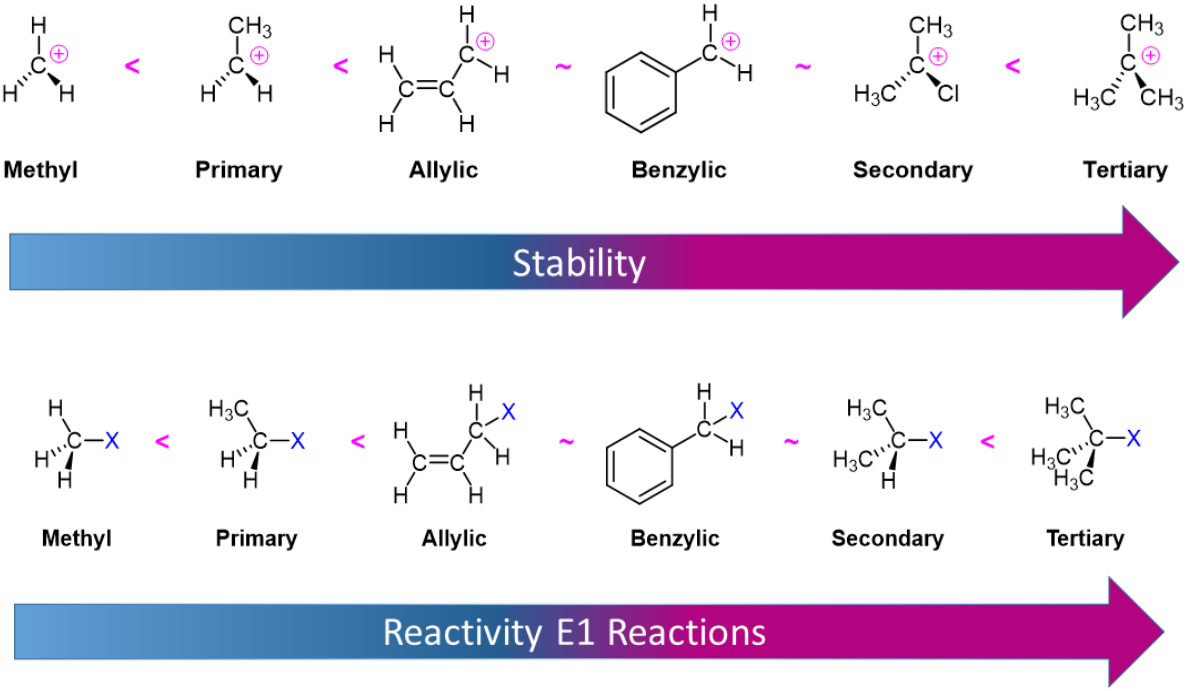
The primary evidence in support of the E1 mechanism is the fact that E1 reaction follow first-order kinetics which is consistent with the reaction mechanism containing a unimolecular dissociation as the rate determining step. Another piece of evidence is seen in the fact that E1 reactions show no deuterium isotope effect. Experiments have shown that there is no difference in reaction rate when deuterated and nondeuterated substrates are used. This is consistent with the E1 mechanism because a C-H bond is not broken in the rate determining step.

Lastly, because the halogen and hydrogen are removed in different steps, the mechanism of E1 reactions predicts that they will not require the anti-periplanar geometry required for E2 reactions. E1 reactions do not have the geometric constraints of E2 reactions discussed in **Sections 11-8** and **11-9**. In Section 11-9 an example showed that trans-1-Chloro-2-methylcyclohexane was capable of only forming the product 3-methylhexene during an E2 reaction due to the anti-periplanar constraints. When the same substrate is reacted under E1 conditions two elimination products (1-methylhexene and 3-methylhexene) are produced. In the substrate, the hydrogen marked as green cannot obtain anti-periplanar geometry with the Cl leaving group. Under E2 conditions this hydrogen and the Cl cannot be eliminated to form an elimination product. However, under E1 conditions the hydrogen and the Cl eliminate, despite the lack of anti-periplanar geometry, to form 1-methylhexene.



ALKYL HALIDE REACTIVITY IN E1 REACTIONS

Due to the fact that E1 reactions create a carbocation intermediate, reactivity of alkyl halides toward E1 reaction mirror those present in S_N1 reactions.

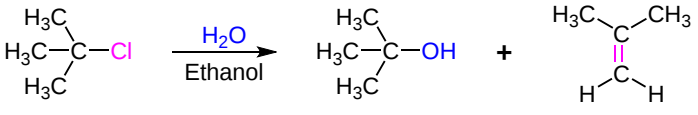


As expected, tertiary carbocations are favored over secondary, primary and methyl carbocations. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon that is more stable. Secondary and Tertiary carbons form more stable carbocations, thus E1 reactions occur quite rapidly at these atoms.

Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good/strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can effect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2/S_N2 from occurring.

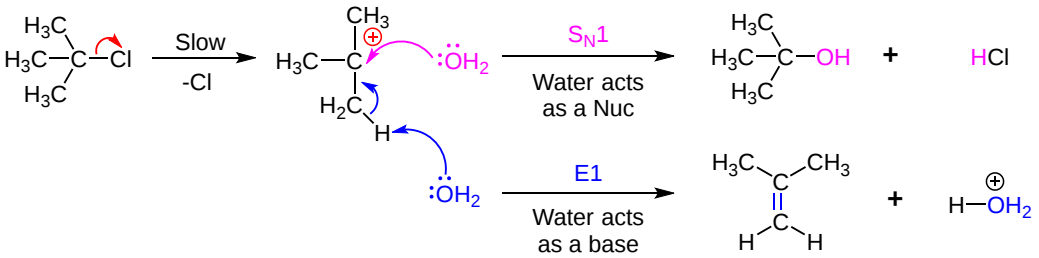
THE CONNECTION BETWEEN S_N1 AND E1 REACTIONS

The E1 and S_N1 mechanisms both begin with the rate-determing step, the unimolecular removal of a leaving group to form a carbocation intermediate. Sharing the rate-determining step causes alkyl halides to produce both S_N1 substitution and E1 elimination products whenever they are reacted with nonbasic nucleophiles in a protic solvent. For example, the hydrolysis of *tert*-butyl chloride in a solution of water and ethanol gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration.



2-Chloro-2-methylpropane **2-Methyl-2-propanol (60%)** **2-Methylpropene (40%)**

To produce the alcohol product, water attacks the carbocation as a nucleophile as part of an S_N1 reaction. To produce the alkene product, water acts as a base and deprotonates an adjacent hydrogen as part of an E1 reaction. As expected, the mechanism of the two reactions have similar characteristics. They both show first order kinetics; neither is much influenced by a change in the nucleophile/base; and both are relatively non-stereospecific.



To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer a adjacent proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

COMPARING E1 AND E2 MECHANISMS

When considering whether an elimination reaction is likely to occur via an E1 or E2 mechanism, we really need to consider three factors:

1) **The base:** strong bases favor the E2 mechanism, whereas, E1 mechanisms only require a weak base.

2) **The solvent**: good ionizing solvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.

3) **The alkyl halide:** primary alkyl halides have the only structure useful in distinguishing between the E2 and E1 pathways. Since primary carbocations do not form, only the E2 mechanism is possible.

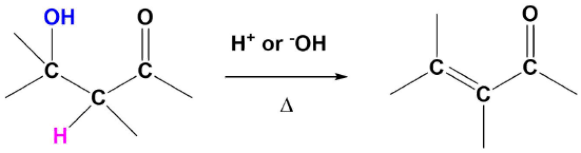
Ultimately, whether the elimination mechanism is E1 or E2 is not very important, since the product is the same alkene. We need to remember, however, that Zeitzev´s rule always determines the most likely alkene to be formed.

Reaction Parameter	E2	E1
alkyl halide structure	tertiary > secondary > primary	tertiary > secondary >>>> primary
nucleophile	high concentration of a strong base	weak base
mechanism	1-step	2-step
rate limiting step	bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Base]	rate = k[R-X]
solvent	not important	polar protic

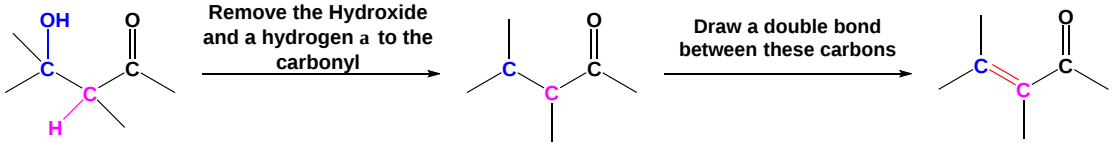
THE E1CB REACTION

Although E1 reactions typically involve a carbocation intermediate, the E1cB reaction utilizes a carbanion intermediate. A proton adjacent to a carbonyl group is removed using a strong base. This proton is acidic because the resulting conjugate base anion is stabilized by delocalization on to the carbonyl group. This anion causes the expulsion of an adjacent leaving group to create an alkene which is conjugated with the carbonyl which is called an enone. This reaction is generally utilized when a poor leaving group, such as a hydroxide, is involved. This poor leaving group makes the direct E1 or E2 reactions difficult. This reaction is used later in a reaction called an aldol condensation which will be discussed in **Section 23-3**.

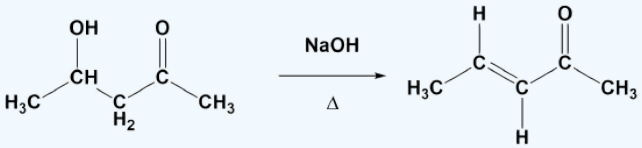
GENERAL REACTION



PREDICTING THE PRODUCT OF AN E1CB REACTION

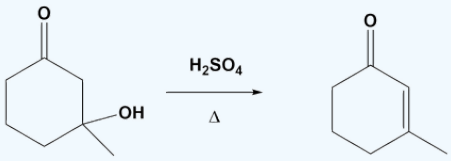


EXAMPLE 11.10.1



4-Hydroxy-2-Pentanone

3-Penten-2-one



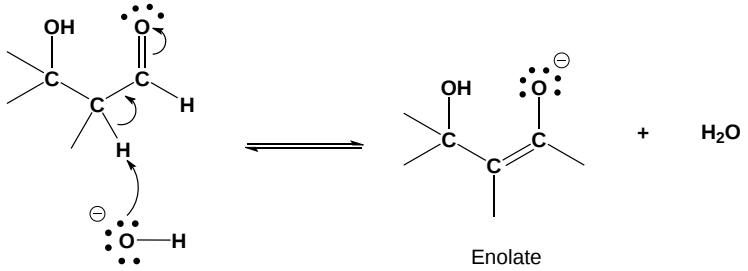
3-Hydroxy-3-methylcyclohexanone

3-Methyl-2-Cyclohexenone

E1CB MECHANISM

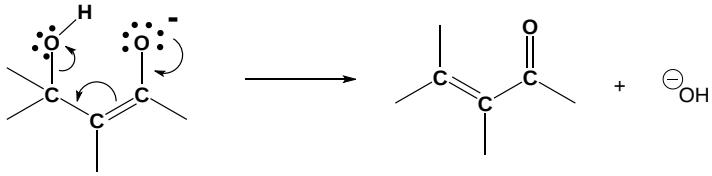
The mechanism starts with the base removing a hydrogen to form an alkoxide anion. The alkoxide reforms the carbonyl C=O bond promoting the elimination of alcohol OH as a leaving group which also reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

1) Deprotonation to form the anion



Enolate

2) Leaving Group Removal

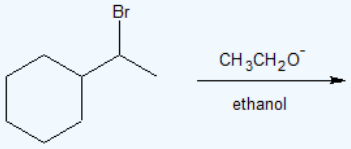


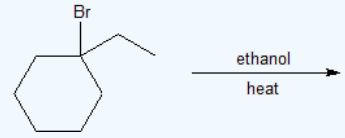
Enone

Note! The double bond always forms in conjugation with the carbonyl.

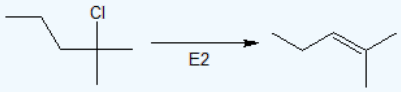
EXERCISE 11.10.1

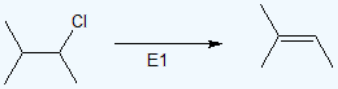
1. Predict the dominant elimination mechanism (E1 or E2) for each reaction below. Explain your reasoning.

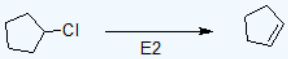
a) 

b) 

2) Specify the reaction conditions to favor the indicated elimination mechanism.

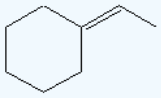
a) 

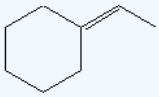
b) 

c) 

Answer

1)

a)  E2 reaction b/c secondary alkyl halide with a strong base.

b)  E1 reaction b/c tertiary alkyl halide with a weak base.

2)

a) strong base, such as hydroxide, an alkoxide, or equivalent

b) water or alcohol or equivalent weak base with heat

c) strong base, such as hydroxide, an alkoxide, or equivalent

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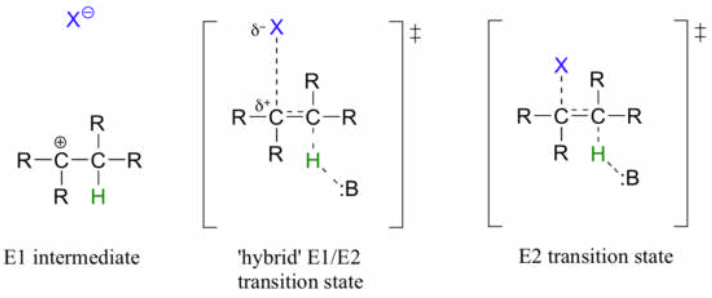
11.11: BIOLOGICAL ELIMINATION REACTIONS

OBJECTIVE

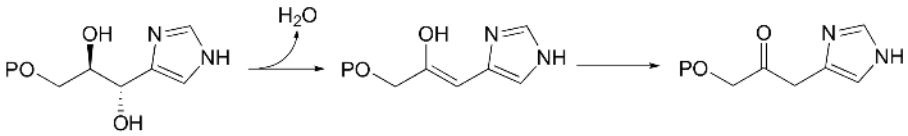
After completing this section, you should have an appreciation that E1, E2 and E1cB mechanisms exist and are well-known in biological chemistry.

ENZYMATIC E1 AND E2 REACTIONS

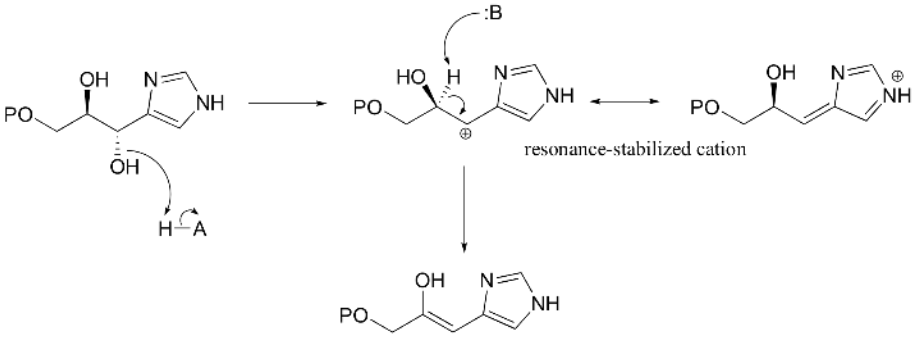
While most biochemical b-elimination reactions are of the E1cb type, some enzymatic E2 and E1 reactions are known. Like the enzymatic S_N2 and S_N1 substitution mechanisms discussed in chapters 8 and 9, the E2 and E1 models represent two possible mechanistic extremes, and actual enzymatic elimination reactions may fall somewhere in between. In an E1/E2 hybrid elimination, for example, C_β-X bond cleavage may be quite advanced (but not complete) before proton abstraction takes place - this would lead to the build-up of transient *partial* positive charge on C_β, but a discreet carbocation intermediate would not form. The extent to which partial positive charge builds up determines whether we refer to the mechanism as 'E1-like' or 'E2-like'.



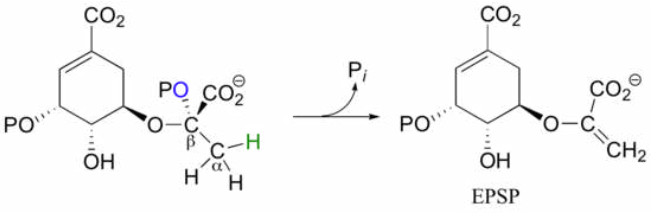
A reaction in the histidine biosynthetic pathway provides a good example of a biological E1-like elimination step (we're looking specifically here at the first, enol-forming step in the reaction below - the second step is simply a tautomerization from the enol to the ketone product (section 13.1A)).



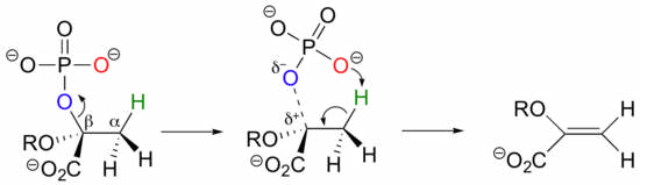
Notice in this mechanism that an E1cb elimination is not possible - there is no electron-withdrawing group (like a carbonyl) to stabilize the carbanion intermediate that would form if the proton were abstracted first. There is, however, an electron-*donating* group (the lone pair on a nitrogen) that can stabilize a positively-charged intermediate that forms when the water leaves.



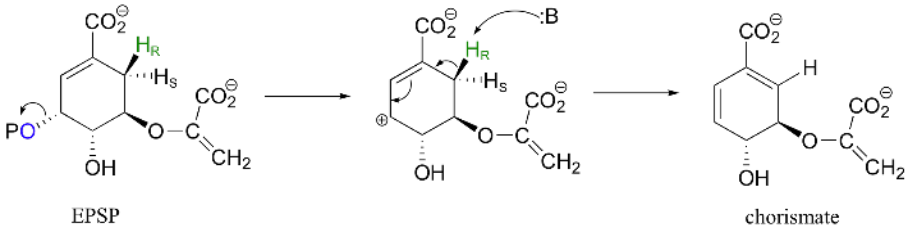
Another good example of a biological E1-like reaction is the elimination of phosphate in the formation of 5-enolpyruvylshikimate-3-phosphate (EPSP), an intermediate in the synthesis of aromatic amino acids.



Experimental evidence indicates that significant positive charge probably builds up on C_β of the starting compound, implying that C-O bond cleavage is advanced before proton abstraction occurs (notice the parallels to the Cope elimination in the previous section):

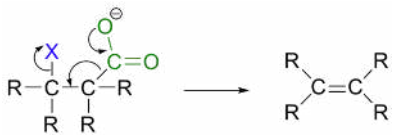


The very next step in the aromatic acid biosynthesis pathway is also an elimination, this time a 1,6-conjugated elimination rather than a simple beta-elimination.

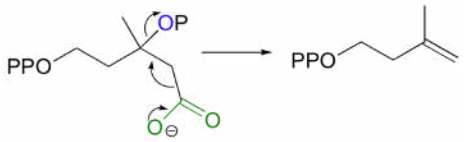


An E1-like mechanism (as illustrated above) has been proposed for this step, but other evidence suggests that a free-radical mechanism may be involved.

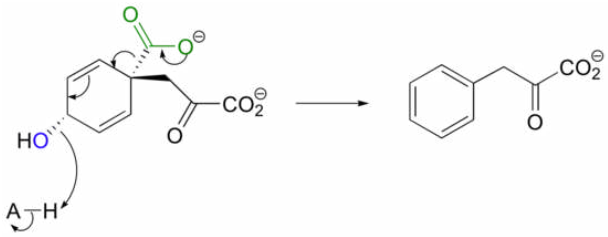
While most E1 and E2 reactions involve proton abstraction, eliminations can also incorporate a decarboxylation step.



Isopentenyl diphosphate, the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.



Phenylpyruvate, a precursor in the biosynthesis of phenylalanine, results from a conjugated 1,6 decarboxylation-elimination.



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11.12: A SUMMARY OF REACTIVITY - SN1, SN2, E1, E1CB, AND E2

OBJECTIVES

After completing this section, you should be able to

1. determine whether a specified substrate is most likely to undergo an E1, E2, S_N1 or S_N2 reaction under a given set of conditions.
2. describe the conditions under which a given substrate is most likely to react by a specified mechanism (E1, E2, S_N1 or S_N2).

STUDY NOTES

This section summarizes much of what has been discussed in the chapter. It focuses on how a given substrate will behave under certain conditions, but does not deal with the stereochemistry of the products.

Having discussed the many factors that influence nucleophilic substitution and elimination reactions of alkyl halides, we must now consider the practical problem of predicting the most likely outcome when a given alkyl halide is reacted with a given nucleophile. As we noted earlier, there are multiple variables to be considered, **the most important being the substitution of the alkyl halide**. S_N2 reactions favor alkyl halides with little steric hindrance such as methyl halides and primary halides. In general, in order for an S_N1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable such as with tertiary halides, secondary allylic halides, and secondary benzylic halides.

The next most import variable for predicting the outcome of a reaction is **the nature of the nucleophilic reactant**. Strong nucleophiles favor S_N2 substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor E2 elimination. Weak nucleophiles that are also weak bases tend to favor S_N1 and E1 reactions.

- **Good Nucleophiles Which are Weak Bases:** I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^-, Amines, etc.
- **Good Nucleophiles Which are Strong Bases:** HO^-, RO^-.
- **Poor Nucleophiles which are Weak Bases:** H_2O, ROH, RSH.

GENERAL RULES FOR PREDICTING A REACTION

Consider these in the order listed.

Methyl Alkyl Halides

- An S_N2 substitution occurs regardless if a good or poor nucleophile is used.

Primary Alkyl Halides

- An E2 elimination occurs if a strong, sterically hindered base is used.
- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An S_N2 substitution occurs if a good nucleophile is used.

Secondary Alkyl Halides

- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An E2 elimination occurs if a strong base is used.
- An S_N2 reaction occurs if a good nucleophile that is a weak bases is used in a polar aprotic solvent.
- An S_N1 reaction along with an E1 reaction occurs if a poor nucleophile that is a weak bases is used in a protic solvent.

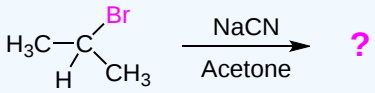
Tertiary Alkyl Halides

- An E1cB elimination occurs if a strong base is used and the leaving group is two carbons away from a carbonyl group.
- An E2 elimination occurs if a strong base is used.
- An S_N1 reaction along with an E1 reaction occurs if a poor nucleophile that is a weak bases is used in a protic solvent.

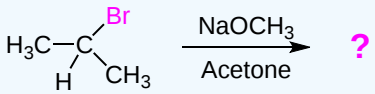
? WORKED EXAMPLE 11.12.1

1) For the following, please determine what kind of reaction is occurring and predict the product(s).

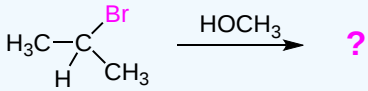
a)



b)

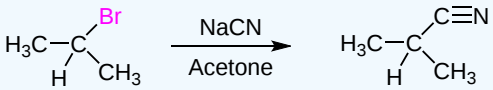


c)

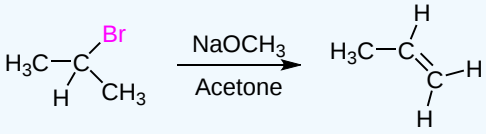


Answer

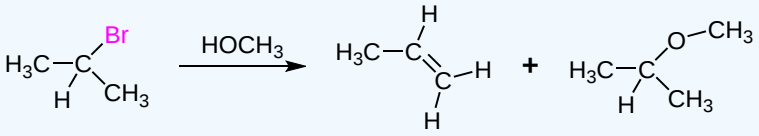
a) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Cyanide ($^-$CN) is a good nucleophile which is a weak base. The fact that the nucleophile is a weak base means that an E2 reaction is not favored. Also, the fact that cyanide is a good nucleophile means that S_N2 substitutions are favored over S_N1. When a secondary halide is reacted with a good nucleophile which is a weak base, the preferred reaction is S_N2. After S_N2 substitution the product is a nitrile.



b) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methoxide ($^-OCH_3$) is a strong base so it could prefer to remove a hydrogen from the substrate. This makes an E2 elimination the preferred reaction and an alkene the product.



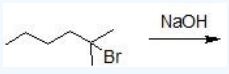
c) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methanol ($HOCH_3$) is a weak nucleophile that is a weak base. Being a weak base means that methanol is not capable of actively removing a hydrogen to cause an E2 reaction. Also, because methanol is a weak nucleophile is not capable of attacking the substrate and causing an S_N2 reaction. For the methanol nucleophile to react the substrate must first eject it leaving group to form the highly reactive carbocation intermediate. Formation of the carbocation is the rate determine step for both the S_N1 and E1 reactions so they each form a separate product.

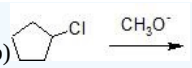


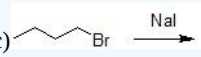
? EXERCISES 11.12.1

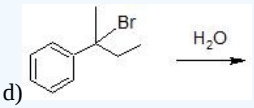
1. Identify the dominant reaction mechanism (S_N1, S_N2, E1, or E2) and predict the major product for the following reactions.

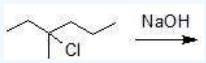
a)



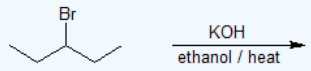
b) 

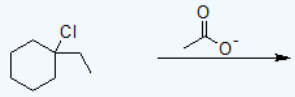
c) 

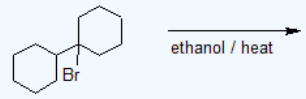
d) 

e) 

a) 

b) 

c) 

d) 

2) Identify the function of the following reagents. The reagents will be a strong/weak nucleophile and/or a strong/weak base.

a) Cl^-

b) NaH

c) t-BuO^-

d) OH^-

e) H_2O

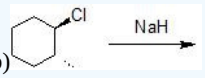
f) HS^-

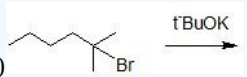
g) MeOH

3) Identify which mechanism the following reactions would undergo.

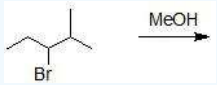
4) Identify all the products of the following reactions and specify the major product.

a) 

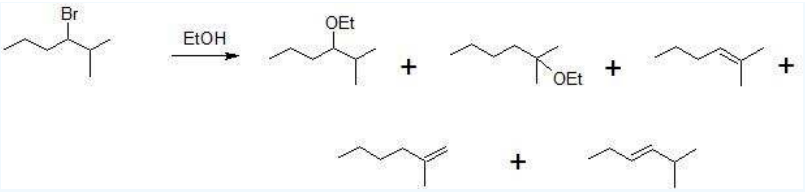
b) 

c) 

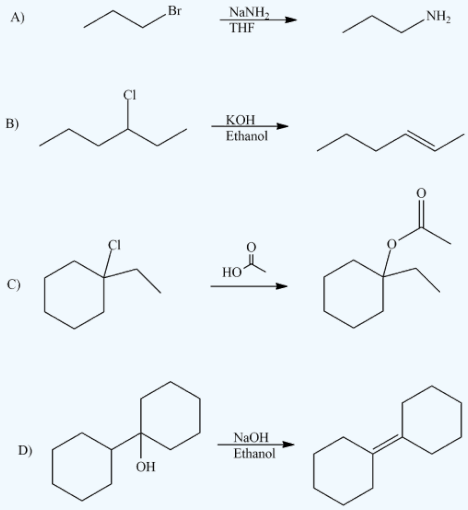
d) 

e) 

5) The following reaction yields five different products. Give the mechanisms for how each is formed.

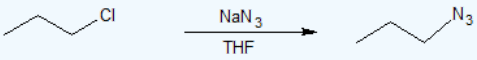


6) Label the following reactions as S_N1, S_N2, E1, or E2.

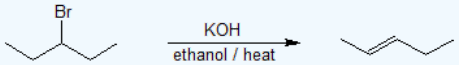


Answer

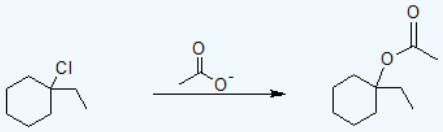
1)

a) 

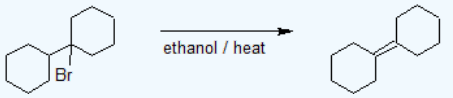
S_N2 b/c primary alkyl halide and strong nucleophile that is a weak base in a polar aprotic solvent

b) 

E2 b/c secondary alkyl halide and a strong base heated

c) 

SN1 b/c tertiary alkyl halide with a weak nucleophile that is a weak base

d) 

E1 b/c tertiary alkyl halide with a weak base heated

2)

a) Cl^- ; strong nucleophile

b) NaH ; strong base

c) t-BuO^- ; strong base

d) OH^- ; strong nucleophile ; strong base

e) H_2O ; weak nucleophile ; weak base

f) HS^- ; strong nucleophile

g) MeOH ; weak nucleophile ; weak base

3)

a) E2, S_N1

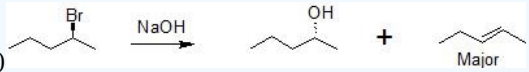
b) S_N2, E2

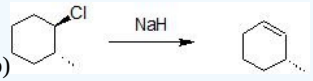
c) S_N2

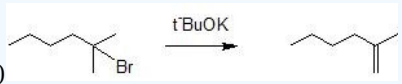
d) S_N1, E1

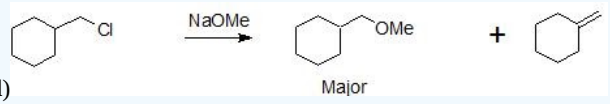
e) E2, S_N1

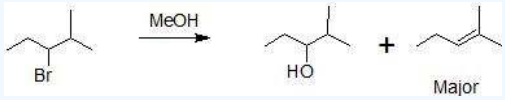
4)

a) 

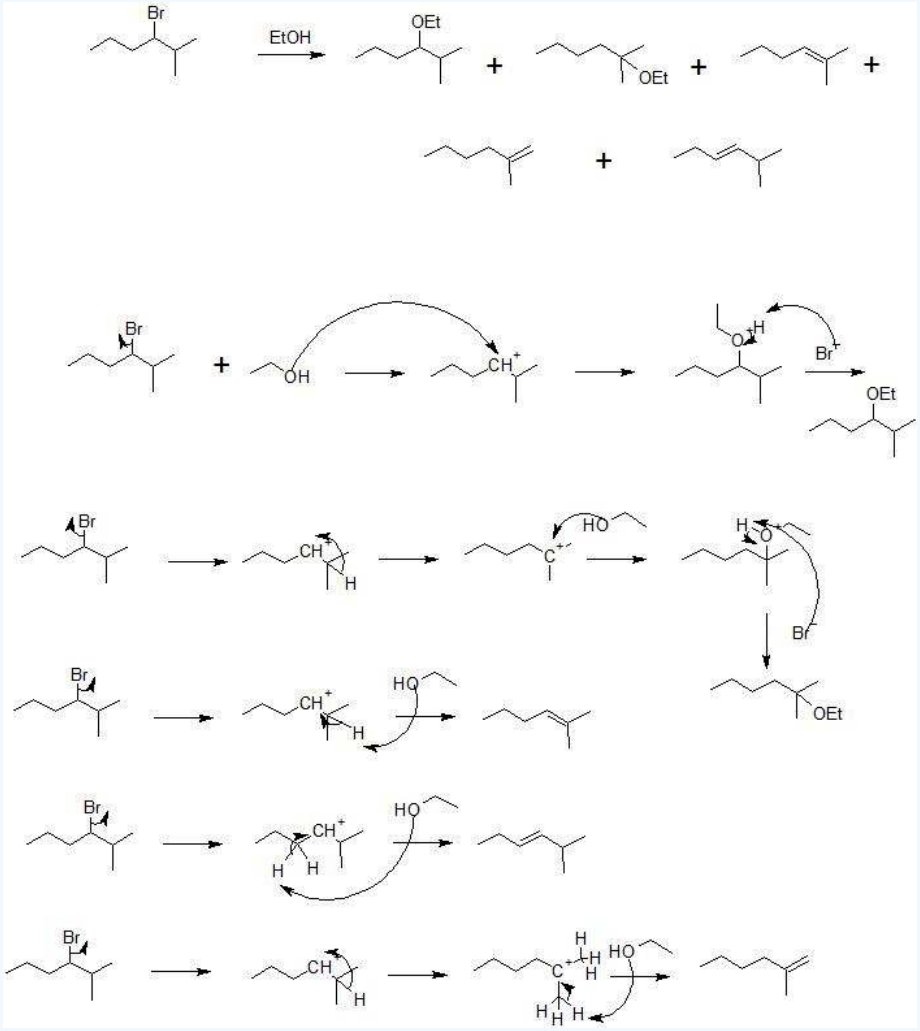
b) 

c) 

d) 

e) 

5)



6)

A – S_N2

B – E1

C – S_N1

D – E2

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11.S: REACTIONS OF ALKYL HALIDES - NUCLEOPHILIC SUBSTITUTIONS AND ELIMINATIONS (SUMMARY)

CONCEPTS & VOCABULARY

11.1 Introduction

- Alkyl halides react as electrophiles and undergo nucleophilic substitution and elimination reactions.

11.2 The Discovery of Nucleophilic Substitution Reactions

- Some nucleophilic substitution reactions invert stereochemistry at the reactive carbon.

11.3 The S_N2 Reaction

- Reaction steps with two molecules involved in the rate determining step are called bimolecular.
- A substitution mechanism that has the nucleophile entering at the same time the leaving group leaves, in a concerted step, is called S_N2 - substitution nucleophilic bimolecular.
- Concerted substitution mechanisms (S_N2) occur via backside attack, which causes inversion of the carbon where the reaction occurs.
- Rates of S_N2 reactions depend on concentration of nucleophile and alkyl halide.

11.4 Characteristics of the S_N2 Reaction

- S_N2 reactions are concerted.
- Sterically hindered substrates reduce S_N2 reaction rate.
- A **transition state** in a reaction mechanism is the highest energy point on a pathway from reactants to an intermediate or products.
- Larger groups (such as alkyl vs. hydrogen) cause greater steric repulsion in S_N2 **transition states**, reducing rates of S_N2 reactions.
- Groups that have electron-rich atoms are typically good nucleophiles.
- In general, stronger bases are better nucleophiles.
- Polar aprotic solvents increase rates of S_N2 reactions.
- Polar protic solvents decrease rates of S_N2 reactions.
- As basicity of leaving groups decreases, their ability to leave increases.

11.5 The S_N1 Reaction

- A substitution mechanism that occurs with the leaving group leaving in the first step, creating a carbocation intermediate, followed by the nucleophile entering is called S_N1 - substitution nucleophilic unimolecular.
- S_N1 reactions occur through a stepwise mechanism.
- The first step (dissociation) of an S_N1 mechanism is rate limiting.
- In S_N1 reactions the nucleophile is not involved in the rate limiting step, therefore nucleophile strength or concentration do not affect the rate.
- The intermediate for S_N1 mechanisms contains a planar carbocation. The nucleophile can then enter from either side of the molecule giving racemic products with no additional stereocenters in the molecule.

11.6 Characteristics of the S_N1 Reaction

- Polar solvents increase rates of S_N1 reactions.
- Better leaving groups increase rates of S_N1 and S_N2 reactions.
- Predicting whether a reaction will follow an S_N1 or S_N2 mechanism requires analysis of:
  - Electrophile - primary favor S_N2, tertiary (and allyl or benzyl) favor S_N1, secondary depends on other factors
  - Nucleophile - strong favor S_N2, weak favor S_N1
  - Solvent - polar aprotic favor S_N2, polar protic favor S_N1

11.7 Biological Substitution Reactions

- When biological substitution reactions occur, the electrophiles are often different though the mechanisms are primarily the same.

11.8 Elimination Reactions - Zaitsev's Rule

- The major product of Elimination reactions is the product with the more substituted double bond. This is known as Zaitsev's rule.

11.9 The E2 Reaction and Deuterium Isotope Effect

- The E2 mechanism is concerted with the base removing a proton and the leaving group leaving at the same time.
- Since E2 mechanisms are concerted, both the base and the electrophile are present in the rate equation.

- E2 reactions require strong bases and polar aprotic solvents.
- Kinetic Isotope Effects can provide evidence for E2 mechanisms since they can show when breaking of the C-H bond is part of the rate-determining step.

11.10 The E2 Reaction and Cyclohexane Conformation

- E2 reactions of cyclic structures show necessity for anti orientation of the proton being removed and the leaving group.

11.11 The E1 and E1cB Reactions

- E1 mechanisms begin with a leaving group leaving which forms a carbocation intermediate, which is then deprotonated in a second step.
- E1 mechanisms are step-wise.
- More substituted electrophiles are more reactive in E1 reactions.
- Zaitsev products are preferred, similarly to E2 reactions.
- E1 and S_N1 proceed via the same carbocation intermediate and the same rate-determining step so typically happen concurrently.
- E1cB reactions begin with deprotonation (usually resulting in a resonance stabilized carbanion), followed by loss of the leaving group in the second step.

11.12 Biological Elimination Reactions

- There are many important examples of biological elimination reactions.

11.13 A Summary of Reactivity - S_N1, S_N2, E1, E1CcB, and E2

SKILLS TO MASTER

- Skill 11.1 Draw S_N1/S_N2 mechanisms showing appropriate stereochemistry.
- Skill 11.2 Explain when S_N1/S_N2 mechanisms are likely to occur.
- Skill 11.3 Describe/draw the intermediate for an S_N1 mechanism and transition state(s) for S_N1/S_N2 mechanisms.
- Skill 11.4 Write out rate laws for S_N1/S_N2 mechanisms.
- Skill 11.5 Differentiate between which mechanism is more likely between S_N1/S_N2.
- Skill 11.6 Draw reaction coordinate diagrams for S_N1/S_N2 mechanisms.
- Skill 11.7 Explain how the electrophile, nucleophile, leaving group, and solvent affect S_N1/S_N2 mechanisms.
- Skill 11.8 Recognize use of nucleophilic substitution and elimination reactions in biological systems.
- Skill 11.9 Draw E1/E2 mechanisms showing appropriate stereochemistry.
- Skill 11.10 Explain when E1/E2 mechanisms are likely to occur.
- Skill 11.11Describe/draw the intermediate for an E1 mechanism and transition state(s) for E1/E2mechanisms.
- Skill 11.12 Write out rate laws for E1/E2 mechanisms.
- Skill 11.13 Differentiate between which mechanism is more likely between E1/E2.
- Skill 11.14 Draw reaction coordinate diagrams for E1/E2 mechanisms.
- Skill 11.15 Explain how kinetic isotope effects can be used to support or refute a proposed mechanism.
- Skill 11.16 Draw an E1cB mechanism and explain when it is a viable option.
- Skill 11.17 Differentiate between which mechanism is more likely between S_N1/S_N2 and E1/E2.

MEMORIZATION TASKS (MT)

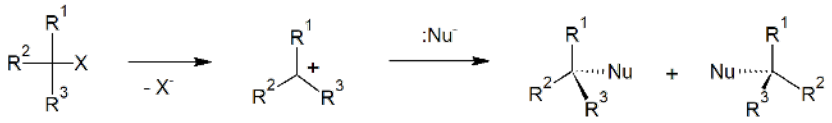
MT 11.1 Memorize the order of good leaving groups.

MT 11.2 Memorize which solvents are polar protic and polar aprotic.

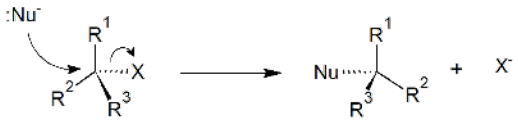
MT 11.3 Memorize the stability order of carbocations.

SUMMARY OF REACTIONS

Nucleophilic Substitutions

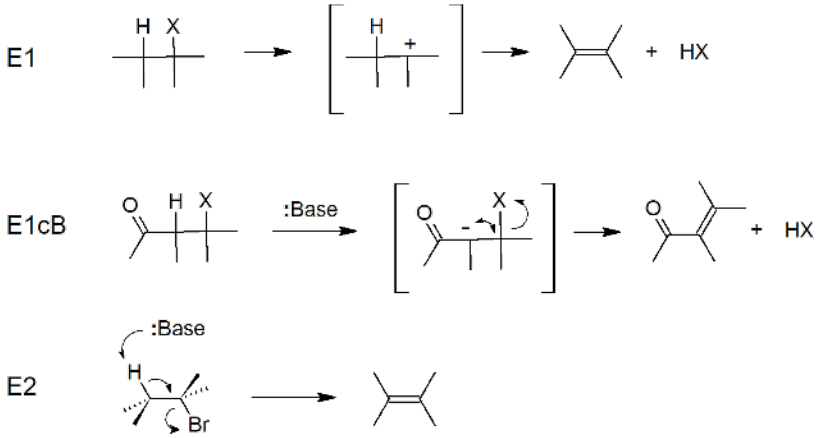


S_N1 (racemic mix of *R* and *S* products)



S_N2 (inverted product)

Eliminations



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CHAPTER OVERVIEW

12: STRUCTURE DETERMINATION - MASS SPECTROMETRY AND INFRARED SPECTROSCOPY

LEARNING OBJECTIVES

After you have completed Chapter 12, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems that include mass spectral data, infrared data, or both.
3. define, and use in context, the key terms introduced.

The processes of identifying and characterizing organic compounds are of great importance to the working organic chemist. With the use of modern instrumental techniques, these tasks can now be accomplished much more readily than in the past. In this chapter, you will learn about two spectroscopic techniques (mass spectroscopy and infrared spectroscopy) that are used to identify organic compounds.

12.0: Introduction
12.1: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments
12.2: Interpreting Mass Spectra
12.3: Mass Spectrometry of Some Common Functional Groups
12.4: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments
12.5: Spectroscopy and the Electromagnetic Spectrum
12.6: Infrared Spectroscopy
12.7: Interpreting Infrared Spectra
12.8: Infrared Spectra of Some Common Functional Groups
12.S: Structure Determination - Mass Spectrometry and Infrared Spectroscopy (Summary)

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12.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to recognize the various spectroscopic techniques used to identify and characterize organic compounds.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- spectroscopy

STUDY NOTES

The term spectroscopy is used to describe a number of techniques used by chemists to obtain information about the structure and bonding of chemical compounds. Four types of spectroscopy are described in the course:

1. mass spectroscopy (also called mass spectrometry, Chapter 12).
2. infrared spectroscopy (often simply called IR, Chapter 12).
3. nuclear magnetic resonance spectroscopy (usually referred to as NMR, Chapter 13).
4. ultraviolet spectroscopy (abbreviated UV, Chapter 14).

Of these four techniques, we shall spend the least time on ultraviolet spectroscopy, as it is much less powerful than the other three. If you do any reading on chemistry outside of the course materials, you will almost certainly see references to other spectroscopic techniques, such as Raman spectroscopy, electron spin resonance (ESR) spectroscopy, and atomic absorption (AA) spectroscopy. Even a description of these techniques and the information they can provide is beyond the scope of this course.

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12.1: MASS SPECTROMETRY OF SMALL MOLECULES - MAGNETIC-SECTOR INSTRUMENTS

OBJECTIVES

After completing this section, you should be able to

1. describe, briefly, how a mass spectrometer works.
2. sketch a simple diagram to show the essential features of a mass spectrometer.
3. identify peaks in a simple mass spectrum, and explain how they arise.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- base peak
- parent peak (molecular ion peak)
- cation radical
- relative abundance
- mass spectrometer
- mass spectroscopy
- mass spectrum
- molecular ion (M+·)
- mass-to-charge ratio (*m*/*z*)

STUDY NOTES

You may remember from general first-year chemistry how mass spectroscopy has been used to establish the atomic mass and abundance of isotopes.

Mass spectrometers are large and expensive, and usually operated only by fully trained personnel, so you may not have the opportunity to use such an instrument as part of this course. Research chemists often rely quite heavily on mass spectra to assist them in the identification of compounds, and you will be required to interpret simple mass spectra both in assignments and on examinations. Note that in most attempts to identify an unknown compound, chemists do not rely exclusively on the results obtained from a single spectroscopic technique. A combination of chemical and physical properties and spectral evidence is usually employed.

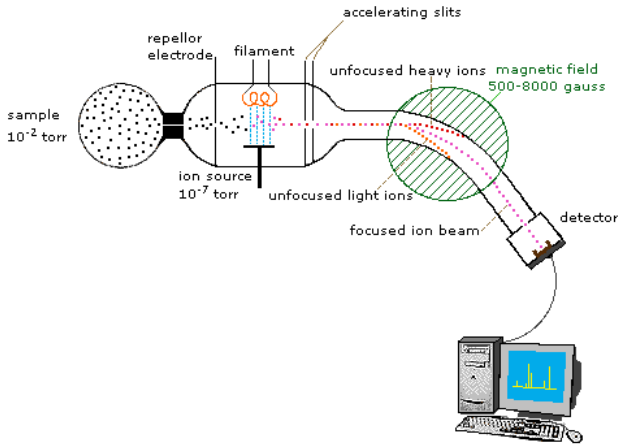
THE MASS SPECTROMETER

In order to measure the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can be moved about and manipulated by external electric and magnetic fields. The three essential functions of a mass spectrometer, and the associated components, are:

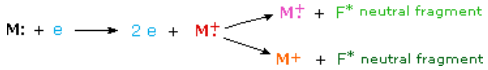
1. A small sample is ionized, usually to cations by loss of an electron. **The Ion Source**
2. The ions are sorted and separated according to their mass and charge. **The Mass Analyzer**
3. The separated ions are then measured, and the results displayed on a chart. **The Detector**

Because ions are very reactive and short-lived, their formation and manipulation must be conducted in a vacuum. Atmospheric pressure is around 760 torr (mm of mercury). The pressure under which ions may be handled is roughly 10^{-5} to 10^{-8} torr (less than a billionth of an atmosphere). Each of the three tasks listed above may be accomplished in different ways. In one common procedure, ionization is effected by a high energy beam of electrons, and ion separation is achieved by accelerating and focusing the ions in a beam, which is then bent by an external magnetic field. The ions are then detected electronically and the resulting information is stored and analyzed in a computer. A mass spectrometer operating in this fashion is outlined in the following diagram. The heart of the spectrometer is the **ion source**. Here molecules of the sample (black dots) are bombarded by electrons (light blue lines) issuing from a heated filament. This is called an **EI** (electron-ionization) source. Gases and volatile liquid samples are allowed to leak into the ion source from a reservoir (as shown). Non-volatile solids and liquids may be introduced directly. Cations formed by the electron bombardment (red dots) are pushed away by a charged repellor plate (anions are attracted to it), and accelerated toward other electrodes, having slits through which the ions pass as a beam. Some of these ions fragment into smaller cations and neutral fragments. A perpendicular magnetic field deflects the ion beam in an arc whose radius is

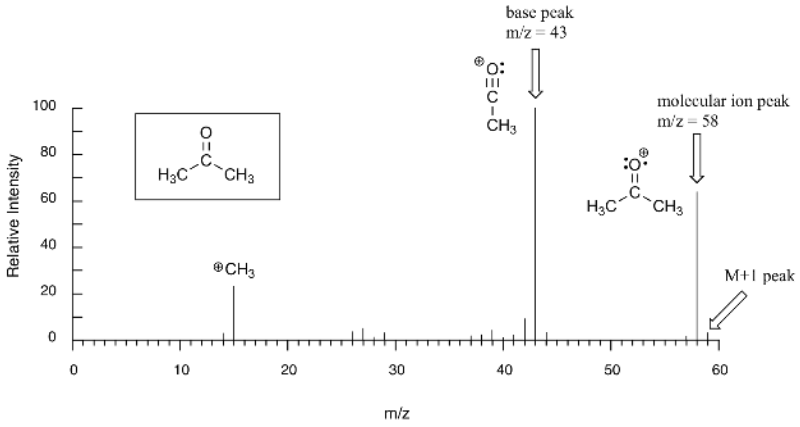
inversely proportional to the mass of each ion. Lighter ions are deflected more than heavier ions. By varying the strength of the magnetic field, ions of different mass can be focused progressively on a detector fixed at the end of a curved tube (also under a high vacuum).



When a high energy electron collides with a molecule it often ionizes it by knocking away one of the molecular electrons (either bonding or non-bonding). This leaves behind a **molecular ion** (colored red in the following diagram). Residual energy from the collision may cause the molecular ion to fragment into neutral pieces (colored green) and smaller **fragment ions** (colored pink and orange). The molecular ion is a radical cation, but the fragment ions may either be radical cations (pink) or carbocations (orange), depending on the nature of the neutral fragment. An animated display of this ionization process will appear if you click on the ion source of the mass spectrometer diagram.



Below is typical output for an electron-ionization MS experiment (MS data below is derived from the Spectral Database for Organic Compounds, a free, web-based service provided by AIST in Japan.



The sample is acetone. On the horizontal axis is the value for m/z, which is the mass to charge ratio (as we stated above, the charge z is almost always +1, so in practice this is the same as mass). On the vertical axis is the relative abundance of each ion detected. On this scale, the most abundant ion, called the **base peak**, is set to 100%, and all other peaks are recorded relative to this value. For acetone, the base peak corresponds to a fragment with m/z = 43 - . The molecular weight of acetone is 58, so we can identify the peak at m/z = 58 as that corresponding to the **molecular ion peak**, or **parent peak**. Notice that there is a small peak at m/z = 59: this is referred to as the **M+1 peak**. How can there be an ion that has a greater mass than the molecular ion? Simple: a small fraction - about 1.1% - of all carbon atoms in nature are actually the ^{13}C rather than the ^{12}C isotope. The ^{13}C isotope is, of course, heavier than ^{12}C by 1 mass unit. In addition, about 0.015% of all hydrogen atoms are actually deuterium, the ^{2}H isotope. So the M+1 peak represents those few acetone molecules in the sample which contained either a ^{13}C or ^{2}H.

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12.2: INTERPRETING MASS SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. suggest possible molecular formulas for a compound, given the *m/z* value for the molecular ion, or a mass spectrum from which this value can be obtained.
2. predict the relative heights of the M+·, (M + 1)+·, etc., peaks in the mass spectrum of a compound, given the natural abundance of the isotopes of carbon and the other elements present in the compound.
3. interpret the fragmentation pattern of the mass spectrum of a relatively simple, known compound (e.g., hexane).
4. use the fragmentation pattern in a given mass spectrum to assist in the identification of a relatively simple, unknown compound (e.g., an unknown alkane).

STUDY NOTES

When interpreting fragmentation patterns, you may find it helpful to know that, as you might expect, the weakest carbon-carbon bonds are the ones most likely to break. You might wish to refer to the table of bond dissociation energies when attempting problems involving the interpretation of mass spectra.

This page looks at how fragmentation patterns are formed when organic molecules are fed into a mass spectrometer, and how you can get information from the mass spectrum.

THE ORIGIN OF FRAGMENTATION PATTERNS

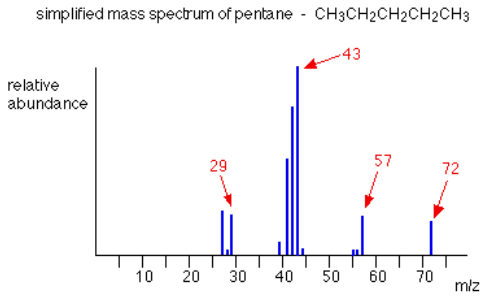
When the vaporized organic sample passes into the ionization chamber of a mass spectrometer, it is bombarded by a stream of electrons. These electrons have a high enough energy to knock an electron off an organic molecule to form a positive ion. This ion is called the **molecular ion - or sometimes the parent ion** and is often given the symbol M^+ or $M^{+\bullet}$. The dot in this second version represents the fact that somewhere in the ion there will be a single unpaired electron. That's one half of what was originally a pair of electrons - the other half is the electron which was removed in the ionization process.

The molecular ions are energetically unstable, and some of them will break up into smaller pieces. The simplest case is that a molecular ion breaks into two parts - one of which is another positive ion, and the other is an uncharged free radical.



The uncharged free radical will **not** produce a line on the mass spectrum. Only charged particles will be accelerated, deflected and detected by the mass spectrometer. These uncharged particles will simply get lost in the machine - eventually, they get removed by the vacuum pump.

The ion, X^+, will travel through the mass spectrometer just like any other positive ion - and will produce a line on the stick diagram. All sorts of fragmentations of the original molecular ion are possible - and that means that you will get a whole host of lines in the mass spectrum. For example, the mass spectrum of pentane looks like this:



https://chem.libretexts.org/@go/page/31523

NOTE

The pattern of lines in the mass spectrum of an *organic compound* tells you something quite different from the pattern of lines in the mass spectrum of an *element*. With an element, each line represents a different isotope of that element. With a compound, each line represents a different fragment produced when the molecular ion breaks up.

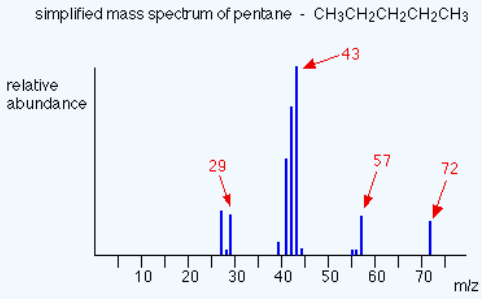
In the stick diagram showing the mass spectrum of pentane, the line produced by the heaviest ion passing through the machine (at m/z = 72) is due to the molecular ion. The tallest line in the stick diagram (in this case at m/z = 43) is called the **base peak**. This is usually given an arbitrary height of 100, and the height of everything else is measured relative to this. The base peak is the tallest peak because it represents the commonest fragment ion to be formed - either because there are several ways in which it could be produced during fragmentation of the parent ion, or because it is a particularly stable ion.

USING FRAGMENTATION PATTERNS

This section will ignore the information you can get from the molecular ion (or ions). That is covered in three other pages which you can get at via the mass spectrometry menu. You will find a link at the bottom of the page.

EXAMPLE 12.2.1: PENTANE

Let's have another look at the mass spectrum for pentane:



What causes the line at m/z = 57?

How many carbon atoms are there in this ion? There cannot be 5 because 5 x 12 = 60. What about 4? 4 x 12 = 48. That leaves 9 to make up a total of 57. How about $C_4H_9^+$ then?

$C_4H_9^+$ would be $[CH_3CH_2CH_2CH_2]^+$, and this would be produced by the following fragmentation:

$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CH_2CH_2]^+ + \bullet CH_3$$

The methyl radical produced will simply get lost in the machine.

The line at m/z = 43 can be worked out similarly. If you play around with the numbers, you will find that this corresponds to a break producing a 3-carbon ion:

$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CH_2]^+ + \bullet CH_2CH_3$$

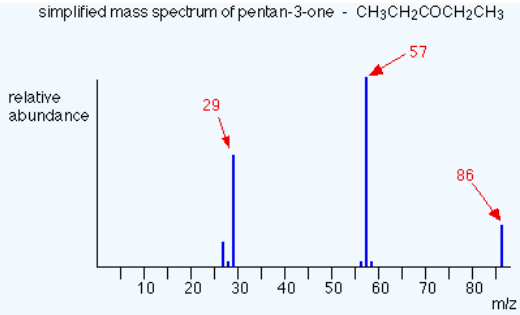
The line at m/z = 29 is typical of an ethyl ion, $[CH_3CH_2]^+$:

$$[CH_3CH_2CH_2CH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2]^+ + \bullet CH_2CH_2CH_3$$

The other lines in the mass spectrum are more difficult to explain. For example, lines with m/z values 1 or 2 less than one of the easy lines are often due to loss of one or more hydrogen atoms during the fragmentation process.

EXAMPLE 12.2.2: PENTAN-3-ONE

This time the base peak (the tallest peak - and so the commonest fragment ion) is at m/z = 57. But this is not produced by the same ion as the same m/z value peak in pentane.



If you remember, the m/z = 57 peak in pentane was produced by $[CH_3CH_2CH_2CH_2]^+$. If you look at the structure of pentan-3-one, it's impossible to get that particular fragment from it.

Work along the molecule mentally chopping bits off until you come up with something that adds up to 57. With a small amount of patience, you'll eventually find $[CH_3CH_2CO]^+$ - which is produced by this fragmentation:

$$[CH_3CH_2COCH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2CO]^+ + \bullet CH_2CH_3$$

You would get exactly the same products whichever side of the CO group you split the molecular ion. The m/z = 29 peak is produced by the ethyl ion - which once again could be formed by splitting the molecular ion either side of the CO group.

$$[CH_3CH_2COCH_2CH_3]^{\ddagger} \longrightarrow [CH_3CH_2]^+ + \bullet COCH_2CH_3$$

PEAK HEIGHTS AND STABILITY

The more stable an ion is, the more likely it is to form. The more of a particular sort of ion that's formed, the higher its peak height will be. We'll look at two common examples of this.

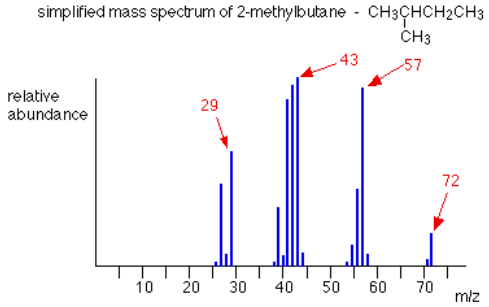
CARBOCATIONS (CARBONIUM IONS)

Summarizing the most important conclusion from the page on carbocations:

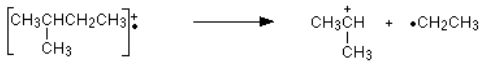
Order of stability of carbocations

primary < secondary < tertiary

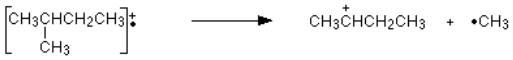
Applying the logic of this to fragmentation patterns, it means that a split which produces a secondary carbocation is going to be more successful than one producing a primary one. A split producing a tertiary carbocation will be more successful still. Let's look at the mass spectrum of 2-methylbutane. 2-methylbutane is an isomer of pentane - isomers are molecules with the same molecular formula, but a different spatial arrangement of the atoms.



Look first at the very strong peak at m/z = 43. This is caused by a different ion than the corresponding peak in the pentane mass spectrum. This peak in 2-methylbutane is caused by:



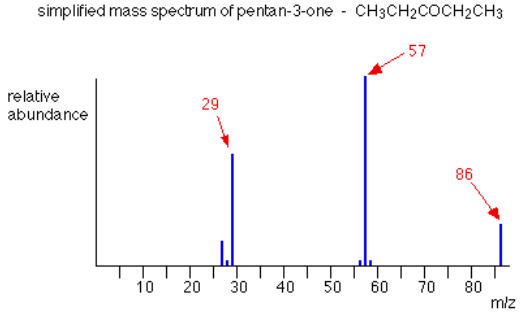
The ion formed is a secondary carbocation - it has two alkyl groups attached to the carbon with the positive charge. As such, it is relatively stable. The peak at m/z = 57 is much taller than the corresponding line in pentane. Again a secondary carbocation is formed - this time, by:



You would get the same ion, of course, if the left-hand CH_3 group broke off instead of the bottom one as we've drawn it. In these two spectra, this is probably the most dramatic example of the extra stability of a secondary carbocation.

ACYLIUM IONS, $[RCO]^+$

Ions with the positive charge on the carbon of a carbonyl group, C=O, are also relatively stable. This is fairly clearly seen in the mass spectra of ketones like pentan-3-one.



The base peak, at m/z=57, is due to the $[CH_3CH_2CO]^+$ ion. We've already discussed the fragmentation that produces this.

NOTE

The more stable an ion is, the more likely it is to form. The more of a particular ion that is formed, the higher will be its peak height.

USING MASS SPECTRA TO DISTINGUISH BETWEEN COMPOUNDS

Suppose you had to suggest a way of distinguishing between pentan-2-one and pentan-3-one using their mass spectra.

pentan-2-one	$CH_3COCH_2CH_2CH_3$
pentan-3-one	$CH_3CH_2COCH_2CH_3$

Each of these is likely to split to produce ions with a positive charge on the CO group. In the pentan-2-one case, there are two different ions like this:

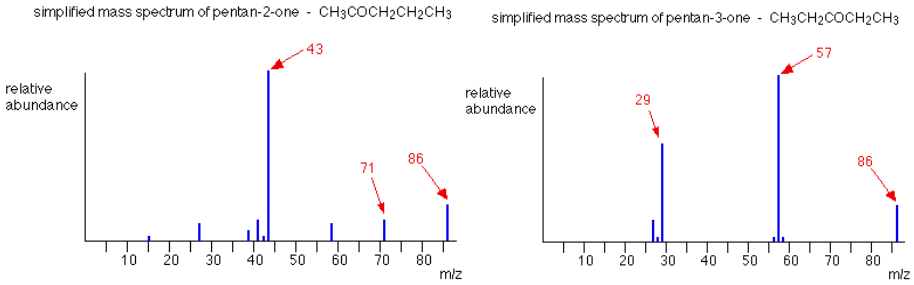
- $[CH_3CO]^+$
- $[COCH_2CH_2CH_3]^+$

That would give you strong lines at m/z = 43 and 71. With pentan-3-one, you would only get one ion of this kind:

- $[CH_3CH_2CO]^+$

In that case, you would get a strong line at 57. You don't need to worry about the other lines in the spectra - the 43, 57 and 71 lines give you plenty of difference between the two. The 43 and 71 lines are missing from the pentan-3-one spectrum, and the 57 line is missing from the pentan-2-one one.

The two mass spectra look like this:



As you've seen, the mass spectrum of even very similar organic compounds will be quite different because of the different fragmentation patterns that can occur. Provided you have a computer data base of mass spectra, any unknown spectrum can be computer analyzed and simply matched against the data base.

EXERCISES

QUESTIONS

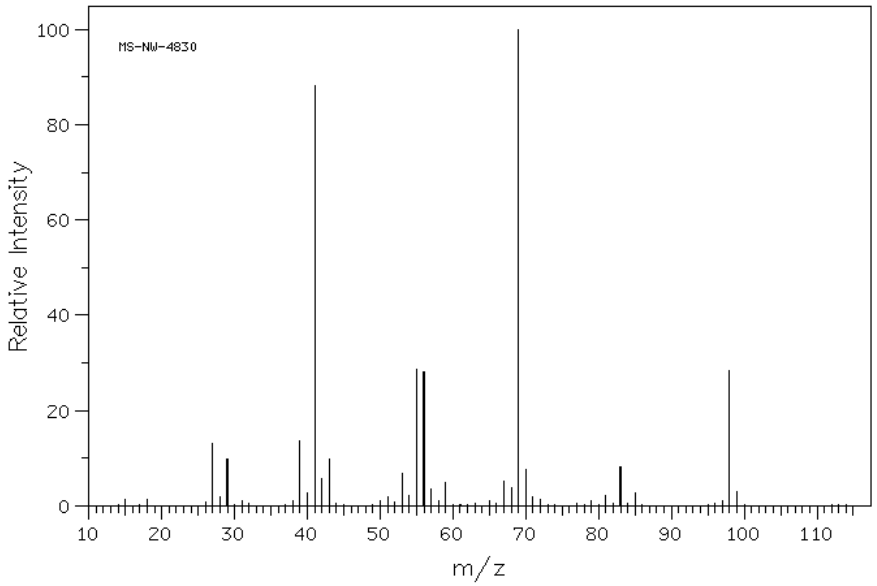
Q12.2.1

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

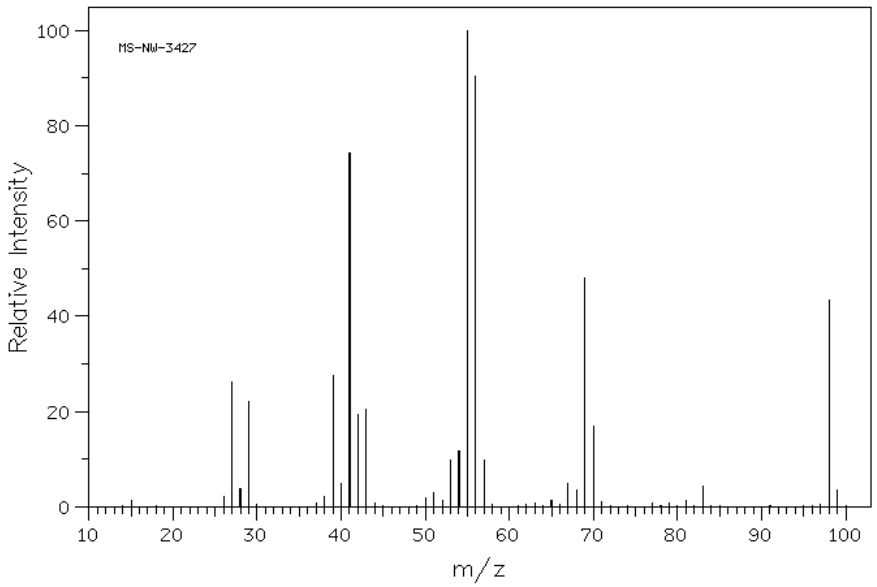
Q12.2.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:



B:



Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

SOLUTIONS

S12.2.1

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

https://chem.libretexts.org/@go/page/31523

N = 14 × 4 = 56

H = 1 × 10 = 10

O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

S12.2.2

The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

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12.3: MASS SPECTROMETRY OF SOME COMMON FUNCTIONAL GROUPS

OBJECTIVE

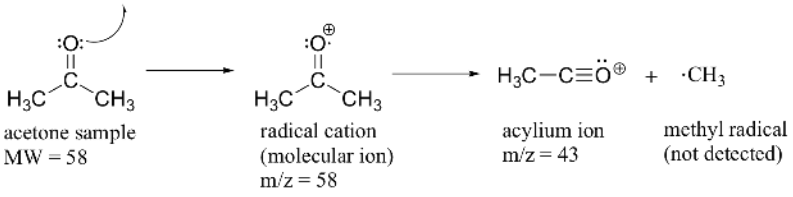
After completing this section, you should be able to predict the expected fragmentation for common functional groups, such as alcohols, amines, and carbonyl compounds.

KEY TERMS

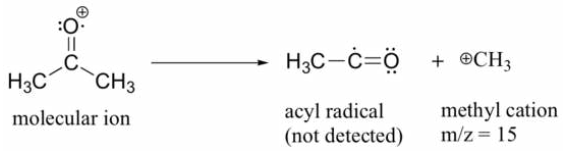
Make certain that you can define, and use in context, the key terms below.

- alpha (α) cleavage
- McLafferty rearrangement

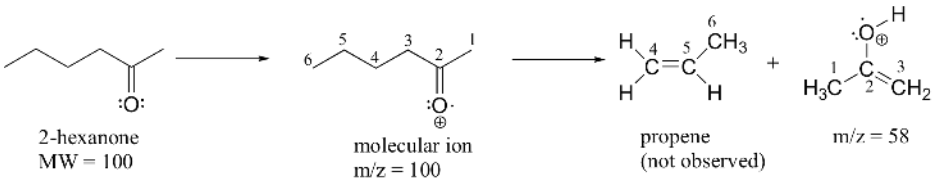
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it is worthwhile to see a few representative examples, even if we don't attempt to understand the exact process by which the fragmentation occurs. We saw, for example, that the base peak in the mass spectrum of acetone is m/z = 43. This is the result of cleavage at the 'alpha' position - in other words, at the carbon-carbon bond adjacent to the carbonyl. Alpha cleavage results in the formation of an acylium ion (which accounts for the base peak at m/z = 43) and a methyl radical, which is neutral and therefore not detected.



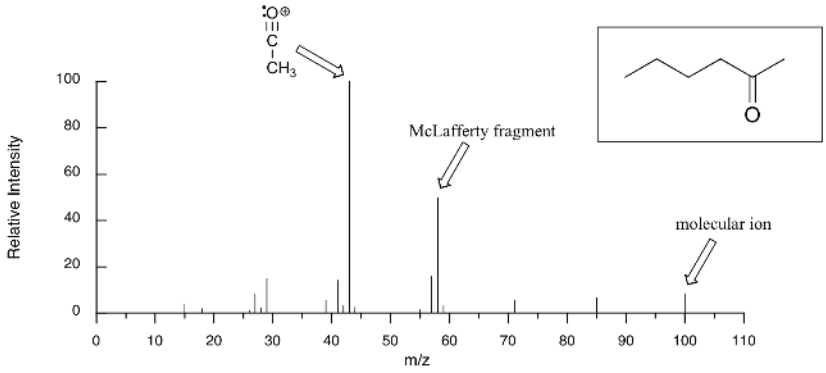
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



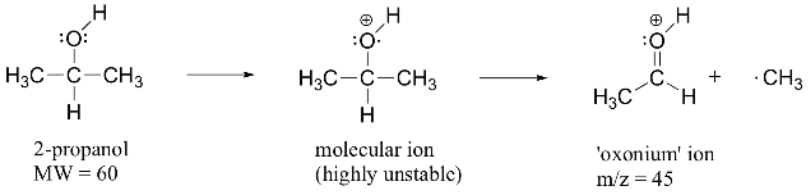
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

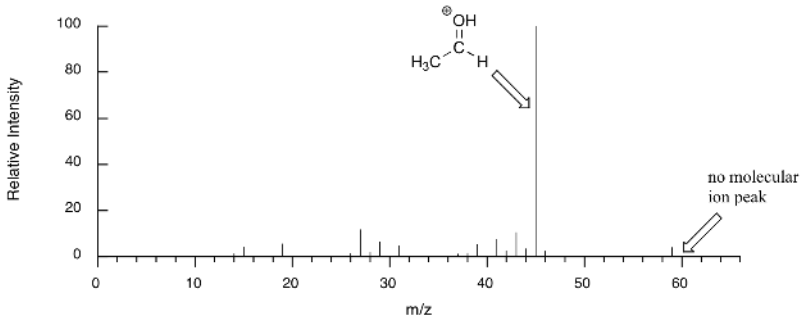


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



When alcohols are subjected to electron ionization MS, the molecular ion is highly unstable and thus a parent peak is often not detected. Often the base peak is from an ‘oxonium’ ion.





Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often ‘put the puzzle together’ and make some very confident predictions about the structure of the starting sample.

Click here for examples of compounds listed by functional group, which demonstrate patterns which can be seen in mass spectra of compounds ionized by electron impact ionization.

EXAMPLE 12.3.1

The mass spectrum of an aldehyde gives prominent peaks at *m/z* = 59 (12%, highest value of *m/z* in the spectrum), 58 (85%), and 29 (100%), as well as others. Propose a structure, and identify the three species whose *m/z* values were listed.

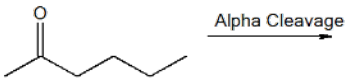
Solution

EXERCISES

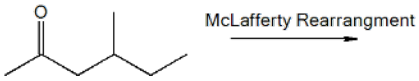
QUESTIONS

Q12.3.1

What are the masses of all the components in the following fragmentations?

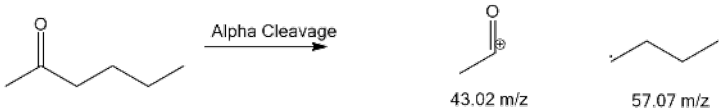


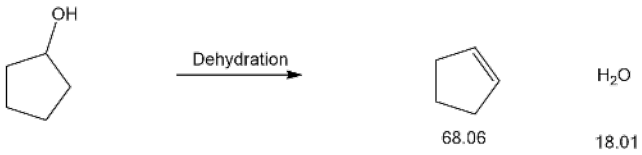




SOLUTIONS

S12.3.1







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12.4: MASS SPECTROMETRY IN BIOLOGICAL - TIME-OF-FLIGHT (TOF) INSTRUMENTS

OBJECTIVE

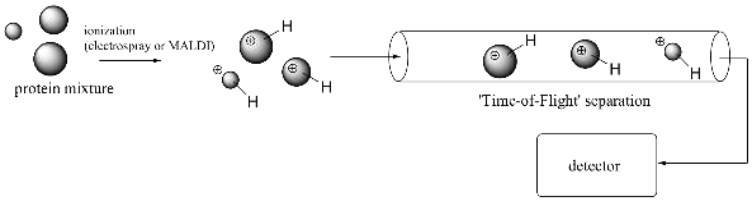
This section is intended only to demonstrate that mass spectrometry can be useful for the investigation of some very large molecules present in biological systems.

MASS SPECTROMETRY OF PROTEINS - APPLICATIONS IN PROTEOMICS

Mass spectrometry has become in recent years an increasingly important tool in the field of **proteomics**. Traditionally, protein biochemists tend to study the structure and function of individual proteins. Proteomics researchers, in contrast, want to learn more about how large numbers of proteins in a living system interact with each other, and how they respond to changes in the state of the organism. One very important subfield of proteomics is the search for protein **biomarkers** for human disease. These can be proteins which are present in greater quantities in a sick person than in a healthy person, and their detection and identification can provide medical researchers with valuable information about possible causes or treatments. Detection in a healthy person of a known biomarker for a disease such as diabetes or cancer could also provide doctors with an early warning that the patient may be especially susceptible, so that preventive measures could be taken to prevent or delay onset of the disease.

New developments in MS technology have made it easier to detect and identify proteins that are present in very small quantities in biological samples. Mass spectrometrists who study proteins often use instrumentation that is somewhat different from the electron-ionization, magnetic deflection system described earlier. When proteins are being analyzed, the object is often to ionize the proteins *without* causing fragmentation, so 'softer' ionization methods are required. In one such method, called **electrospray ionization**, the protein sample, in solution, is sprayed into a tube and the molecules are induced by an electric field to pick up extra protons from the solvent. Another common 'soft ionization' method is 'matrix-assisted laser desorption ionization' (**MALDI**). Here, the protein sample is adsorbed onto a solid matrix, and protonation is achieved with a laser.

Typically, both electrospray ionization and MALDI are used in conjunction with a time-of-flight (TOF) mass analyzer component.



The ionized proteins are accelerated by an electrode through a column, and separation is achieved because lighter ions travel at greater velocity than heavier ions with the same overall charge. In this way, the many proteins in a complex biological sample (such as blood plasma, urine, etc.) can be separated and their individual masses determined very accurately. Modern protein MS is extremely sensitive – very recently, scientists were even able to obtain a mass spectrum of *Tyrannosaurus rex* protein from fossilized bone! (Science **2007**, 316, 277).

In one recent study, MALDI-TOF mass spectrometry was used to compare fluid samples from lung transplant recipients who had suffered from tissue rejection to control samples from recipients who had not suffered rejection. Three peptides (short proteins) were found to be present at elevated levels specifically in the tissue rejection samples. It is hoped that these peptides might serve as biomarkers to identify patients who are at increased risk of rejecting their transplanted lungs (Proteomics **2005**, 5, 1705).

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12.5: SPECTROSCOPY AND THE ELECTROMAGNETIC SPECTRUM

OBJECTIVES

After completing this section, you should be able to

1. write a brief paragraph discussing the nature of electromagnetic radiation.
2. write the equations that relate energy to frequency, frequency to wavelength and energy to wavelength, and perform calculations using these relationships.
3. describe, in general terms, how absorption spectra are obtained.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electromagnetic radiation
- electromagnetic spectrum
- hertz (Hz)
- infrared spectroscopy
- photon
- quantum

STUDY NOTES

From your studies in general chemistry or physics, you should be familiar with the idea that electromagnetic radiation is a form of energy that possesses wave character and travels through space at a speed of $3.00 \times 10^8 \text{m} \cdot \text{s}^{-1}$. However, such radiation also displays some of the properties of particles, and on occasion it is more convenient to think of electromagnetic radiation as consisting of a stream of particles called *photons*.

In spectroscopy, the frequency of the electromagnetic radiation being used is usually expressed in *hertz* (*Hz*), that is, cycles per second. Note that $1 \text{ Hz} = \text{s}^{-1}$.

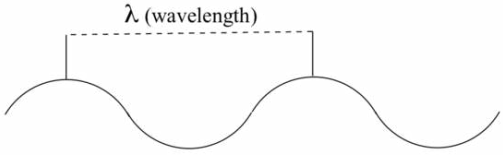
A *quantum* is a small, definite quantity of electromagnetic radiation whose energy is directly proportional to its frequency. (The plural is "quanta.") If you wish, you can read about the properties of electromagnetic radiation and the relationships among wavelength, frequency and energy, or refer to your general chemistry textbook if you still have it.

Note also that in SI units, Planck's constant is $6.626 \times 10^{-34} \text{J} \cdot \text{s}$.

THE ELECTROMAGNETIC SPECTRUM

Electromagnetic radiation, as you may recall from a previous chemistry or physics class, is composed of electrical and magnetic waves which oscillate on perpendicular planes. Visible light is electromagnetic radiation. So are the gamma rays that are emitted by spent nuclear fuel, the x-rays that a doctor uses to visualize your bones, the ultraviolet light that causes a painful sunburn when you forget to apply sun block, the infrared light that the army uses in night-vision goggles, the microwaves that you use to heat up your frozen burritos, and the radio-frequency waves that bring music to anybody who is old-fashioned enough to still listen to FM or AM radio.

Just like ocean waves, electromagnetic waves travel in a defined direction. While the speed of ocean waves can vary, however, the speed of electromagnetic waves – commonly referred to as the speed of light – is essentially a constant, approximately 300 million meters per second. This is true whether we are talking about gamma radiation or visible light. Obviously, there is a big difference between these two types of waves – we are surrounded by the latter for more than half of our time on earth, whereas we hopefully never become exposed to the former to any significant degree. The different properties of the various types of electromagnetic radiation are due to differences in their wavelengths, and the corresponding differences in their energies: *shorter wavelengths correspond to higher energy.*



High-energy radiation (such as gamma- and x-rays) is composed of very short waves – as short as 10^{-16} meter from crest to crest. Longer waves are far less energetic, and thus are less dangerous to living things. Visible light waves are in the range of 400 – 700 nm (nanometers, or 10^{-9} m), while radio waves can be several hundred meters in length.

The notion that electromagnetic radiation contains a quantifiable amount of energy can perhaps be better understood if we talk about light as a stream of *particles*, called **photons**, rather than as a wave. (Recall the concept known as 'wave-particle duality': at the quantum level, wave behavior and particle behavior become indistinguishable, and very small particles have an observable 'wavelength'). If we describe light as a stream of photons, the energy of a particular wavelength can be expressed as:

$$E = \frac{hc}{\lambda} \tag{12.5.1}$$

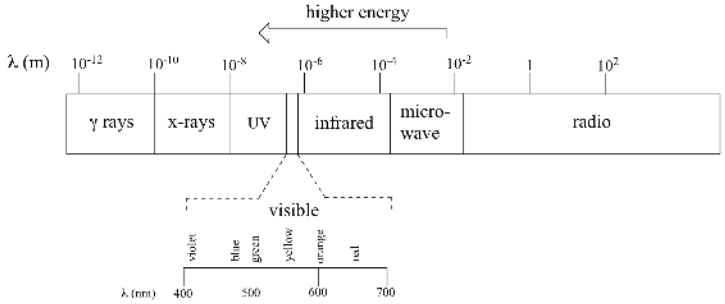
where E is energy in kcal/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^8 m/s (the speed of light), and *h* is 6.626 × 10^{-34} J · s, a number known as Planck's constant.

Because electromagnetic radiation travels at a constant speed, each wavelength corresponds to a given frequency, which is the number of times per second that a crest passes a given point. Longer waves have lower frequencies, and shorter waves have higher frequencies. Frequency is commonly reported in hertz (Hz), meaning 'cycles per second', or 'waves per second'. The standard unit for frequency is s^{-1}.

When talking about electromagnetic waves, we can refer either to wavelength or to frequency - the two values are interconverted using the simple expression:

$$\lambda\nu = c \tag{12.5.2}$$

where **ν** (the Greek letter '*nu*') is frequency in s^{-1}. Visible red light with a wavelength of 700 nm, for example, has a frequency of 2.84 x 10^{-19} J per photon or 171 kJ per mole of photons (remember Avogadro's number = 6.02 × 10^{23} mol^{-1}). The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



Notice in the figure above that visible light takes up just a narrow band of the full spectrum. White light from the sun or a light bulb is a mixture of all of the visible wavelengths. You see the visible region of the electromagnetic spectrum divided into its different wavelengths every time you see a rainbow: violet light has the shortest wavelength, and red light has the longest.

EXAMPLE 12.5.1

Visible light has a wavelength range of about 400-700 nm. What is the corresponding frequency range? What is the corresponding energy range, in kcal/mol of photons?

Answer

Using λν = *c*, we first rearrange to ν = *c*/λ to solve for frequency.

For light with a wavelength of 400 nm, the frequency is 7.50 × 10^{14} Hz:

$$\nu = \frac{3 \times 10^8 \text{ m s}^{-1}}{400 \times 10^{-9} \text{ m}} = 7.50 \times 10^{14} \text{ s}^{-1}$$

In the same way, we calculate that light with a wavelength of 700 nm has a frequency of 4.29 × 10^{14} Hz.

To calculate corresponding energies using *hc*/λ. We find for light at 400 nm:

$$E = \frac{(6.626 \times 10^{-34}\ \text{J s mol}^{-1})(3.00 \times 10^{8}\ \text{m s}^{-1})}{400 \times 10^{-9}\ \text{m}}$$

$$= 4.97 \times 10^{-19}\ \text{J per photon}$$

$$E\ (\text{one mole}) = E \times N$$

$$= (4.97 \times 10^{-19}\ \text{J})(6.02 \times 10^{23}\ \text{mol}^{-1})$$

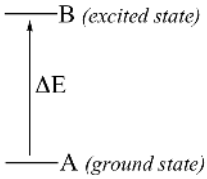
$$= 299\ \text{kJ mol}^{-1}$$

Using the same equation, we find that light at 700 nm corresponds to 171 kJ mol^{-1}.

MOLECULAR SPECTROSCOPY – THE BASIC IDEA

In a spectroscopy experiment, electromagnetic radiation of a specified range of wavelengths is allowed to pass through a sample containing a compound of interest. The sample molecules absorb energy from some of the wavelengths, and as a result jump from a low energy 'ground state' to some higher energy 'excited state'. Other wavelengths are *not* absorbed by the sample molecule, so they pass on through. A detector on the other side of the sample records which wavelengths were absorbed, and to what extent they were absorbed.

Here is the key to molecular spectroscopy: *a given molecule will specifically absorb only those wavelengths which have energies that correspond to the energy difference of the transition that is occurring.* Thus, if the transition involves the molecule jumping from ground state A to excited state B, with an energy difference of **Δ**E, the molecule will specifically absorb radiation with wavelength that corresponds to **Δ**E, while allowing other wavelengths to pass through unabsorbed.



By observing which wavelengths a molecule absorbs, and to what extent it absorbs them, we can gain information about the nature of the energetic transitions that a molecule is able to undergo, and thus information about its structure.

These generalized ideas may all sound quite confusing at this point, but things will become much clearer as we begin to discuss specific examples.

EXERCISES

QUESTIONS

Q12.5.1

Which of the following frequencies/wavelengths are higher energy

A. $\lambda = 2.0 \times 10^{-6}$ m or $\lambda = 3.0 \times 10^{-9}$ m

B. $\upsilon = 3.0 \times 10^{9}$ Hz or $\upsilon = 3.0 \times 10^{-6}$ Hz

Q12.5.2

Calculate the energies for the following;

A. Gamma Ray $\lambda = 4.0 \times 10^{-11}$ m

B. X-Ray $\lambda = 4.0 \times 10^{-9}$ m

C. UV light $\upsilon = 5.0 \times 10^{15}$ Hz

D. Infrared Radiation $\lambda = 3.0 \times 10^{-5}$ m

E. Microwave Radiation $\upsilon = 3.0 \times 10^{11}$ Hz

SOLUTIONS

S12.5.1

A. $\lambda = 3.0 \times 10^{-9}$ m

B. $\upsilon = 3.0 \times 10^{9}$ Hz

S12.5.2

A. 4.965×10^{-15} J

B. 4.965×10^{-17} J

C. 3.31×10^{-18} J

D. 6.62×10^{-21} J

E. 1.99×10^{-22} J

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12.6: INFRARED SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. identify (by wavelength, wavenumber, or both) the region of the electromagnetic spectrum which is used in infrared (IR) spectroscopy.
2. interconvert between wavelength and wavenumber.
3. discuss, in general terms, the effect that the absorption of infrared radiation can have on a molecule.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- infrared spectrum
- wavenumber (reciprocal centimetres)

STUDY NOTES

Notice that the scale at the bottom of the infrared spectrum for 2-hexanone shown is calibrated in wavenumbers (cm^{-1}). A wavenumber is the reciprocal of a wavelength (1/λ); thus, a wavenumber of 1600 cm^{-1} corresponds to a wavelength of

$$\frac{1}{1600\ \text{cm}^{-1}} = 6.25 \times 10^{-4}\text{cm or} 6.25\ \mu\text{m}$$

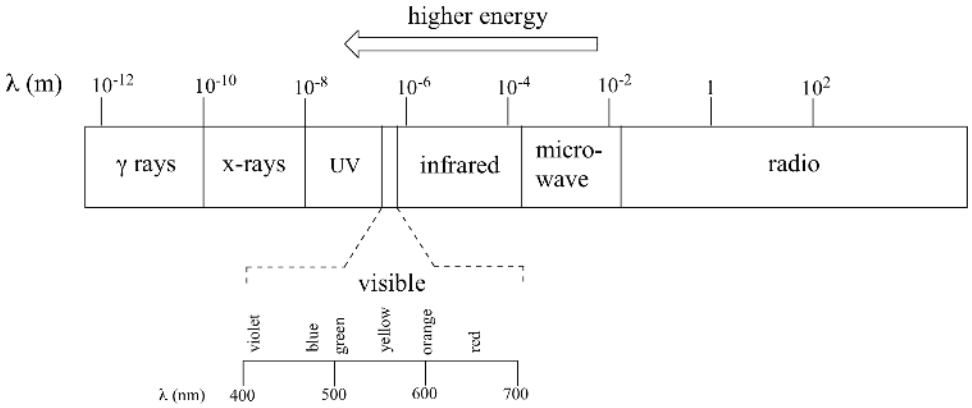
Organic chemists find it more convenient to deal with wavenumbers rather than wavelengths when discussing infrared spectra.

You will obtain infrared spectra for a number of the compounds you will synthesize in the laboratory component of this course.

The inverted peaks observed in the spectra correspond to molecular stretching and bending vibrations that only occur at certain quantized frequencies. When infrared radiation matching these frequencies falls on the molecule, the molecule absorbs energy and becomes excited. Eventually the molecule returns to its original (ground) state, and the energy which was absorbed is released as heat.

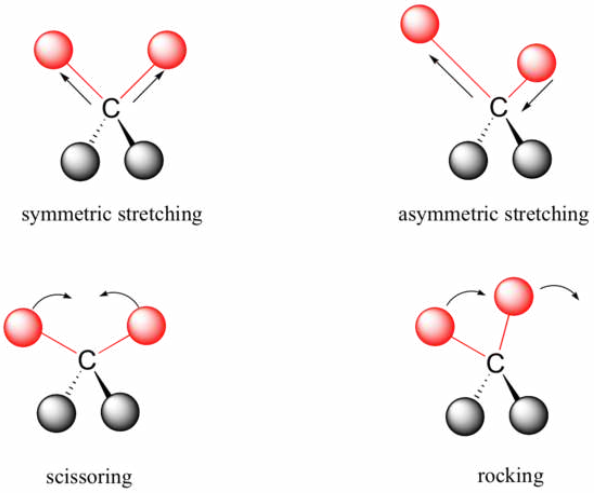
INFRARED SPECTROSCOPY

The full range of electromagnetic radiation wavelengths is referred to as the **electromagnetic spectrum**.



Notice in the figure above that infrared light is lower energy than visible light. The wavelengths of infrared radiation are between 0.8 and 250 μm. The units that are typically used for infrared spectroscopy are wavenumbers (which is cm^{-1}). IR spectroscopy analyzes radiation between 40 to 13,000 cm^{-1}. But what type of excitation is occurring when infrared radiation is absorbed by a molecule?

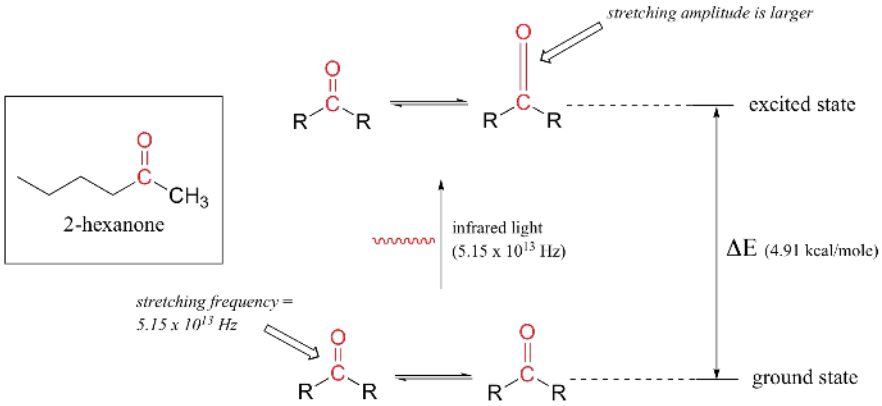
Covalent bonds in organic molecules are not rigid sticks – rather, they behave more like springs. At room temperature, organic molecules are always in motion, as their bonds stretch, bend, and twist. These complex vibrations can be broken down mathematically into individual **vibrational modes**, a few of which are illustrated below.



The energy of molecular vibration is *quantized* rather than continuous, meaning that a molecule can only stretch and bend at certain 'allowed' frequencies. If a molecule is exposed to electromagnetic radiation that matches the frequency of one of its vibrational modes, it will in most cases absorb energy from the radiation and jump to a higher vibrational energy state - what this means is that the *amplitude* of the vibration will increase, but the vibrational *frequency* will remain the same. The difference in energy between the two vibrational states is equal to the energy associated with the wavelength of radiation that was absorbed. It turns out that it is the *infrared* region of the electromagnetic spectrum which contains frequencies corresponding to the vibrational frequencies of organic bonds.

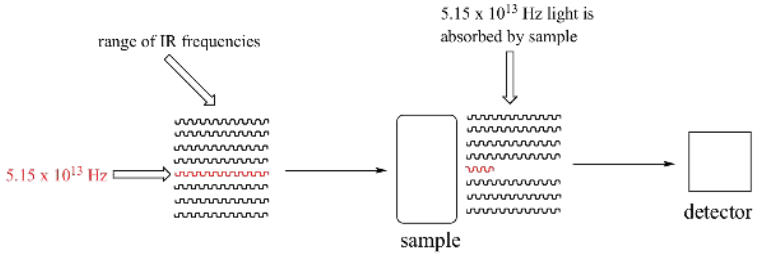
Let's take 2-hexanone as an example. Picture the carbonyl bond of the ketone group as a spring. This spring is constantly bouncing back and forth, stretching and compressing, pushing the carbon and oxygen atoms further apart and then pulling them together. This is the **stretching mode** of the carbonyl bond. In the space of one second, the spring 'bounces' back and forth 5.15 x 10^{13} times - in other words, the ground-state frequency of carbonyl stretching for a the ketone group is about 5.15 x 10^{13} Hz.

If our ketone sample is irradiated with infrared light, the carbonyl bond will specifically absorb light with this same frequency, which by equations 4.1 and 4.2 corresponds to a wavelength of 5.83 x 10^{-6} m and an energy of 4.91 kcal/mol. When the carbonyl bond absorbs this energy, it jumps up to an excited vibrational state.



The value of **ΔE** - the energy difference between the low energy (ground) and high energy (excited) vibrational states - is equal to 4.91 kcal/mol, the same as the energy associated with the absorbed light frequency. The molecule does not remain in its excited vibrational state for very long, but quickly releases energy to the surrounding environment in form of heat, and returns to the ground state.

With an instrument called an infrared spectrophotometer, we can 'see' this vibrational transition. In the spectrophotometer, infrared light with frequencies ranging from about 10^{13} to 10^{14} Hz is passed though our sample of cyclohexane. Most frequencies pass right through the sample and are recorded by a detector on the other side.



Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

The vibrations of a 2-hexanone molecule are not, of course, limited to the simple stretching of the carbonyl bond. The various carbon-carbon bonds also stretch and bend, as do the carbon-hydrogen bonds, and all of these vibrational modes also absorb different frequencies of infrared light.

The power of infrared spectroscopy arises from the observation that *different functional groups have different characteristic absorption frequencies*. The carbonyl bond in a ketone, as we saw with our 2-hexanone example, typically absorbs in the range of 5.11 - 5.18 x 10^{13} Hz, depending on the molecule. The carbon-carbon triple bond of an alkyne, on the other hand, absorbs in the range 6.30 - 6.80 x 10^{13} Hz. The technique is therefore very useful as a means of identifying which functional groups are present in a molecule of interest. If we pass infrared light through an unknown sample and find that it absorbs in the carbonyl frequency range but not in the alkyne range, we can infer that the molecule contains a carbonyl group but not an alkyne.

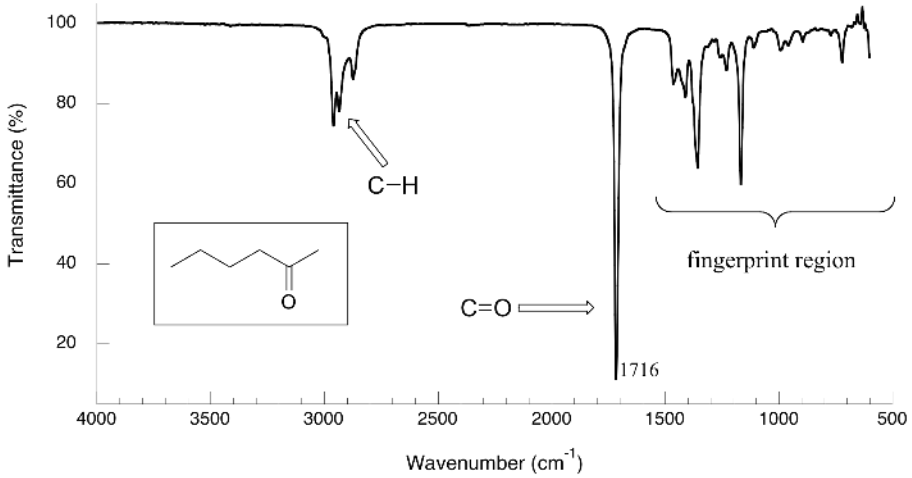
Some bonds absorb infrared light more strongly than others, and some bonds do not absorb at all. *In order for a vibrational mode to absorb infrared light, it must result in a periodic change in the dipole moment of the molecule*. Such vibrations are said to be **infrared active**. In general, the greater the polarity of the bond, the stronger its IR absorption. The carbonyl bond is very polar, and absorbs very strongly. The carbon-carbon triple bond in most alkynes, in contrast, is much less polar, and thus a stretching vibration does not result in a large change in the overall dipole moment of the molecule. Alkyne groups absorb rather weakly compared to carbonyls.

Some kinds of vibrations are **infrared inactive**. The stretching vibrations of completely symmetrical double and triple bonds, for example, do not result in a change in dipole moment, and therefore do not result in any absorption of light (but other bonds and vibrational modes in these molecules *do* absorb IR light).



infrared-inactive double and triple bonds

Now, let's look at some actual output from IR spectroscopy experiments. Below is the IR spectrum for 2-hexanone.



There are a number of things that need to be explained in order for you to understand what it is that we are looking at. On the horizontal axis we see IR wavelengths expressed in terms of a unit called **wavenumber** (cm^{-1}), which tells us how many waves fit into one centimeter. On the vertical axis we see '**% transmittance**', which tells us how strongly light was absorbed at each frequency (100% transmittance means no absorption occurred at that frequency). The solid line traces the values of % transmittance for every wavelength – the 'peaks' (which are actually pointing down) show regions of strong absorption. For some reason, it is typical in IR spectroscopy to report wavenumber values rather than wavelength (in meters) or frequency (in Hz). The 'upside down' vertical axis, with absorbance peaks pointing down rather than up, is also a curious convention in IR spectroscopy. We wouldn't want to make things too easy for you!

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12.7: INTERPRETING INFRARED SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. describe how the so-called “fingerprint region” of an infrared spectrum can assist in the identification of an unknown compound.
2. identify the functional group or groups present in a compound, given a list of the most prominent absorptions in the infrared spectrum and a table of characteristic absorption frequencies.
3. identify the broad regions of the infrared spectrum in which occur absorptions caused by
   a. $\mathbf{N-H}$, $\mathbf{C-H}$, and $\mathbf{O-H}$
   b. You can't use 'macro parameter character #' in math mode and You can't use 'macro parameter character #' in math mode
   c. $\mathbf{C=O}$, $\mathbf{C=N\$, \textit{and}\$C=C}$

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- fingerprint region

STUDY NOTES

When answering assignment questions, you may use this IR table to find the characteristic infrared absorptions of the various functional groups. However, you should be able to indicate in broad terms where certain characteristic absorptions occur. You can achieve this objective by memorizing the following table.

Region of Spectrum (cm^{-1})	Absorption
2500-4000	$\ce{\sf{N−H}}$, $\ce{\sf{O−H}}$, $\ce{\sf{C−H}}$
2000-2500	$\ce{\sf{C#C}}$, $\ce{\sf{C#N}}$
1500-2000	$\ce{\sf{C=O}}$, $\ce{\sf{C=N}}$, $\ce{\sf{C=C}}$
below 1500	Fingerprint region

THE ORIGIN OF GROUP FREQUENCIES

An important observation made by early researchers is that many functional group absorb infrared radiation at about the same wavenumber, regardless of the structure of the rest of the molecule. For example, C-H stretching vibrations usually appear between 3200 and 2800cm^{-1} and carbonyl(C=O) stretching vibrations usually appear between 1800 and 1600cm^{-1}. This makes these bands diagnostic markers for the presence of a functional group in a sample. These types of infrared bands are called group frequencies because they tell us about the presence or absence of specific functional groups in a sample.

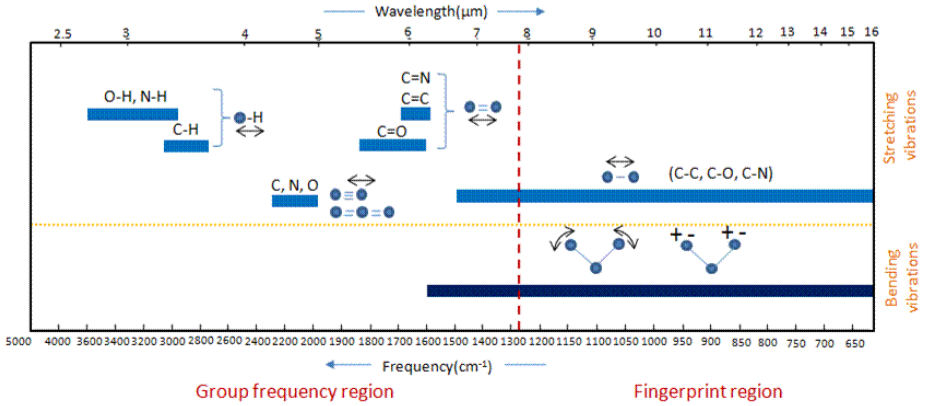
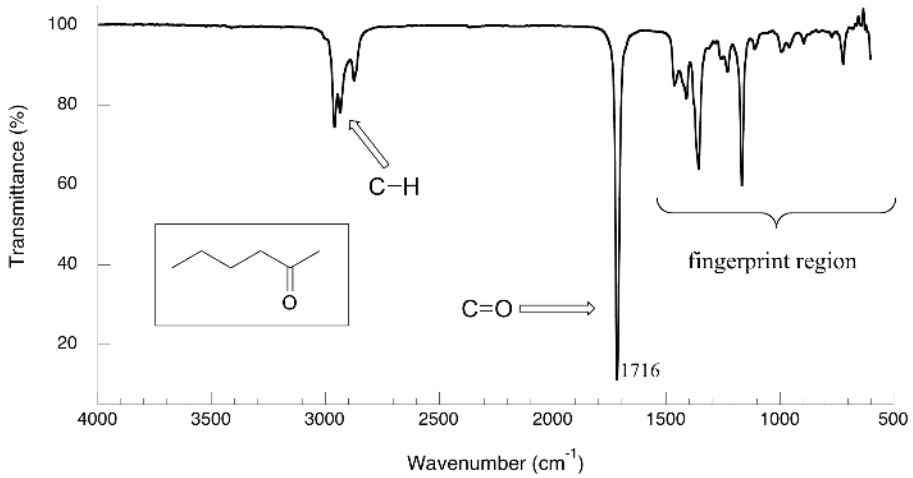


Figure 2. Group frequency and fingerprint regions of the mid-infrared spectrum

The region of the infrared spectrum from 1200 to 700 cm^{-1} is called the fingerprint region. This region is notable for the large number of infrared bands that are found there. Many different vibrations, including C-O, C-C and C-N single bond stretches, C-H bending vibrations, and some bands due to benzene rings are found in this region. The fingerprint region is often the most complex and confusing region to interpret, and is usually the last section of a spectrum to be interpreted. However, the utility of the fingerprint region is that the many bands there provide a fingerprint for a molecule.

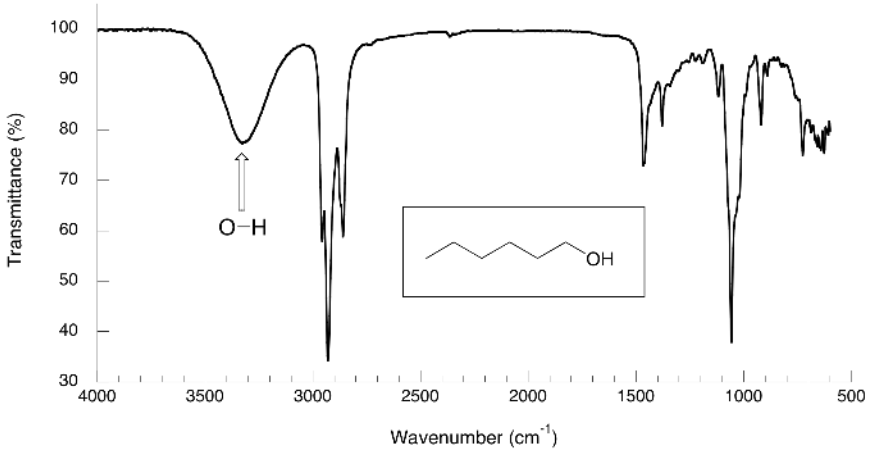


The key absorption peak in this spectrum is that from the carbonyl double bond, at 1716 cm^{-1} (corresponding to a wavelength of 5.86 mm, a frequency of 5.15 x 10^{13} Hz, and a **ΔE** value of 4.91 kcal/mol). Notice how strong this peak is, relative to the others on the spectrum: *a strong peak in the 1650-1750 cm^{-1} region is a dead giveaway for the presence of a carbonyl group*. Within that range, carboxylic acids, esters, ketones, and aldehydes tend to absorb in the shorter wavelength end (1700-1750 cm-1), while conjugated unsaturated ketones and amides tend to absorb on the longer wavelength end (1650-1700 cm^{-1}).

The jagged peak at approximately 2900-3000 cm^{-1} is characteristic of tetrahedral carbon-hydrogen bonds. This peak is not terribly useful, as just about every organic molecule that you will have occasion to analyze has these bonds. Nevertheless, it can serve as a familiar reference point to orient yourself in a spectrum.

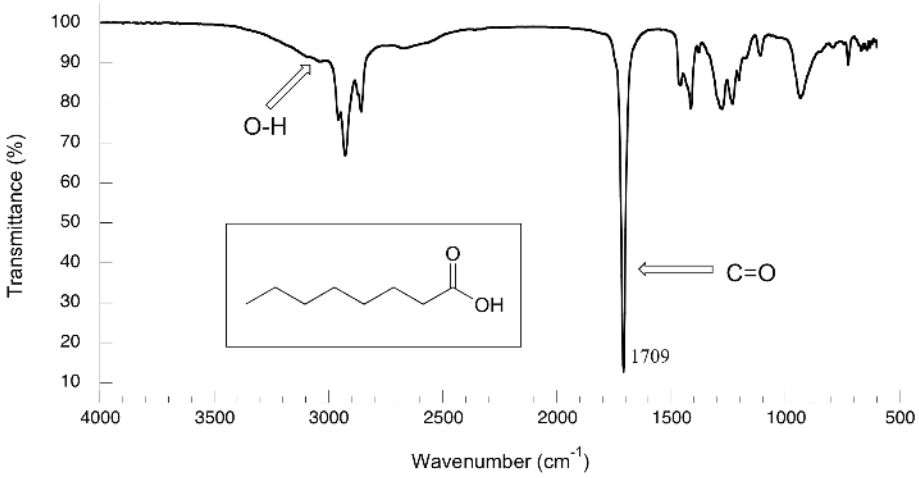
You will notice that there are many additional peaks in this spectrum in the longer-wavelength 400 -1400 cm^{-1} region. This part of the spectrum is called the **fingerprint region**. While it is usually very difficult to pick out any specific functional group identifications from this region, it does, nevertheless, contain valuable information. The reason for this is suggested by the name: just like a human fingerprint, the pattern of absorbance peaks in the fingerprint region is unique to every molecule, meaning that the data from an unknown sample can be compared to the IR spectra of known standards in order to make a positive identification. In the mid-1990's, for example, several paintings were identified as forgeries because scientists were able to identify the IR footprint region of red and yellow pigment compounds that would not have been available to the artist who supposedly created the painting (for more details see Chemical and Engineering News, Sept 10, 2007, p. 28).

Now, let’s take a look at the IR spectrum for 1-hexanol.



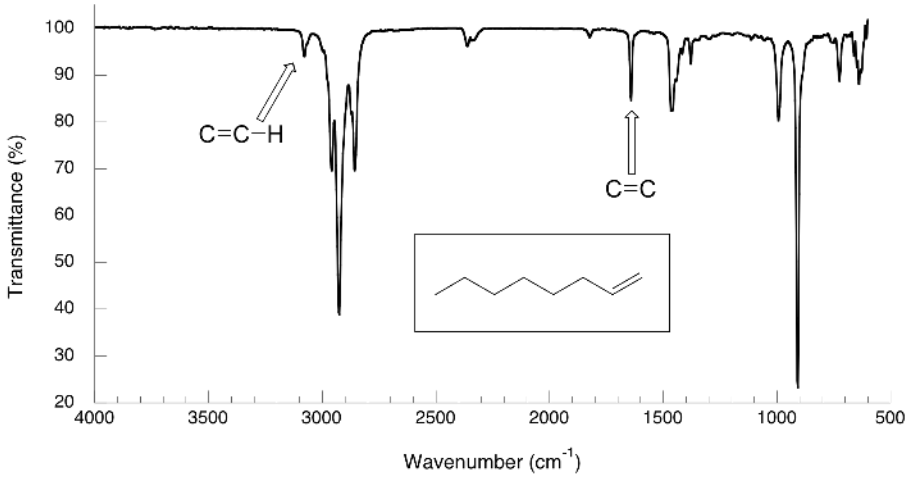
As you can see, the carbonyl peak is gone, and in its place is a very broad 'mountain' centered at about 3400 cm^{-1}. This signal is characteristic of the O-H stretching mode of alcohols, and is a dead giveaway for the presence of an alcohol group. The breadth of this signal is a consequence of hydrogen bonding between molecules.

In the spectrum of octanoic acid we see, as expected, the characteristic carbonyl peak, this time at 1709 cm^{-1}.



We also see a low, broad absorbance band that looks like an alcohol, except that it is displaced slightly to the right (long-wavelength) side of the spectrum, causing it to overlap to some degree with the C-H region. This is the characteristic carboxylic acid O-H single bond stretching absorbance.

The spectrum for 1-octene shows two peaks that are characteristic of alkenes: the one at 1642 cm^{-1} is due to stretching of the carbon-carbon double bond, and the one at 3079 cm-1 is due to stretching of the s bond between the alkene carbons and their attached hydrogens.



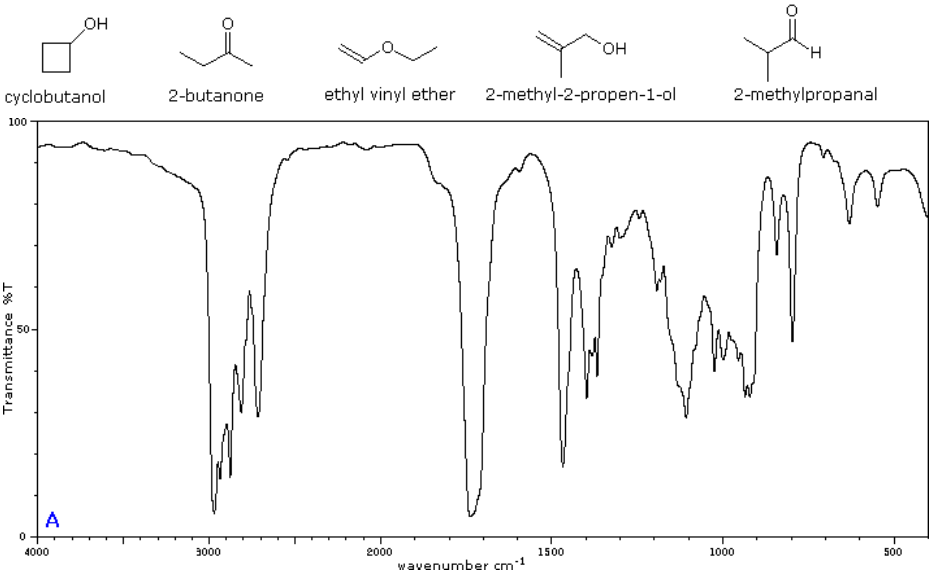
Alkynes have characteristic IR absorbance peaks in the range of 2100-2250 cm^{-1} due to stretching of the carbon-carbon triple bond, and terminal alkenes can be identified by their absorbance at about 3300 cm-1, due to stretching of the bond between the sp-hybridized carbon and the terminal hydrogen.

It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily recognized functional groups, which are summarized in this table.

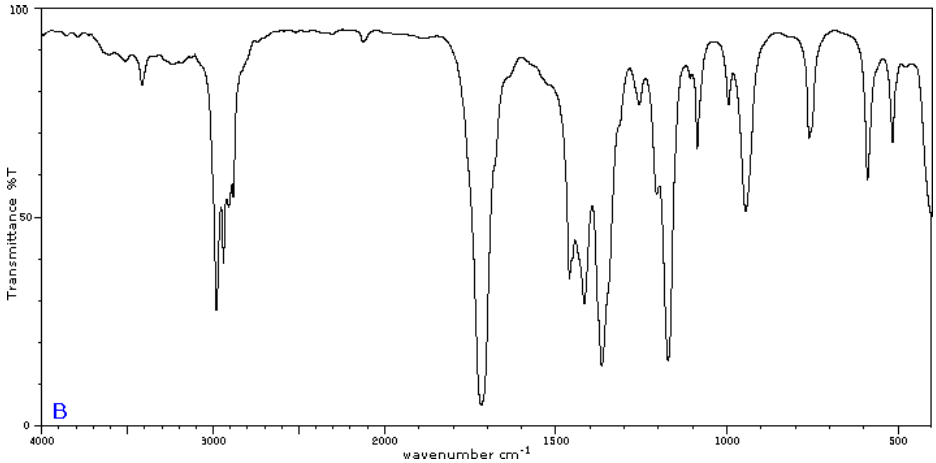
As you can imagine, obtaining an IR spectrum for a compound will not allow us to figure out the complete structure of even a simple molecule, unless we happen to have a reference spectrum for comparison. In conjunction with other analytical methods, however, IR spectroscopy can prove to be a very valuable tool, given the information it provides about the presence or absence of key functional groups. IR can also be a quick and convenient way for a chemist to check to see if a reaction has proceeded as planned. If we were to run a reaction in which we wished to convert cyclohexanone to cyclohexanol, for example, a quick comparison of the IR spectra of starting compound and product would tell us if we had successfully converted the ketone group to an alcohol.

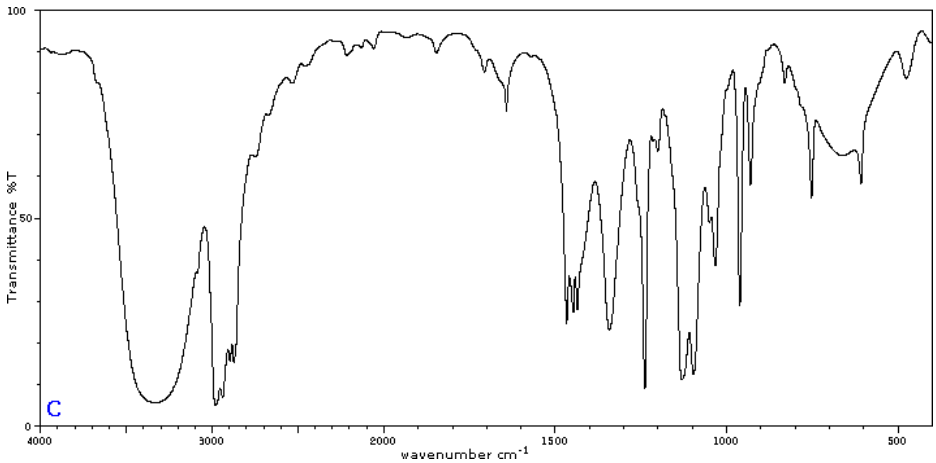
MORE EXAMPLES OF IR SPECTRA

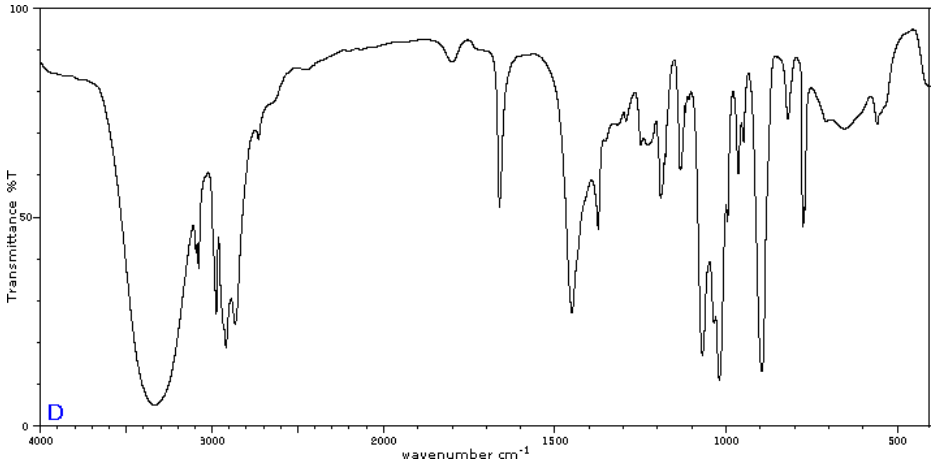
To illustrate the usefulness of infrared absorption spectra, examples for five C_4H_8O isomers are presented below their corresponding structural formulas. Try to associate each spectrum with one of the isomers in the row above it.

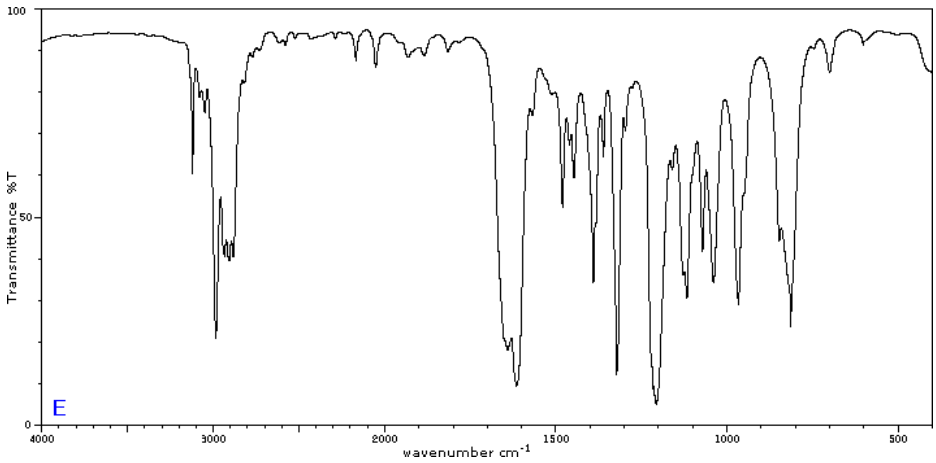


https://chem.libretexts.org/@go/page/31528


100
50
0
Transmittance %T
B
4000
3000
2000
1500
1000
500
wavenumber cm-1


100
50
0
Transmittance %T
C
4000
3000
2000
1500
1000
500
wavenumber cm-1





EXERCISES

QUESTIONS

Q12.7.1

What functional groups give the following signals in an IR spectrum?

A) 1700 cm^{-1}

B) 1550 cm^{-1}

C) 1700 cm^{-1} and 2510-3000 cm^{-1}

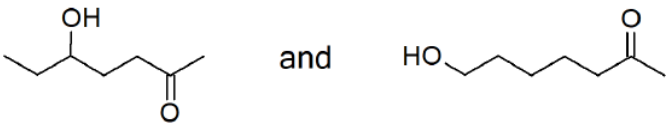
Q12.7.2

How can you distinguish the following pairs of compounds through IR analysis?

A) CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)

B) Cyclopentane and 1-pentene.

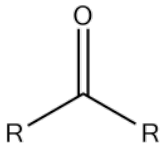
C)

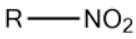


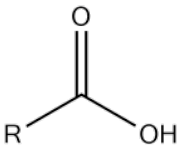
(i) (ii)

SOLUTIONS

S12.7.1

A)  Carbonyl

B)  Nitro

C)  Carboxylic Acid

S12.7.2

A) A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.

B) 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene

C) Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

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12.8: INFRARED SPECTRA OF SOME COMMON FUNCTIONAL GROUPS

OBJECTIVE

After completing this section, you should be able to use an infrared spectrum to determine the presence of functional groups, such as alcohols, amines and carbonyl groups, in an unknown compound, given a list of infrared absorption frequencies.

STUDY NOTES

In Chapter 12.7 you should have learned, in broad terms, where a few key absorptions occur. Otherwise, to find the characteristic infrared absorptions of the various functional groups, refer to this IR table.

SPECTRAL INTERPRETATION BY APPLICATION OF GROUP FREQUENCIES

One of the most common application of infrared spectroscopy is to the identification of organic compounds. The major classes of organic molecules are shown in this category and also linked on the bottom page for the number of collections of spectral information regarding organic molecules.

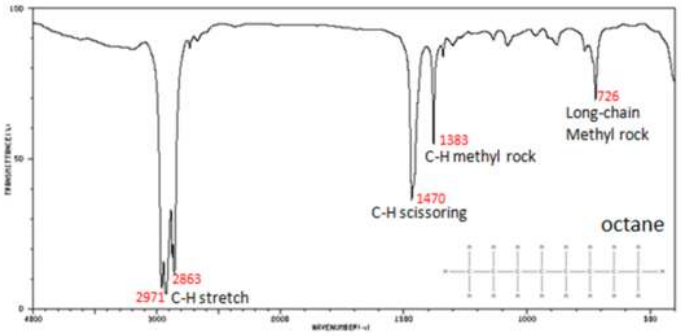
HYDROCARBONS

Hydrocarbons compounds contain only C-H and C-C bonds, but there is plenty of information to be obtained from the infrared spectra arising from C-H stretching and C-H bending.

In alkanes, which have very few bands, each band in the spectrum can be assigned:

- C–H stretch from 3000–2850 cm^{-1}
- C–H bend or scissoring from 1470-1450 cm^{-1}
- C–H rock, methyl from 1370-1350 cm^{-1}
- C–H rock, methyl, seen only in long chain alkanes, from 725-720 cm^{-1}

Figure **12.8.1** shows the IR spectrum of octane. Since most organic compounds have these features, these C-H vibrations are usually not noted when interpreting a routine IR spectrum. Note that the change in dipole moment with respect to distance for the C-H stretching is greater than that for others shown, which is why the C-H stretch band is the more intense.



12.8.1: Infrared Spectrum of Octane

In alkenes compounds, each band in the spectrum can be assigned:

- C=C stretch from 1680-1640 cm^{-1}
- =C–H stretch from 3100-3000 cm^{-1}
- =C–H bend from 1000-650 cm^{-1}

Figure **12.8.2** shows the IR spectrum of 1-octene. As alkanes compounds, these bands are not specific and are generally not noted because they are present in almost all organic molecules.

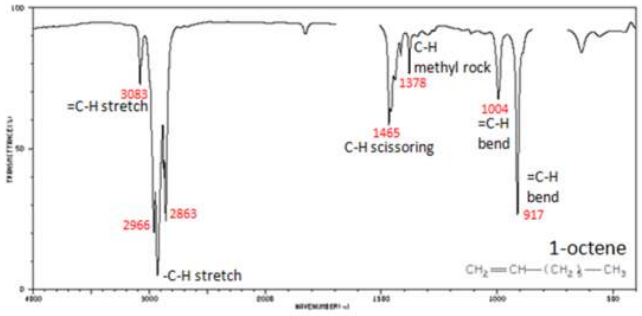


Figure **12.8.2**: Infrared Spectrum of 1-Octene

In alkynes, each band in the spectrum can be assigned:

- –C≡C– stretch from 2260-2100 cm^{-1}
- –C≡C–H: C–H stretch from 3330-3270 cm^{-1}
- –C≡C–H: C–H bend from 700-610 cm^{-1}

The spectrum of 1-hexyne, a terminal alkyne, is shown below.

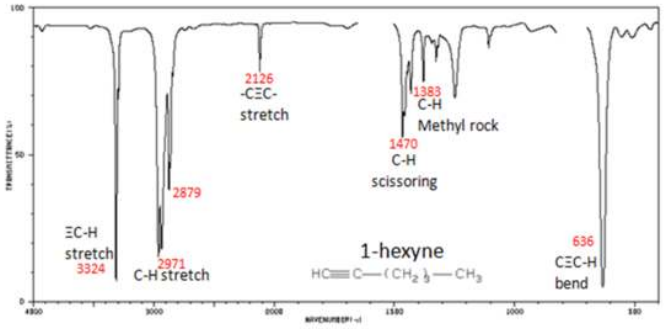


Figure **12.8.3**: Infrared Spectrum of 1-Hexyne

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}. Figure **12.8.4** shows the spectrum of toluene.

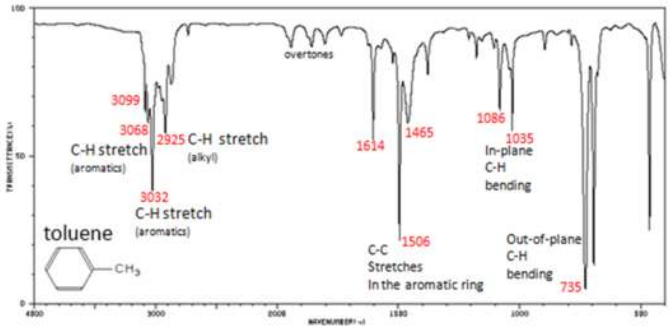


Figure **12.8.4**: Infrared Spectrum of Toluene

FUNCTIONAL GROUPS CONTAINING THE C-O BOND

Alcohols have IR absorptions associated with both the O-H and the C-O stretching vibrations.

- O–H stretch, hydrogen bonded 3500-3200 cm^{-1}
- C–O stretch 1260-1050 cm^{-1} (s)

Figure 12.8.5 shows the spectrum of ethanol. Note the very broad, strong band of the O–H stretch.

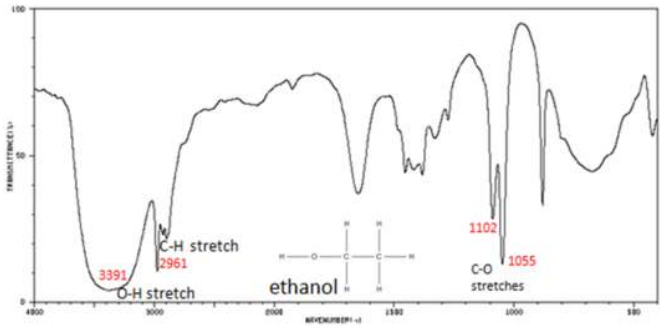


Figure 12.8.5: Infrared Spectrum of Ethanol

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

- C=O stretch - aliphatic ketones 1715 cm^{-1}
- α, β -unsaturated ketones 1685-1666 cm^{-1}

Figure 12.8.6 shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

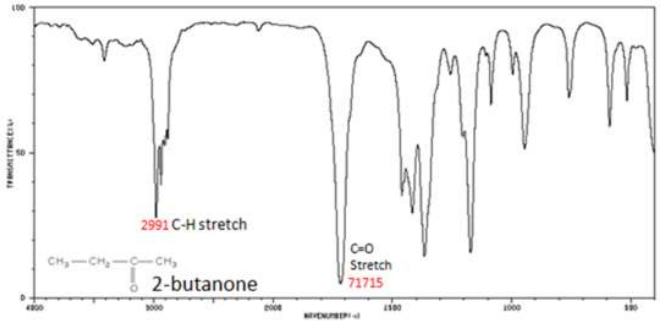


Figure 12.8.6: Infrared Spectrum of 2-Butanone

If a compound is suspected to be an aldehyde, a peak always appears around 2720 cm^{-1} which often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

- H–C=O stretch 2830-2695 cm^{-1}
- C=O stretch:
  - aliphatic aldehydes 1740-1720 cm^{-1}
  - α, β -unsaturated aldehydes 1710-1685 cm^{-1}

Figure 12.8.7 shows the spectrum of butyraldehyde.

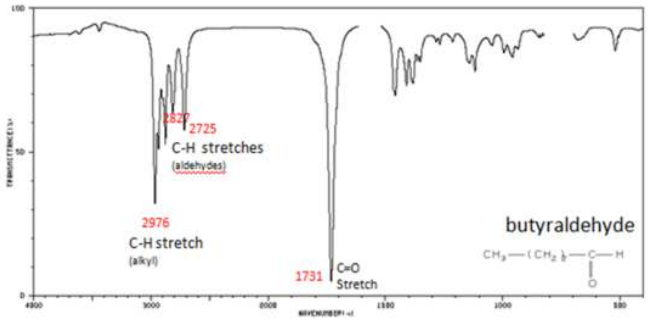


Figure 12.8.7: Infrared Spectrum of Butyraldehyde

The carbonyl stretch C=O of esters appears:

- C=O stretch
  - aliphatic from 1750-1735 cm^{-1}

- α, β -unsaturated from 1730-1715 cm^{-1}

- C–O stretch from 1300-1000 cm^{-1}

Figure **12.8.8**: shows the spectrum of ethyl benzoate.

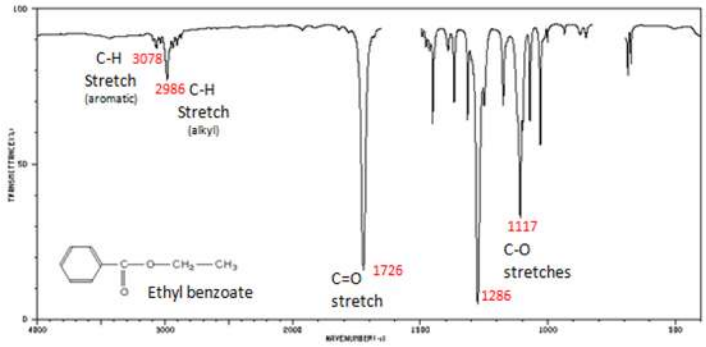


Figure **12.8.8**: Infrared Spectrum of Ethyl benzoate

The carbonyl stretch C=O of a carboxylic acid appears as an intense band from 1760-1690 cm^{-1}. The exact position of this broad band depends on whether the carboxylic acid is saturated or unsaturated, dimerized, or has internal hydrogen bonding.

- O–H stretch from 3300-2500 cm^{-1}
- C=O stretch from 1760-1690 cm^{-1}
- C–O stretch from 1320-1210 cm^{-1}
- O–H bend from 1440-1395 and 950-910 cm^{-1}

Figure **12.8.9**: shows the spectrum of hexanoic acid.

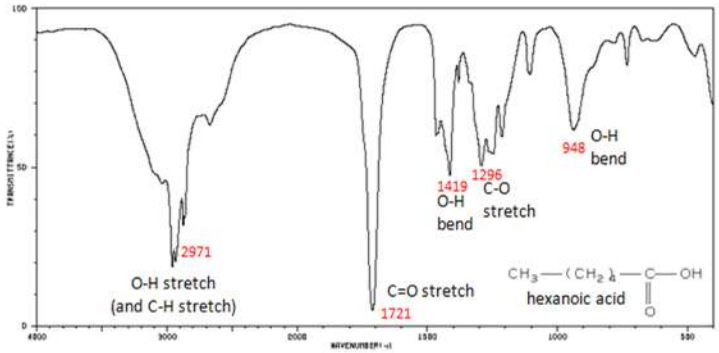


Figure **12.8.9**: Infrared Spectrum of Hexanoic acid

ORGANIC NITROGEN COMPOUNDS

- N–O asymmetric stretch from 1550-1475 cm^{-1}
- N–O symmetric stretch from 1360-1290 cm^{-1}

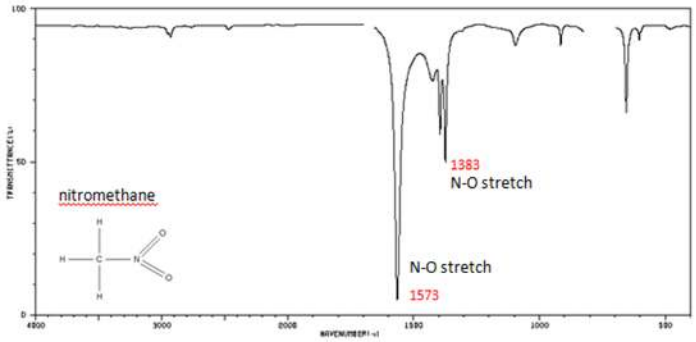


Figure **12.8.10**: Infrared Spectrum of Nitomethane

ORGANIC COMPOUNDS CONTAINING HALOGENS

Alkyl halides are compounds that have a C–X bond, where X is a halogen: bromine, chlorine, fluorene, or iodine.

- C–H wag (-CH_2X) from 1300-1150 cm^{-1}
- C–X stretches (general) from 850-515 cm^{-1}
  - C–Cl stretch 850-550 cm^{-1}
  - C–Br stretch 690-515 cm^{-1}

The spectrum of 1-chloro-2-methylpropane are shown below.

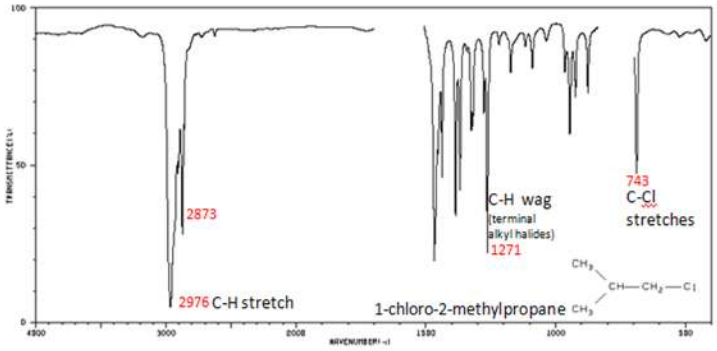


Figure **12.8.11**: Infrared Spectrum of 1-chloro-2-methylpropane

For more Infrared spectra Spectral database of organic molecules is introduced to use free database. Also, the infrared spectroscopy correlation table is linked on bottom of page to find other assigned IR peaks.

? EXERCISE 12.8.1

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

Answer

$C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

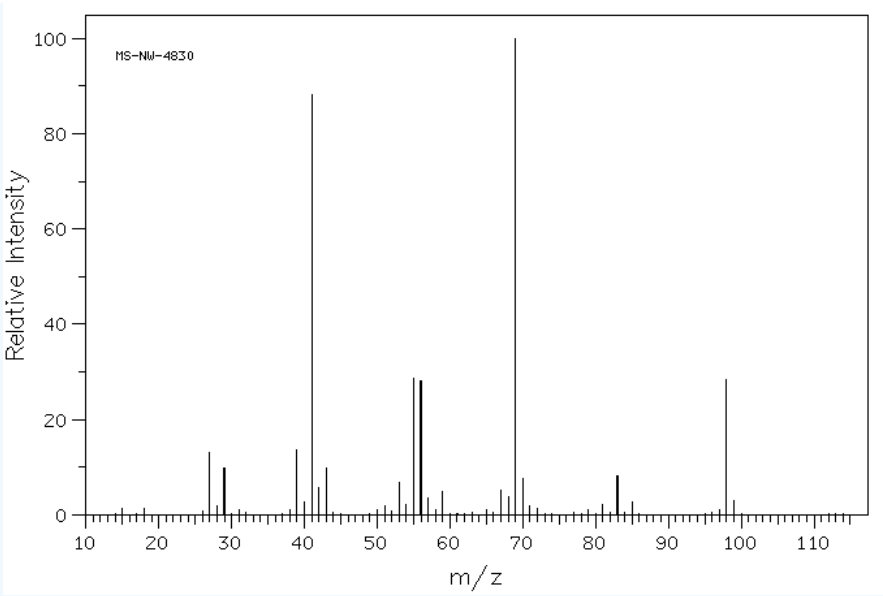
O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

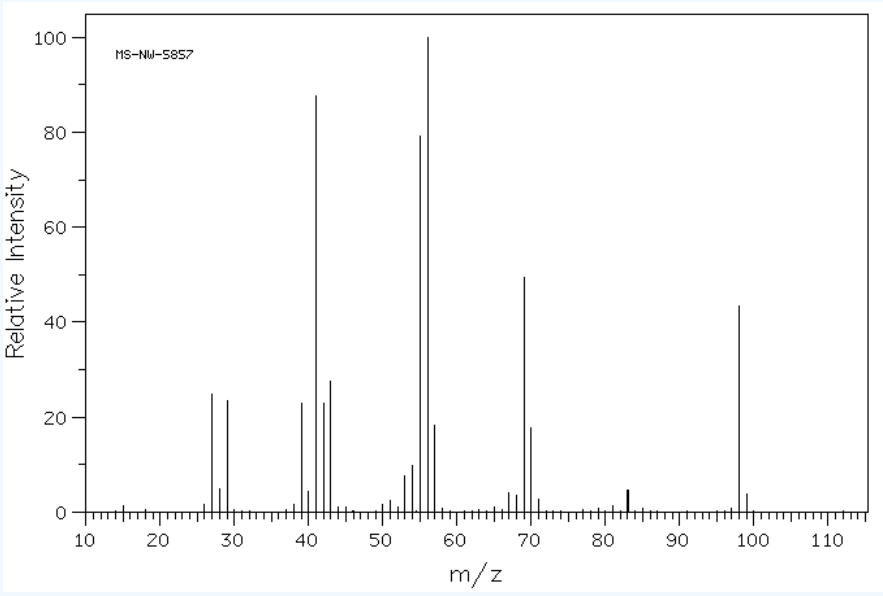
? EXERCISE 12.8.2

The following are the spectra for 2-methyl-2-hexene and 2-heptene, which spectra belongs to the correct molecule. Explain.

A:



B:



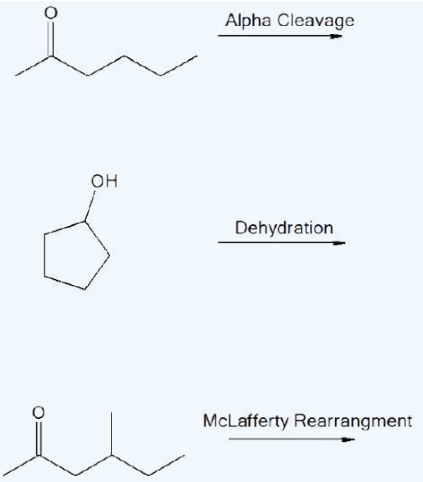
Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

Answer

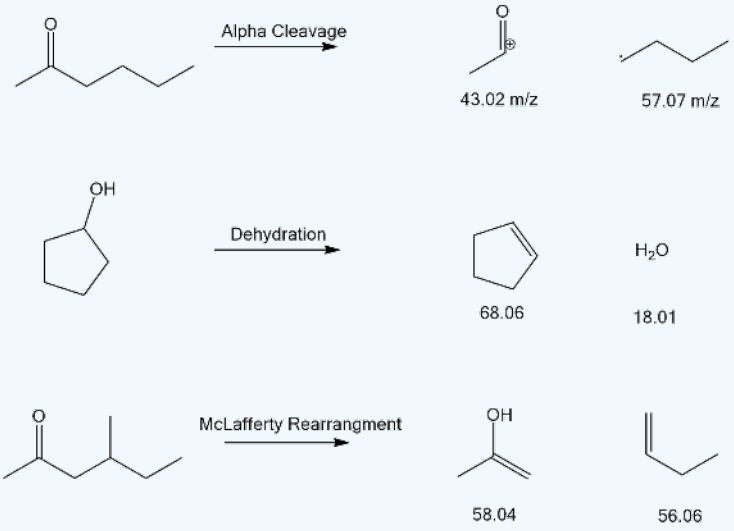
The (A) spectrum is 2-methyl-2-hexene and the (B) spectrum is 2-heptene. Looking at (A) the peak at 68 *m/z* is the fractioned molecule with just the tri-substituted alkene present. While (B) has a strong peak around the 56 *m/z*, which in this case is the di-substituted alkene left behind from the linear heptene.

? EXERCISE 12.8.3

What are the masses of all the components in the following fragmentations?



Answer



EXERCISE 12.8.4

Which of the following frequencies/wavelengths are higher energy

a. $\lambda = 2.0 \times 10^{-6}$ m or $\lambda = 3.0 \times 10^{-9}$ m
b. $\upsilon = 3.0 \times 10^{9}$ Hz or $\upsilon = 3.0 \times 10^{-6}$ Hz

Answer

a. $\lambda = 3.0 \times 10^{-9}$ m
b. $\upsilon = 3.0 \times 10^{9}$ Hz

EXERCISE 12.8.5

Calculate the energies for the following;

a. Gamma Ray $\lambda = 4.0 \times 10^{-11}$ m
b. X-Ray $\lambda = 4.0 \times 10^{-9}$ m
c. UV light $\upsilon = 5.0 \times 10^{15}$ Hz
d. Infrared Radiation $\lambda = 3.0 \times 10^{-5}$ m
e. Microwave Radiation $\upsilon = 3.0 \times 10^{11}$ Hz

Answer

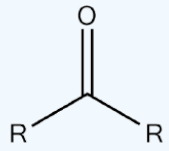
a. 4.965×10^{-15} J
b. 4.965×10^{-17} J
c. 3.31×10^{-18} J
d. 6.62×10^{-21} J
e. 1.99×10^{-22} J

EXERCISE 12.8.6

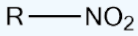
What functional groups give the following signals in an IR spectrum?

a. 1700 cm^{-1}
b. 1550 cm^{-1}
c. 1700 cm^{-1} and 2510-3000 cm^{-1}

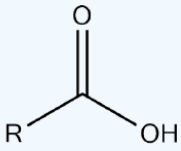
Answer

A) 

Carbonyl

B) 

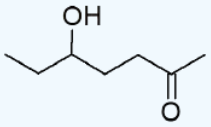
Nitro

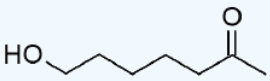
C) 

Carboxylic Acid

EXERCISE 12.8.7

How can you distinguish the following pairs of compounds through IR analysis?

a. CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)
b. Cyclopentane and 1-pentene.
c. 

(i) and 

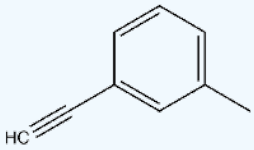
(ii)

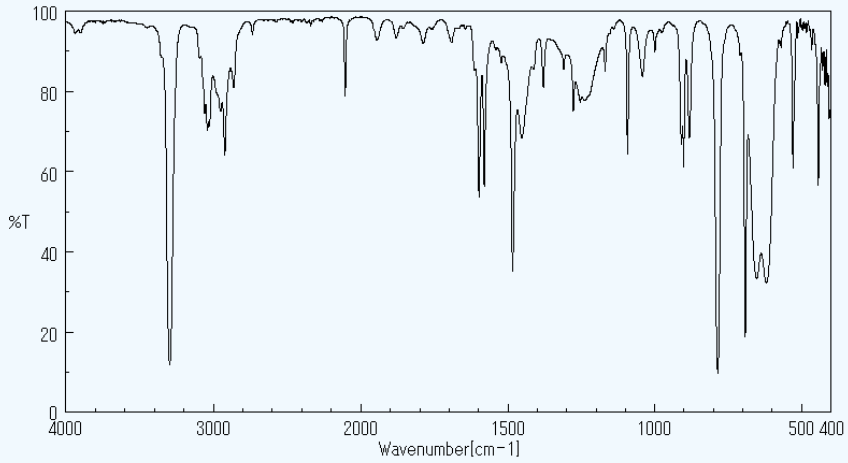
Answer

a. A OH peak will be present around 3300 cm^{-1} for methanol and will be absent in the ether.
b. 1-pentene will have a alkene peak around 1650 cm^{-1} for the C=C and there will be another peak around 3100 cm^{-1} for the sp^2 C-H group on the alkene
c. Cannot distinguish these two isomers. They both have the same functional groups and therefore would have the same peaks on an IR spectra.

EXERCISE 12.8.8

The following spectra is for the accompanying compound. What are the peaks that you can I identify in the spectrum?





Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

Answer

Frequency (cm^{-1}) Functional Groups

3200 C≡C-H

2900-3000 C-C-H, C=C-H

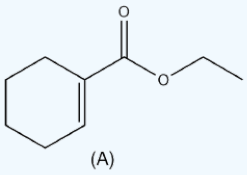
2100 C≡C

1610 C=C

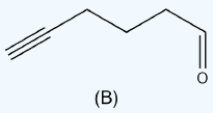
(There is also an aromatic undertone region between 2000-1600 which describes the substitution on the phenyl ring.)

EXERCISE 12.8.9

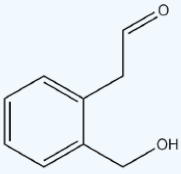
What absorptions would the following compounds have in an IR spectra?



(A)



(B)



(C)

Answer

A)

Frequency (cm-1) Functional Group

2900-3000 C-C-H, C=C-H

1710 C=O

1610 C=C

1100 C-O

B)

Frequency (cm-1) Functional Group

3200 C≡C-H

2900-3000 C-C-H, C=C-H

2100 C≡C

1710 C=O

C)

Frequency (cm-1) Functional Group

3300 (broad) O-H

2900-3000 C-C-H, C=C-H

2000-1800 Aromatic Overtones

1710 C=O

1610 C=C

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12.S: STRUCTURE DETERMINATION - MASS SPECTROMETRY AND INFRARED SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

12.1 Introduction

- Spectroscopy describes several techniques used by chemists to understand chemical structures and bonds.

12.2 Mass Spectrometry of Small Molecules - Magnetic Sector Instruments

- Mass spectrometers consist of an **ion source**, **mass analyzer** and dectector.
- There are several common **ion sources** including **electron ionization** and **chemical ionization**.
- Upon ionization, a molecular ion is formed (the molecule after losing a single electron) which will break into smaller pieces (fragments).
- Fragments that are charged will appear in the mass spectrum and are helpful in identifying the parent molecule.
- The most abundant ion in a mass spectrum is called the **base peak**.
- The ion with the same mass as the parent molecule is called the **molecular ion**.
- Isotopes of carbon and hydrogen lead to common M+1 peaks.
- The x-axis of a mass spectrum is **m/z -** the mass to charge ratio, which in practice equals the mass of the ion.

12.3 Interpreting Mass Spectra

- Uncharged particles do not appear in mass spectra.
- The y-axis of a mass spectrum is the relative abundance, with the base peak set at 100 as the most abundant ion.
- Abundance of ions is related to their stability.

12.4 Mass Spectrometry of Some Common Functional Groups

12.5 Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

12.6 Spectroscopy and the Electromagnetic Spectrum

- Electromagnetic radiation is composed of waves where shorter wavelengths correspond to higher energy radiation.
- Electromagnetic radiation can also be thought of as a stream of particles called **photons**.
- The electromagnetic spectrum is made up of many types of radiation including infrared, ultraviolet, and visible lights as well as x-rays, gamma rays, microwaves, and radio waves.
- Molecular spectroscopy works by exposing a chemical sample to electromagnetic radiation. It will only absorb radiation with energy that corresponds to some excited state, while all other energies will pass through unabsorbed.

12.7 Infrared Spectroscopy

- When infrared radiation is absorbed, molecules will move to a higher vibrational energy state.
- Examples of molecular vibrations include bending and stretching of bonds. These vibrations can be symmetric or asymmetric.
- In general, more polar bonds have stronger IR absorption.
- IR spectra typically use wavenumbers (cm^{-1}) as units for the x-axis.
- The y-axis for IR spectra is usually % transmittance, with 100% at the top of the spectrum and absorbances looking like valleys (or downward peaks).

12.8 Interpreting Infrared Spectra

- Functional groups have standard regions within the IR spectrum where they absorb.
- The general regions include hydrogen bonding (O-H and N-H), carbon-hydrogen bonds, triple bonds, carbonyls, alkenes, and fingerprint region.

12.9 Infrared Spectra of Some Common Functional Groups

SKILLS TO MASTER

- Skill 12.1 Determine specific atoms from mass spectra based on molecular ion and M+2 peaks (N, Cl, Br).
- Skill 12.2 Interpret mass spectra fragments - recognizing common fragments.
- Skill 12.3 Interpret infrared spectra to determine functional groups that are present or absent.

MEMORIZATION TASKS (MT)

- MT 12.1 Memorize common mass spectra fragments.
- MT 12.2 Memorize common functional group regions in infrared spectroscopy.

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CHAPTER OVERVIEW

13: STRUCTURE DETERMINATION - NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

LEARNING OBJECTIVES

- fulfillall of the detailed objectives listed under each individual section.
- solve road-map problems which may require the interpretation of ^{1}H NMR spectra in addition to other spectral data.
- define, and use in context, the key terms introduced.

In Chapter 12, you learned how an organic chemist could use two spectroscopic techniques, mass spectroscopy and infrared spectroscopy, to assist in determining the structure of an unknown compound. This chapter introduces a third technique, nuclear magnetic resonance (NMR). The two most common forms of NMR spectroscopy, ^{1}H NMR and ^{13}C NMR, will be discussed, the former in much more detail than the latter. Nuclear magnetic resonance spectroscopy is a very powerful tool, particularly when used in combination with other spectroscopic techniques.

13.0: Nuclear Magnetic Resonance Spectroscopy
13.1: The Nature of NMR Absorptions
13.2: The Chemical Shift
13.3: Chemical Shifts in ^{1}H NMR Spectroscopy
13.4: Integration of ^{1}H NMR Absorptions - Proton Counting
13.5: Spin-Spin Splitting in ^{1}H NMR Spectra
13.6: ^{1}H NMR Spectroscopy and Proton Equivalence
13.7: More Complex Spin-Spin Splitting Patterns
13.8: Uses of ^{1}H NMR Spectroscopy
13.9: ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR
13.10: Characteristics of ^{13}C NMR Spectroscopy
13.11: DEPT ^{13}C NMR Spectroscopy
13.12: Uses of ^{13}C NMR Spectroscopy
13.S: Structure Determination - Nuclear Magnetic Resonance Spectroscopy (Summary)

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13.0: NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. discuss the principles of NMR spectroscopy.
2. identify the two magnetic nuclei that are most important to an organic chemist.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- resonance

STUDY NOTES

Notice that the word “resonance” has a different meaning when we are discussing nuclear magnetic resonance spectroscopy than it does when discussing molecular structures.

INTRODUCTION

Some types of atomic nuclei act as though they spin on their axis similar to the Earth. Since they are positively charged they generate an electromagnetic field just as the Earth does. So, in effect, they will act as tiny bar magnetics. Not all nuclei act this way, but fortunately both ^{1}H and ^{13}C do have nuclear spins and will respond to this technique.



NMR Spectrometer

In the absence of an external magnetic field the direction of the spin of the nuclei will be randomly oriented (see figure below left). However, when a sample of these nuclei is place in an external magnetic field, the nuclear spins will adopt specific orientations much as a compass needle responses to the Earth’s magnetic field and aligns with it. Two possible orientations are possible, with the external field (*i.e.* parallel to and in the same direction as the external field) or against the field (*i.e.* antiparallel to the external field) - see Figure **13.0.1**.

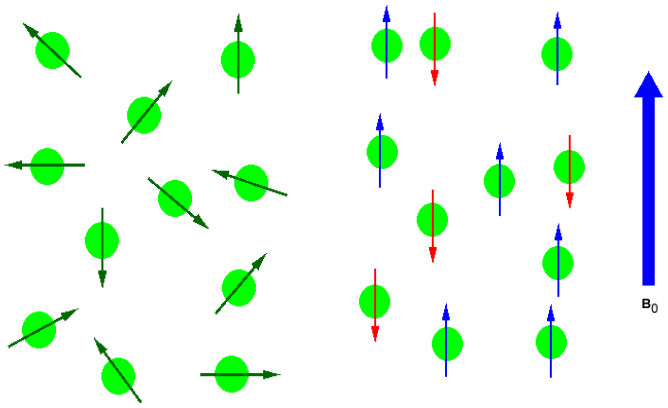
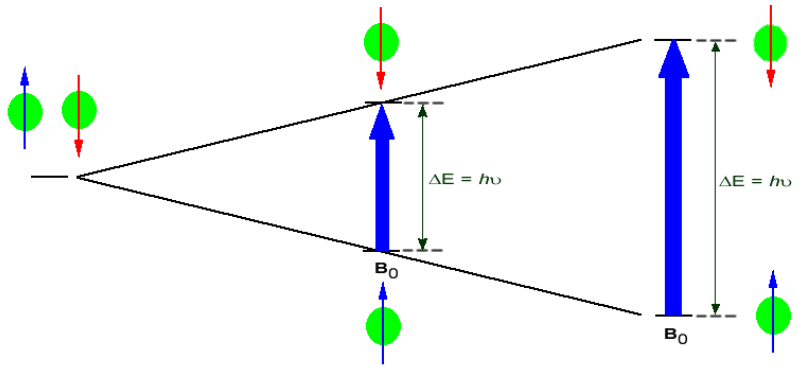


Figure **13.0.1**: (Left) Random nuclear spin without an external magnetic field. (Right) Ordered nuclear spin in an external magnetic field

If the ordered nuclei are now subjected to EM radiation of the proper frequency the nuclei aligned with the field will absorb energy and "spin-flip" to align themselves against the field, a higher energy state. When this spin-flip occurs the nuclei are said to be in "resonance" with the field, hence the name for the technique, **N**uclear **M**agentic **R**esonance or NMR.

The amount of energy, and hence the exact frequency of EM radiation required for resonance to occur is dependent on both the strength of the magnetic field applied and the type of the nuclei being studied. As the strength of the magnetic field increases the energy difference between the two spin states increases and a higher frequency (more energy) EM radiation needs to be applied to achieve a spin-flip (see image below).



Superconducting magnets can be used to produce very strong magnetic field, on the order of 21 tesla (T). Lower field strengths can also be used, in the range of 4 - 7 T. At these levels the energy required to bring the nuclei into resonance is in the MHz range and corresponds to radio wavelength energies, *i.e.* at a field strength of 4.7 T 200 MHz bring ^{1}H nuclei into resonance and 50 MHz bring ^{13}C into resonance. This is considerably less energy then is required for IR spectroscopy, ~10^{-4} kJ/mol versus ~5 - ~50 kJ/mol.

^{1}H and ^{13}C are not unique in their ability to undergo NMR. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P ...) or nuclei with an odd number of neutrons (*i.e.* ^{13}C) show the magnetic properties required for NMR. Only nuclei with even number of both protons and neutrons (^{12}C and ^{16}O) do not have the required magnetic properties.

? EXERCISE 13.0.1

If in a field strength of 4.7 T, H^1 requires 200 MHz of energy to maintain resonance. If atom X requires 150 MHz, calculate the amount of energy required to spin flip atom X's nucleus. Is this amount greater than the energy required for hydrogen?

Answer

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(150\ \text{MHz})$

$E = 9.93 \times 10^{-26}\ \text{J}$

The energy is equal to 9.93×10^{-26} J. This value is smaller than the energy required for hydrogen (1.324×10^{-25} J).

EXERCISE 13.0.1

Calculate the energy required to spin flip at 400 MHz. Does changing the frequency to 500 MHz decrease or increase the energy required? What about 300 MHz.

Answer

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(400 \text{ MHz})$

$E = 2.648 \times 10^{-25}$ J

The energy would increase if the frequency would increase to 500 MHz, and decrease if the frequency would decrease to 300 MHz.

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13.1: THE NATURE OF NMR ABSORPTIONS

OBJECTIVES

After completing this section, you should be able to

1. explain, in general terms, the origin of shielding effects in NMR spectroscopy.
2. explain the number of peaks occurring in the ^{1}H or ^{13}C NMR spectrum of a simple compound, such as methyl acetate.
3. describe, and sketch a diagram of, a simple NMR spectrometer.
4. explain the difference in time scales of NMR and infrared spectroscopy.
5. predict the number of peaks expected in the ^{1}H or ^{13}C NMR spectrum of a given compound.

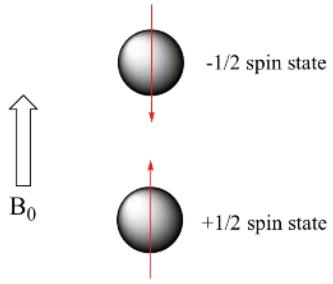
STUDY NOTES

Before you go on, make sure that you understand that each signal in the ^{1}H NMR spectrum shown for methyl acetate is due to a different proton environment. The three protons on the same methyl group are equivalent and appear in the spectrum as one signal. However, the two methyl groups are in two different environments (one is more deshielded) and so we see two signals in the whole spectrum (aside from the TMS reference peak).

Methyl acetate has a very simple ^{1}H NMR spectrum, because there is no proton-proton coupling, and therefore no splitting of the signals. In later sections, we discuss splitting patterns in ^{1}H NMR spectra and how they help a chemist determine the structure of organic compounds.

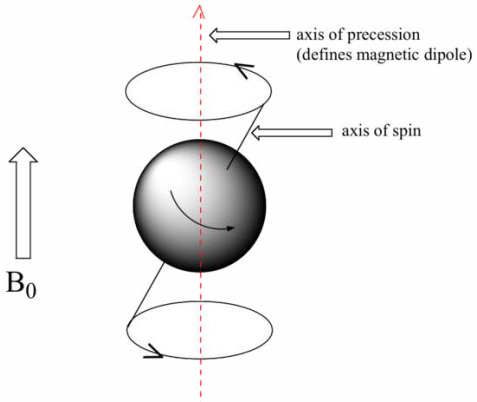
NUCLEAR PRECESSION, SPIN STATES, AND THE RESONANCE CONDITION

When a sample of an organic compound is sitting in a flask on a laboratory benchtop, the magnetic moments of its hydrogen atoms are randomly oriented. When the same sample is placed within the field of a very strong magnet in an NMR instrument (this field is referred to by NMR spectroscopists as the **applied field**, abbreviated $\mathbf{B_0}$) each hydrogen will assume one of two possible **spin states**. In what is referred to as the +½ spin state, the hydrogen's magnetic moment is aligned *with* the direction of B_0, while in the -½ spin state it is aligned *opposed to* the direction of B_0.



Because the +½ spin state is slightly lower in energy, in a large population of organic molecules slightly more than half of the hydrogen atoms will occupy this state, while slightly less than half will occupy the –½ state. *The difference in energy between the two spin states increases with increasing strength of B_0.*This last statement is in italics because it is one of the key ideas in NMR spectroscopy, as we shall soon see.

At this point, we need to look a little more closely at how a proton spins in an applied magnetic field. You may recall playing with spinning tops as a child. When a top slows down a little and the spin axis is no longer completely vertical, it begins to exhibit **precessional motion**, as the spin axis rotates slowly around the vertical. In the same way, hydrogen atoms spinning in an applied magnetic field also exhibit precessional motion about a vertical axis. It is this axis (which is either parallel or antiparallel to B_0) that defines the proton's magnetic moment. In the figure below, the proton is in the +1/2 spin state.

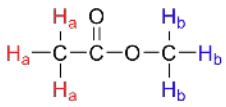


The **frequency of precession** (also called the **Larmour frequency,** abbreviated $\boldsymbol{\omega_L}$) is simply the number of times per second that the proton precesses in a complete circle. A proton`s precessional frequency increases with the strength of B_0.

If a proton that is precessing in an applied magnetic field is exposed to electromagnetic radiation of a frequency ν that matches its precessional frequency ω_L, we have a condition called **resonance**. *In the resonance condition, a proton in the lower-energy +½ spin state (aligned with B_0) will transition (flip) to the higher energy –½ spin state (opposed to B_0). In doing so, it will absorb radiation at this resonance frequency* $\boldsymbol{\nu} = \boldsymbol{\omega_L}$. This frequency, as you might have already guessed, corresponds to the energy difference between the proton's two spin states. With the strong magnetic fields generated by the superconducting magnets used in modern NMR instruments, the resonance frequency for protons falls within the radio-wave range, anywhere from 100 MHz to 800 MHz depending on the strength of the magnet.

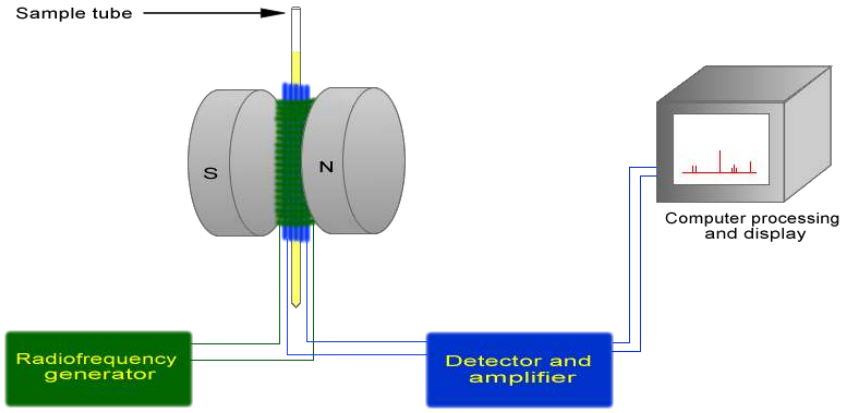
THE BASICS OF AN NMR EXPERIMENT

So far, you may have the impression that all ^{1}H nuclei in a molecule would absorb the same frequency. However, this would be of little use to organic chemists if that were the case. It turns out that not all ^{1}H nuclei absorb the same frequency and this is the same for all other NMR active nuclei. It turns out that chemically nonequivalent protons (or other nuclei) have different resonance frequencies in the same applied magnetic field. Nonequivalent protons are in different chemical environments. This allows NMR spectroscopy to provide us with useful information about the structure of an organic molecule. A full explanation of how a modern NMR instrument functions is beyond the scope of this text, but here is what happens. First, a sample compound (we'll use methyl acetate) is placed inside a very strong applied magnetic field (B_0). There are two types of protons in methyl acetate. H_a are bonded to a C that is then bonded to a carbonyl, whereas H_b are bonded to a carbon that is then bonded to an oxygen atom. This difference in bonding leads to different types of environments for H_a and H_b. All the H_a protons are the same since they all have the same type of bonding and will be in the same chemical environment and the same is true for H_b.



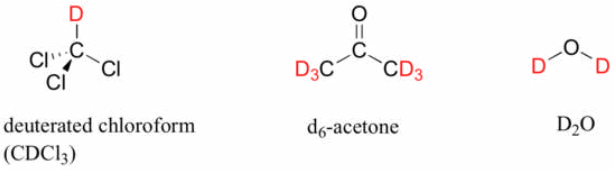
methyl acetate

The basic arrangement of an NMR spectrometer is displayed below. A sample (in a small glass tube, where the methyl acetate is in solution) is placed between the poles of a strong magnet. A radio frequency generator pulses the sample and excites the nuclei causing a spin-flip. The spin flip is detected by the detector and the signal sent to a computer where it is processed.



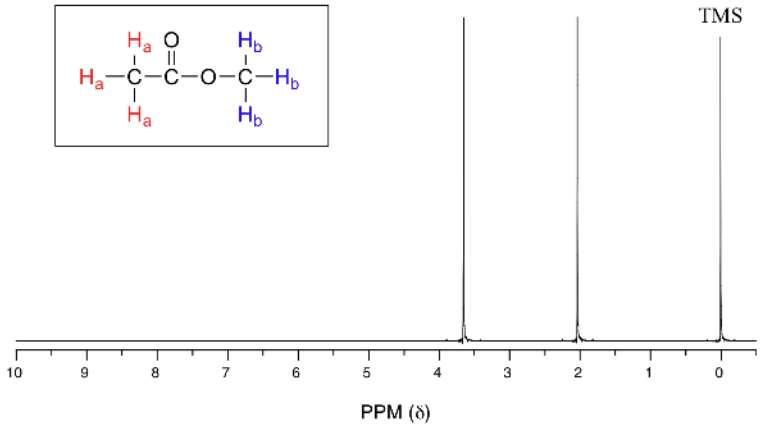
In the magnet, all of the protons begin to precess: the H_a protons at precessional frequency ω_a, the H_b protons at ω_b. At first, the magnetic moments of (slightly more than) half of the protons are aligned with B_0, and half (slightly less than half) are aligned against B_0. Then, the sample is hit with electromagnetic radiation in the radio frequency range. The two specific frequencies which match ω_a and ω_b (i.e. the resonance frequencies) cause those H_a and H_b protons which are aligned *with* B_0 to 'flip' so that they are now aligned *against* B_0. In doing so, the protons absorb radiation at the two resonance frequencies. The NMR instrument records which frequencies were absorbed, as well as the intensity of each absorbance.

In most cases, a sample being analyzed by NMR is in solution. If we used a common laboratory solvent (diethyl ether, acetone, dichloromethane, ethanol, water, etc.) to dissolve our NMR sample, however, we run into a problem – there many more solvent protons in solution than there are sample protons, therefore the signals from the sample protons will be overwhelmed. To get around this problem, we use special NMR solvents in which all protons have been replaced by deuterium. Recall that deuterium is NMR-active, but its resonance frequency is very different from that of protons, and thus it is `invisible` in ^{1}H-NMR. Some common NMR solvents are shown below. There are multiple deuterated solvents since molecules have different solubilities, so one molecule may dissolve in deuterated chloroform while others may not.

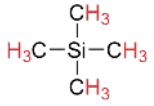


THE CHEMICAL SHIFT

Let's look at an actual ^{1}H-NMR plot for methyl acetate. Just as in IR and UV-vis spectroscopy, the vertical axis corresponds to intensity of absorbance, the horizontal axis to frequency (typically the vertical axis is not shown in an NMR spectrum).



We see three absorbance signals: two of these correspond to H_a and H_b, while the peak at the far right of the spectrum corresponds to the 12 chemically equivalent protons in tetramethylsilane (TMS), a standard reference compound that was added to our sample.



tetramethylsilane (TMS)

You may be wondering about a few things at this point - why is TMS necessary, and what is the meaning of the `ppm (δ)` label on the horizontal axis? Shouldn't the frequency units be in Hz? Keep in mind that NMR instruments of many different applied field strengths are used in organic chemistry laboratories, and that the proton's resonance frequency range depends on the strength of the applied field. The spectrum above was generated on an instrument with an applied field of approximately 7.1 Tesla, at which strength protons resonate in the neighborhood of 300 million Hz (chemists refer to this as a 300 MHz instrument). If our colleague in another lab takes the NMR spectrum of the same molecule using an instrument with a 2.4 Tesla magnet, the protons will resonate at around 100 million Hz (so we'd call this a 100 MHz instrument). It would be inconvenient and confusing to always have to convert NMR data according to the field strength of the instrument used. Therefore, chemists report resonance frequencies not as absolute values in Hz, but rather as values *relative to a common standard*, generally the signal generated by the protons in TMS. This is where the ppm – parts per million – term comes in. Regardless of the magnetic field strength of the instrument being used, the resonance frequency of the 12 equivalent protons in TMS is defined as a zero point. The resonance frequencies of protons in the sample molecule are then reported in terms of how much higher they are, in ppm, relative to the TMS signal (almost all protons in organic molecules have a higher resonance frequency than those in TMS, for reasons we shall explore quite soon).

The two proton groups in our methyl acetate sample are recorded as resonating at frequencies 2.05 and 3.67 ppm higher than TMS. One-millionth (1.0 ppm) of 300 MHz is 300 Hz. Thus 2.05 ppm, on this instrument, corresponds to 615 Hz, and 3.67 ppm corresponds to 1101 Hz. If the TMS protons observed by our 7.1 Tesla instrument resonate at exactly 300,000,000 Hz, this means that the protons in our ethyl acetate samples are resonating at 300,000,615 and 300,001,101 Hz, respectively. Likewise, if the TMS protons in our colleague's 2.4 Tesla instrument resonate at exactly 100 MHz, the methyl acetate protons in her sample resonate at 100,000,205 and 100,000,367 Hz (on the 100 MHz instrument, 1.0 ppm corresponds to 100 Hz). The absolute frequency values in each case are not very useful – they will vary according to the instrument used – but the *difference* in resonance frequency from the TMS standard, expressed in parts per million, should be the same regardless of the instrument.

Expressed this way, the resonance frequency for a given proton in a molecule is called its **chemical shift**. A frequently used symbolic designation for chemical shift in ppm is the lower-case Greek letter *delta* (δ). Most protons in organic compounds have chemical shift values between 0 and 12 ppm from TMS, although values below zero and above 12 are occasionally observed. By convention, the left-hand side of an NMR spectrum (higher chemical shift) is called **downfield**, and the right-hand direction is called **upfield**.

In our methyl acetate example we included for illustrative purposes a small amount of TMS standard directly in the sample, as was the common procedure for determining the zero point with older NMR instruments. That practice is generally no longer necessary, as modern NMR instruments are designed to use the deuterium signal from the solvent as a standard reference point, then to extrapolate the 0 ppm baseline that corresponds to the TMS proton signal (in an applied field of 7.1 Tesla, the deuterium atom in $CDCl_3$ resonates at 32 MHz, compared to 300 MHz for the protons in TMS). In the remaining NMR spectra that we will see in this text we will not see an actual TMS signal, but we can always assume that the 0 ppm point corresponds to where the TMS protons *would* resonate if they were present.

✔ EXAMPLE

A proton has a chemical shift (relative to TMS) of 4.56 ppm.

a. a) What is its chemical shift, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?
b. b) What is its resonance frequency, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?

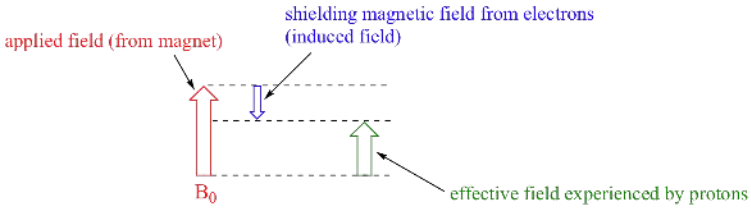
(Assume that in these instruments, the TMS protons resonate at exactly 300 or 200 MHz, respectively)

Solution

DIAMAGNETIC SHIELDING AND DESHIELDING

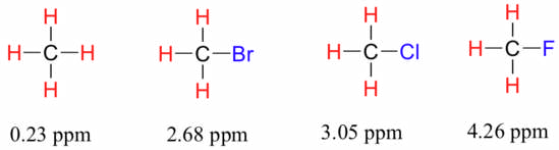
We come now to the question of *why* nonequivalent protons have different chemical shifts. The chemical shift of a given proton is determined primarily by its immediate electronic environment. Consider the methane molecule (CH_4), in which the protons have a chemical shift of 0.23 ppm. The valence electrons around the methyl carbon, when subjected to B_0, are induced to circulate and thus generate their own very small magnetic field that *opposes* B_0. This **induced field**, to a small but significant degree, *shields* the nearby protons from

experiencing the full force of B_0, an effect known as **local diamagnetic shielding**. The methane protons therefore do not experience the full force of B_0 - what they experience is called B_{eff}, or the **effective field**, which is slightly *weaker* than B_0.

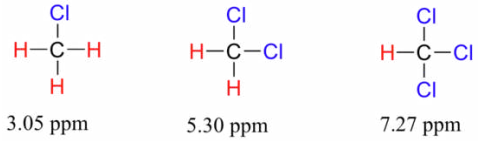


Therefore, their resonance frequency is slightly lower than what it would be if they did not have electrons nearby to shield them.

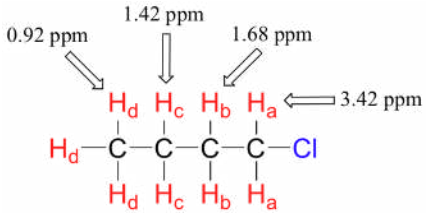
Now consider methyl fluoride, CH_3F, in which the protons have a chemical shift of 4.26 ppm, significantly higher than that of methane. This is caused by something called the **deshielding effect**. Because fluorine is more electronegative than carbon, it pulls valence electrons away from the carbon, effectively *decreasing* the electron density around each of the protons. For the protons, lower electron density means less diamagnetic shielding, which in turn means a greater overall exposure to B_0, a stronger B_{eff}, and a higher resonance frequency. Put another way, the fluorine, by pulling electron density away from the protons, is *deshielding* them, leaving them more exposed to B_0. As the electronegativity of the substituent increases, so does the extent of deshielding, and so does the chemical shift. This is evident when we look at the chemical shifts of methane and three halomethane compounds (remember that electronegativity increases as we move up a column in the periodic table).



To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton. The chemical shift of trichloromethane is, as expected, higher than that of dichloromethane, which is in turn higher than that of chloromethane.



The deshielding effect of an electronegative substituent diminishes sharply with increasing distance:



The presence of an electronegative oxygen, nitrogen, sulfur, or sp^2-hybridized carbon also tends to shift the NMR signals of nearby protons slightly downfield:

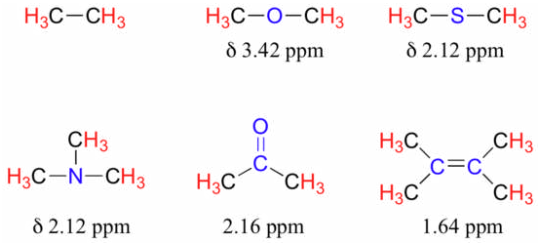
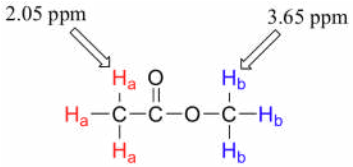
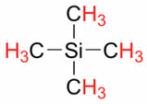


Table 2 lists typical chemical shift values for protons in different chemical environments.

Armed with this information, we can finally assign the two peaks in the the ^{1}H-NMR spectrum of methyl acetate that we saw a few pages back. The signal at 3.65 ppm corresponds to the methyl ester protons (H_b), which are deshielded by the adjacent oxygen atom. The upfield signal at 2.05 ppm corresponds to the acetate protons (H_a), which is deshielded - but to a lesser extent - by the adjacent carbonyl group.



Finally, a note on the use of TMS as a standard in NMR spectroscopy: one of the main reasons why the TMS proton signal was chosen as a zero-point is that the TMS protons are highly shielded: silicon is slightly *less* electronegative than carbon, and therefore *donates* some additional shielding electron density. Very few organic molecules contain protons with chemical shifts that are negative relative to TMS.



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13.2: THE CHEMICAL SHIFT

OBJECTIVES

After completing this section, you should be able to

1. describe the delta scale used in NMR spectroscopy.
2. perform calculations based on the relationship between the delta value (in ppm), the observed chemical shift (in Hz), and the operating frequency of an NMR spectrometer (in Hz).

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chemical shift
- delta scale
- upfield/downfield

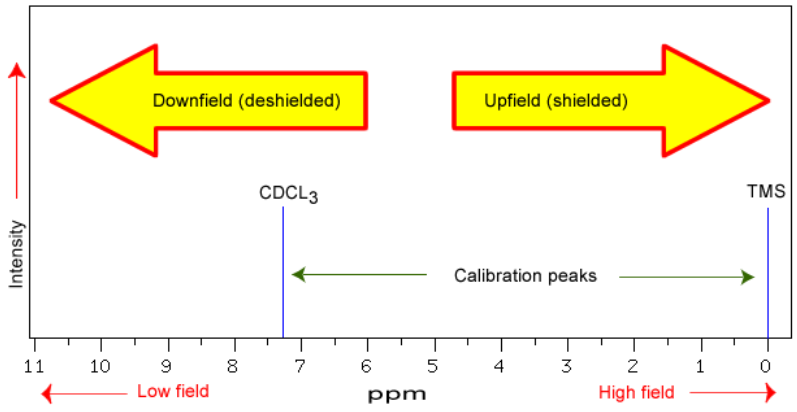
STUDY NOTES

Although the calculations described in this section will help you understand the principles of NMR, it is the actual delta values, not the calculations, which are of greatest importance to the beginning organic chemist. Thus, we shall try to focus on the interpretation of NMR spectra, not the mathematical aspects of the technique.

In Section 13.9 we discuss ^{1}H NMR chemical shifts in more detail. Although you will eventually be expected to associate the approximate region of a ^{1}H NMR spectrum with a particular type of proton, you are expected to use a general table of ^{1}H NMR chemical shifts such as the one shown in Section 13.9.

CHEMICAL SHIFTS

The NMR spectra is displayed as a plot of the applied radio frequency versus the absorption. The applied frequency decreases from left to right, thus the left side of the plot is the low field, downfield or deshielded side and the right side of the plot is the high field, upfield or shielded side (see the figure below). The concept of shielding will be explained shortly.



The position on the plot at which the nuclei absorbs is called the **chemical shift**. Since this has an arbitrary value a standard reference point must be used. The two most common standards are TMS (tetramethylsilane, $(Si(CH_3)_4)$ which has been assigned a chemical shift of zero, and $CDCl_3$ (deuterochloroform) which has a chemical shift of 7.26 for ^{1}H NMR and 77 for ^{13}C NMR. The scale is commonly expressed as parts per million (ppm) which is independent of the spectrometer frequency. The scale is the **delta (δ) scale**.

$$\delta = \frac{\text{frequency of signal} - \text{frequency of standard}}{\text{spectrometerfrequency}} \times 10^{6}$$

The range at which most NMR absorptions occur is quite narrow. Almost all ^{1}H absorptions occur downfield within 10 ppm of TMS. For ^{13}C NMR almost all absorptions occurs within 220 ppm downfield of the C atom in TMS.

SHIELDING IN NMR

Structural features of the molecule will have an effect on the exact magnitude of the magnetic field experienced by a particular nucleus. This means that H atoms which have different chemical environments will have different chemical shifts. This is what makes NMR so useful for structure determination in organic chemistry. There are three main features that will affect the shielding of the nucleus, electronegativity, magnetic anisotropy of π systems and hydrogen bonding.

ELECTRONEGATIVITY

The electrons that surround the nucleus are in motion so they created their own electromagnetic field. This field opposes the the applied magnetic field and so reduces the field experienced by the nucleus. Thus the electrons are said to **shield** the nucleus. Since the magnetic field experienced at the nucleus defines the energy difference between spin states it also defines what the chemical shift will be for that nucleus. Electron with-drawing groups can decrease the electron density at the nucleus, deshielding the nucleus and result in a larger chemical shift. Compare the data in the table below.

Compound, CH_3X	CH_3F	CH_3OH	CH_3Cl	CH_3Br	CH_3I	CH_4	$(CH_3)_4Si$
Electronegativity of X	4.0	3.5	3.1	2.8	2.5	2.1	1.8
Chemical shift δ (ppm)	4.26	3.4	3.05	2.68	2.16	0.23	0

As can be seen from the data, as the electronegativity of X increases the chemical shift, δ increases. This is an effect of the halide atom pulling the electron density away from the methyl group. This exposes the nuclei of both the C and H atoms, "deshielding" the nuclei and shifting the peak downfield.

The effects are cumulative so the presence of more electron withdrawing groups will produce a greater deshielding and therefore a larger chemical shift, *i.e.*

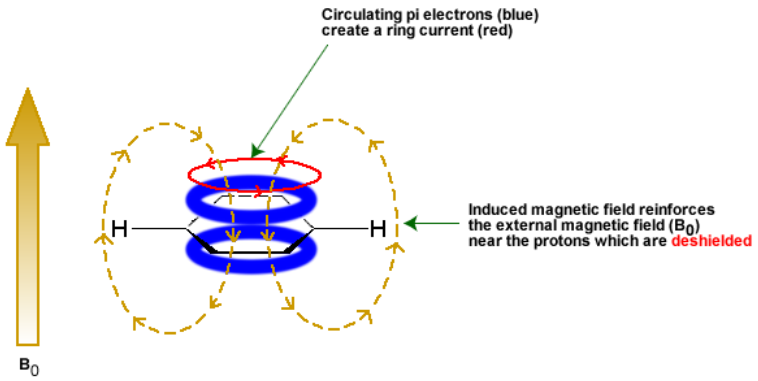
Compound	CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$
δ (ppm)	0.23	3.05	5.30	7.27

These **inductive effects** are not only felt by the immediately adjacent atoms, but the deshielding can occur further down the chain, *i.e.*

NMR signal	$-CH_2-CH_2-CH_2Br$
δ (ppm)	1.25 1.69 3.30

MAGNETIC ANISOTROPY: Π ELECTRON EFFECTS

The π electrons in a compound, when placed in a magnetic field, will move and generate their own magnetic field. The new magnetic field will have an effect on the shielding of atoms within the field. The best example of this is benzene (see the figure below).

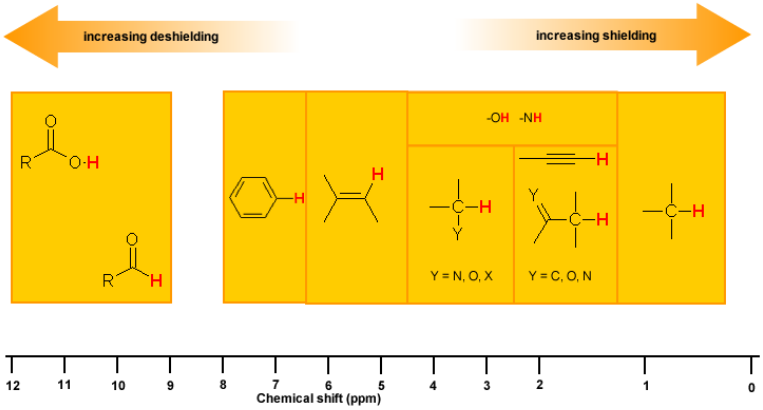


This effect is common for any atoms near a π bond, *i.e.*

Proton Type	Effect	Chemical shift (ppm)
C_6H_5-H	highly deshielded	6.5 - 8
C=C-H	deshielded	4.5 - 6
C≡C-H	shielded*	~2.5
O=C-H	very highly deshielded	9 - 10
* the acetylene H is shielded due to its location relative to the π system		

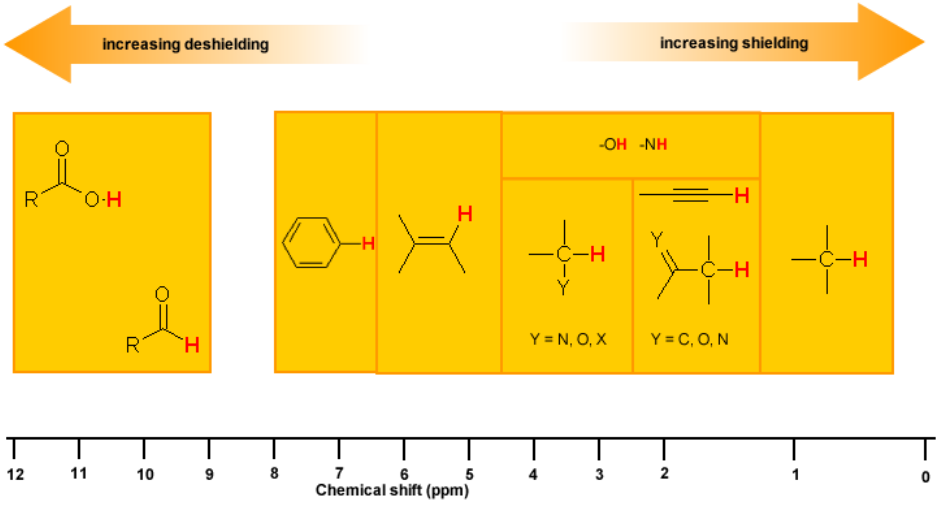
HYDROGEN BONDING

Protons that are involved in hydrogen bonding (*i.e.*-OH or -NH) are usually observed over a wide range of chemical shifts. This is due to the deshielding that occurs in the hydrogen bond. Since hydrogen bonds are dynamic, constantly forming, breaking and forming again, there will be a wide range of hydrogen bonds strengths and consequently a wide range of deshielding. This as well as solvation effects, acidity, concentration and temperature make it very difficult to predict the chemical shifts for these atoms.



Experimentally -OH and -NH can be identified by carrying out a simple D_2O exchange experiment since these protons are exchangeable.

- run the normal H-NMR experiment on your sample
- add a few drops of D_2O
- re-run the H-NMR experiment
- compare the two spectra and look for peaks that have "disappeared"



? EXERCISE 13.2.1

The following peaks were from a H^1 NMR spectra from a 400 MHz spectrometer. Convert to δ units

a. $CHCl_3$ 1451 Hz
b. CH_3Cl 610 Hz

c. CH_3OH 693 Hz
d. CH_2Cl_2 1060 Hz

Answer

a. 3.627 ppm
b. 1.525 ppm
c. 1.732 ppm
d. 2.65 ppm

EXERCISE 13.2.2

Butan-2-one shows a chemical shift around 2.1 on a 300 MHz spectrometer in the H^1 NMR spectrum.

a. How far downfield is this peak from TMS in Hz?
b. If the spectrum was done with a 400 MHz instrument, would a different chemical shift be seen?
c. On this new 400 MHz spectrum, what would be the difference in Hz from the chemical shift and TMS?

Answer

a. Since TMS is at 0 δ = 0 Hz for reference, the difference between the two would be 630 Hz
b. No not a different chemical shift, but a different frequency would be seen, 840 Hz
c. 840 Hz

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13.3: CHEMICAL SHIFTS IN ^{1}H NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. state the approximate chemical shift (δ) for the following types of protons:
   a. aromatic.
   b. vinylic.
   c. those bonded to carbon atoms which are in turn bonded to a highly electronegative element.
   d. those bonded to carbons which are next to unsaturated centres.
   e. those bonded to carbons which are part of a saturated system.
2. predict the approximate chemical shifts of each of the protons in an organic compound, given its structure and a table of chemical shift correlations.

STUDY NOTES

You should not attempt to memorize the chemical shifts listed in the table of this section, although it is probable that you will need to refer to it quite frequently throughout the remainder of this course. To fulfill Objective 1, above, you should be familiar with the information presented in the figure of chemical shift ranges for organic compounds. If you have an approximate idea of the chemical shifts of some of the most common types of protons, you will find the interpretation of ^{1}H NMR spectra less arduous than it might otherwise be. Notice that we shall not try to understand why aromatic protons are deshielded or why alkynyl protons are not deshielded as much as vinylic protons. These phenomena can be explained, but the focus is on the interpretation of ^{1}H NMR spectra, not on the underlying theory.

^{1}H NMR CHEMICAL SHIFTS

Chemical shifts in NMR (Nuclear Magnetic Resonance) spectroscopy refer to the phenomenon where the resonant frequency of a nucleus in a magnetic field is influenced by its chemical environment. This effect arises from the shielding or deshielding of the nucleus by the surrounding electron cloud. When a nucleus experiences different local electron densities due to nearby atoms or functional groups, its resonant frequency is altered relative to a reference standard, usually tetramethylsilane in organic solvents. This alteration is expressed in parts per million (ppm) and is known as the chemical shift. Tetramethylsilane [TMS;$(CH_3)_4Si$] is generally used for standard to determine chemical shift of compounds: δ_{TMS}=0 ppm. In other words, frequencies for chemicals are measured for a ^{1}H nucleus of a sample from the ^{1}H or resonance of TMS. It is important to understand trend of chemical shift in terms of NMR interpretation. The proton NMR chemical shift is affect by nearness to electronegative atoms (O, N, halogen.) and unsaturated groups (C=C,C=O, aromatic). Electronegative groups move to the down field (left; increase in ppm). Unsaturated groups shift to downfield (left) when affecting nucleus is in the plane of the unsaturation, but reverse shift takes place in the regions above and below this plane. ^{1}H chemical shift play a role in identifying many functional groups. Figure 1. indicates important example to figure out the functional groups.

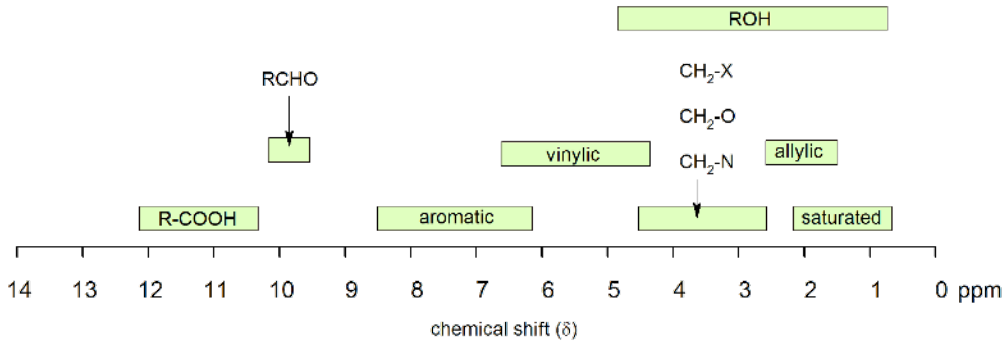
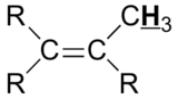
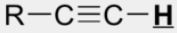
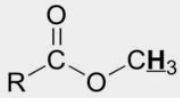
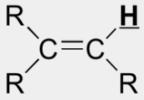
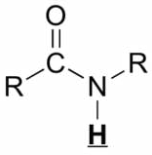
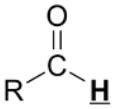
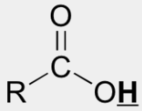


Figure 1. 1H chemical shift ranges for organic compounds

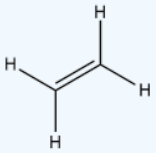
Chemical shift values are in parts per million (ppm) relative to tetramethylsilane.

Table **13.3.1**: Common Chemical Shift values

Hydrogen type	Chemical shift (ppm)
$RC\underline{H}_3$	0.9 - 1.0
$RC\underline{H}_2R$	1.2 - 1.7
$R_3C\underline{H}$	1.5 – 2.0
	2.0 – 2.3
	1.5 – 1.8
$RN\underline{H}_2$	1 - 3
$ArC\underline{H}_3$	2.2 – 2.4
	2.3 – 3.0
$ROC\underline{H}_3$	3.7 – 3.9
	3.7 – 3.9
$RO\underline{H}$	1 - 5
	3.7 – 6.5
	5 - 9
$Ar\underline{H}$	6.0 – 8.7
	9.5 – 10.0
	10 - 13

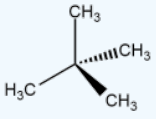
EXERCISE 13.3.1

The following have one H^1 NMR peak. In each case predict approximately where this peak would be in a spectra.

A) 

B) 

C) 

D) 

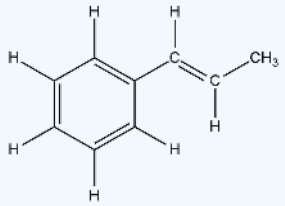
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Answer

A. 5.20 δ; B. 1.50 δ; C. 6.40 δ; D. 1.00 δ

? EXERCISE 13.3.2

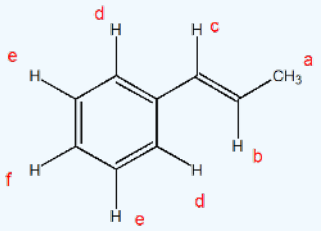
Identify the different equivalent protons in the following molecule and predict their expected chemical shift.



Answer

There are 6 different protons in this molecule

The shifts are (close) to the following: (a) 2 δ; (b) 6 δ; (c) 6.5 δ; (d) 7 δ; (e) 7.5 δ; (f) 7 δ



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13.4: INTEGRATION OF ^{1}H NMR ABSORPTIONS - PROTON COUNTING

OBJECTIVES

After completing this section, you should be able to

- explain what information can be obtained from an integrated ^{1}H NMR spectrum, and use this information in the interpretation of such a spectrum.
- use an integrated ^{1}H NMR spectrum to determine the ratio of the different types of protons present in an organic compound.

STUDY NOTES

The concept of peak integration is that the area of a given peak in a ^{1}H NMR spectrum is proportional to the number of (equivalent) protons giving rise to the peak. Thus, a peak which is caused by a single, unique proton has an area which measures one third of the area of a peak resulting from a methyl (CH_3) group in the same spectrum.

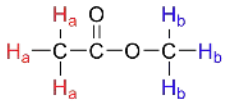
In practice, we do not have to measure these areas ourselves: it is all done electronically by the spectrometer, and an integration curve is superimposed on the rest of the spectrum. The integration curve appears as a series of steps, with the height of each step being proportional to the area of the corresponding absorption peak, and consequently, to the number of protons responsible for the absorption.

As it can be difficult to decide precisely where to start and stop when measuring integrations, you should not expect your ratios to be exact whole numbers.

Signal integration in NMR (Nuclear Magnetic Resonance) spectroscopy is crucial for quantifying the relative number of nuclei contributing to each signal in the spectrum. This process involves measuring the area under each peak in the NMR spectrum, which directly correlates to the abundance of the corresponding nuclei in the sample.

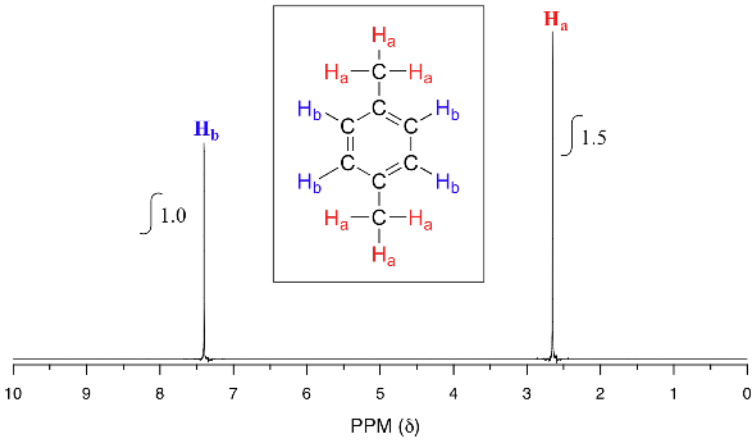
SIGNAL INTEGRATION

The computer in an NMR instrument can be instructed to automatically integrate the area under a signal or group of signals. This is very useful, because *in ^{1}H-NMR spectroscopy the area under a signal is proportional to the number of hydrogens to which the peak corresponds*. In the previous example of methyl acetate from Section 13.2, for example, the Ha and H_b peaks would integrate to approximately the same area, because they both correspond to a set of three equivalent protons.



methyl acetate

Now, take a look next at the spectrum of *para*-xylene (IUPAC name 1,4-dimethylbenzene):



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This molecule has two sets of protons: the six methyl (H_a) protons and the four aromatic (H_b) protons. When we instruct the instrument to integrate the areas under the two signals, we find that the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at 7.4 ppm, which is the case with 6 methyl protons and 4 aromatic protons. This (along with the actual chemical shift values, which we'll discuss soon) tells us which set of protons corresponds to which NMR signal.

The integration function can also be used to determine the relative amounts of two or more compounds in a *mixed* sample. If we have a sample that is a 50:50 (mole/mole) mixture of benzene and acetone, for example, the acetone signal should integrate to the same value as the benzene sample, because both signals represent six equivalent protons. If we have a 50:50 mixture of acetone and cyclopentane, on the other hand, the ratio of the acetone peak area to the cylopentane peak area will be 3:5 (or 6:10), because the cyclopentane signal represents ten protons.

EXAMPLE 13.4.1

You take a ^{1}H-NMR spectrum of a mixed sample of acetone ($CH_3(CO)CH_3$) and dichloromethane (CH_2Cl_2). The integral ratio of the two signals (acetone : dichloromethane) is 2.3 to 1. What is the molar ratio of the two compounds in the sample?

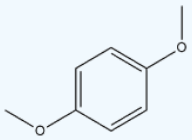
EXAMPLE 13.4.2

You take the ^{1}H-NMR spectrum of a mixed sample of 36% *para*-xylene and 64% acetone in $CDCl_3$ solvent (structures are shown earlier in this chapter). How many peaks do you expect to see? What is the expected ratio of integration values for these peaks? (set the acetone peak integration equal to 1.0)

Solutions

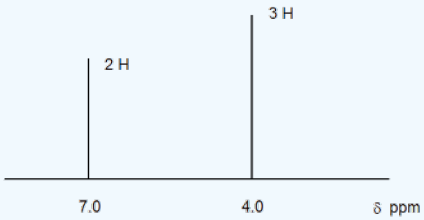
EXERCISE 13.4.1

Predict how many signals the following molecule would have? Sketch the spectra and estimate the integration of the peaks.



Answer

There will be two peaks. Ideal general spectrum shown with integration.



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13.5: SPIN-SPIN SPLITTING IN ^{1}H NMR SPECTRA

OBJECTIVES

After completing this section, you should be able to

1. explain the spin-spin splitting pattern observed in the ^{1}H NMR spectrum of a simple organic compound, such as chloroethane or 2-bromopropane.
2. interpret the splitting pattern of a given ^{1}H NMR spectrum.
3. determine the structure of a relatively simple organic compound, given its ^{1}H NMR spectrum and other relevant information.
4. use coupling constants to determine which groups of protons are coupling with one another in a ^{1}H NMR spectrum.
5. predict the splitting pattern which should be observed in the ^{1}H NMR spectrum of a given organic compound.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- coupling constant
- multiplet
- quartet
- triplet
- doublet

STUDY NOTES

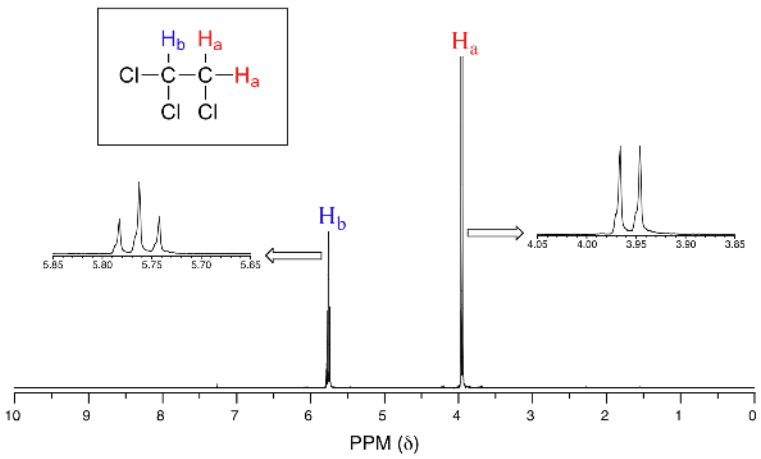
From what we have learned about ^{1}H NMR spectra so far, we might predict that the spectrum of 1,1,2-trichloroethane, $CHCl_2CH_2Cl$, would consist of two peaks—one, at about 2.5-4.0 δ, expected for CH_2-halogen compounds and one shifted downfield because of the presence of an additional electronegative chlorine atom on the second carbon. However, when we look at the spectrum it appears to be much more complex. True, we see absorptions in the regions we predicted, but these absorptions appear as a group of two peaks (a *doublet*) and a group of three peaks (a *triplet*). This complication, which may be disturbing to a student who longs for the simple life, is in fact very useful to the organic chemist, and adds greatly to the power of NMR spectroscopy as a tool for the elucidation of chemical structures. The split peaks (*multiplets*) arise because the magnetic field experienced by the protons of one group is influenced by the spin arrangements of the protons in an adjacent group.

Spin-spin coupling is often one of the more challenging topics for organic chemistry students to master. Remember the $n + 1$ rule and the associated coupling patterns.

THE SOURCE OF SPIN-SPIN COUPLING

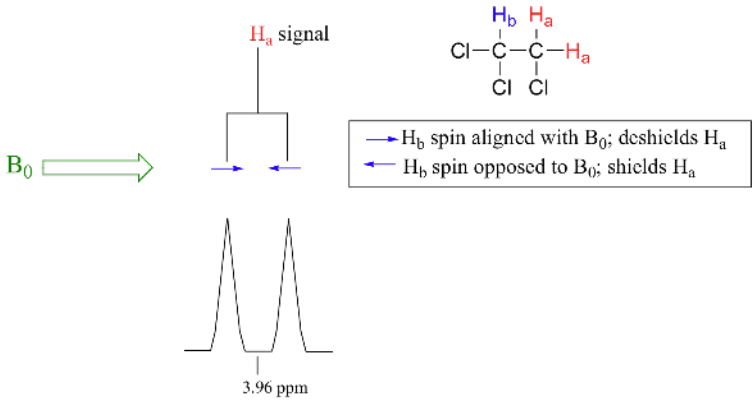
The ^{1}H-NMR spectra that we have seen so far (of methyl acetate and *para*-xylene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^{1}H-NMR spectra of most organic molecules contain proton signals that are 'split' into two or more sub-peaks. Rather than being a complication, however, this splitting behavior actually provides us with more information about our sample molecule.

Consider the spectrum for 1,1,2-trichloroethane. In this and in many spectra to follow, we show enlargements of individual signals so that the signal splitting patterns are recognizable.

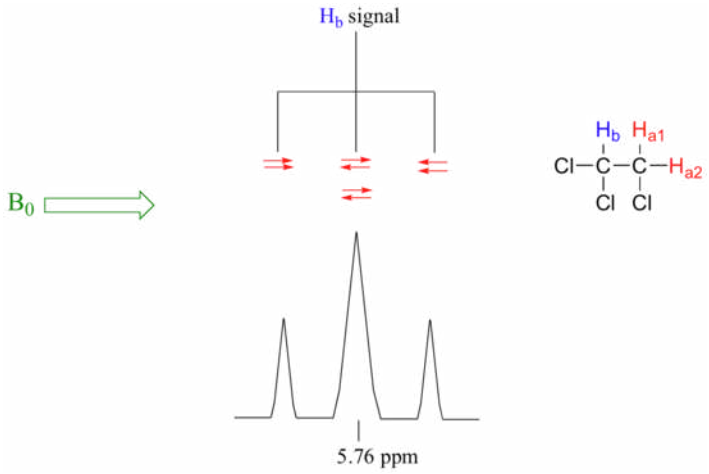


The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a **doublet**. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were to integrate each subpeak, we would see that the area under the middle peak is twice that of each of the outside peaks. This is called a **triplet**.

The source of signal splitting is a phenomenon called **spin-spin coupling**, a term that describes the magnetic interactions between neighboring, non-equivalent NMR-active nuclei. In our 1,1,2 trichloromethane example, the H_a and H_b protons are spin-coupled to each other. Here's how it works, looking first at the H_a signal: in addition to being shielded by nearby valence electrons, each of the H_a protons is also influenced by the small magnetic field generated by H_b next door (remember, each spinning proton is like a tiny magnet). The magnetic moment of H_b will be aligned *with* B_0 in (slightly more than) half of the molecules in the sample, while in the remaining half of the molecules it will be opposed to B_0. The B_{eff} 'felt' by H_a is a slightly weaker if H_b is aligned against B_0, or slightly stronger if H_b is aligned with B_0. In other words, in half of the molecules H_a is *shielded* by H_b (thus the NMR signal is shifted slightly upfield) and in the other half H_a is *deshielded* by H_b(and the NMR signal shifted slightly downfield). What would otherwise be a single H_a peak has been split into two sub-peaks (a doublet), one upfield and one downfield of the original signal. These ideas an be illustrated by a **splitting diagram**, as shown below.

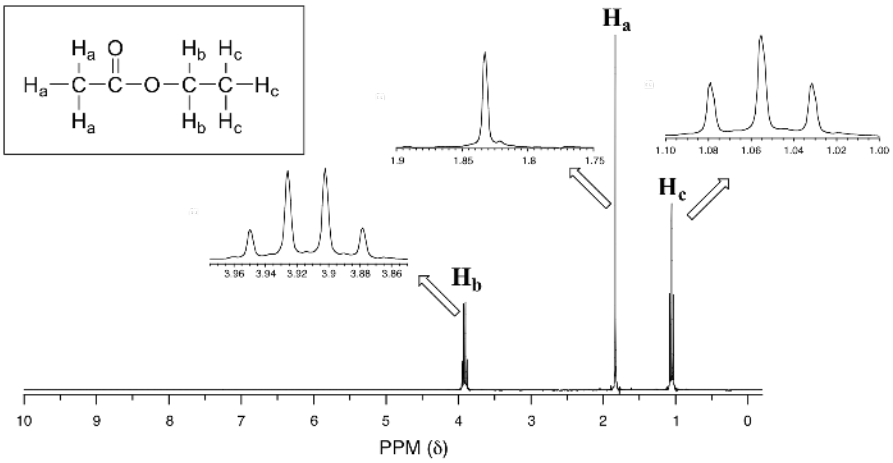


Now, let's think about the $H_b$signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_{a1} and H_{a2}. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_{a1} and H_{a2} could be aligned with B_0, which would deshield H_b, shifting its NMR signal slightly downfield. Second, both the H_{a1} and H_{a2} magnetic fields could be aligned opposed to B_0, which would shield H_b, shifting its resonance signal slightly upfield. Third and fourth, H_{a1} could be with B_0 and H_{a2} opposed, or H_{a1}opposed to B_0 and H_{a2} with B_0. In each of the last two cases, the shielding effect of one H_a proton would cancel the deshielding effect of the other, and the chemical shift of H_b would be unchanged.



So in the end, the signal for H_b is a **triplet**, with the middle peak twice as large as the two outer peaks because there are *two* ways that H_{a1} and H_{a2} can cancel each other out.

Now, consider the spectrum for ethyl acetate:



We see an unsplit '**singlet**' peak at 1.833 ppm that corresponds to the acetyl (H_a) hydrogens – this is similar to the signal for the acetate hydrogens in methyl acetate that we considered earlier. This signal is unsplit because there are no adjacent hydrogens on the molecule. The signal at 1.055 ppm for the H_c hydrogens is split into a triplet by the two H_b hydrogens next door. The explanation here is the same as the explanation for the triplet peak we saw previously for 1,1,2-trichloroethane.

The $H_b$hydrogens give rise to a **quartet** signal at 3.915 ppm – notice that the two middle peaks are taller then the two outside peaks. This splitting pattern results from the spin-coupling effect of the *three* H_c hydrogens next door, and can be explained by an analysis similar to that which we used to explain the doublet and triplet patterns.

EXAMPLE 13.11.1

a. Explain, using left and right arrows to illustrate the possible combinations of nuclear spin states for the H_c hydrogens, why the H_b signal in ethyl acetate is split into a quartet.

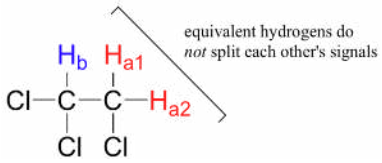
b. The integration ratio of doublets is 1:1, and of triplets is 1:2:1. What is the integration ratio of the H_b quartet in ethyl acetate? (Hint – use the illustration that you drew in part a to answer this question.)

Solution

By now, you probably have recognized the pattern which is usually referred to as the ***n* + 1 rule**: if a set of hydrogens has *n* neighboring, non-equivalent hydrogens, it will be split into *n* + 1 subpeaks. Thus the two H_b hydrogens in ethyl acetate split the H_c signal into a triplet, and the three H_c hydrogens split the H_b signal into a quartet. This is very useful information if we are trying to determine the structure of an unknown molecule: if we see a triplet signal, we know that the corresponding hydrogen or set of hydrogens has two `neighbors`. When we

begin to determine structures of unknown compounds using ^{1}H-NMR spectral data, it will become more apparent how this kind of information can be used.

Three important points need to be emphasized here. First, signal splitting only occurs between non-equivalent hydrogens – in other words, H_{a1} in 1,1,2-trichloroethane is *not* split by H_{a2}, and vice-versa.

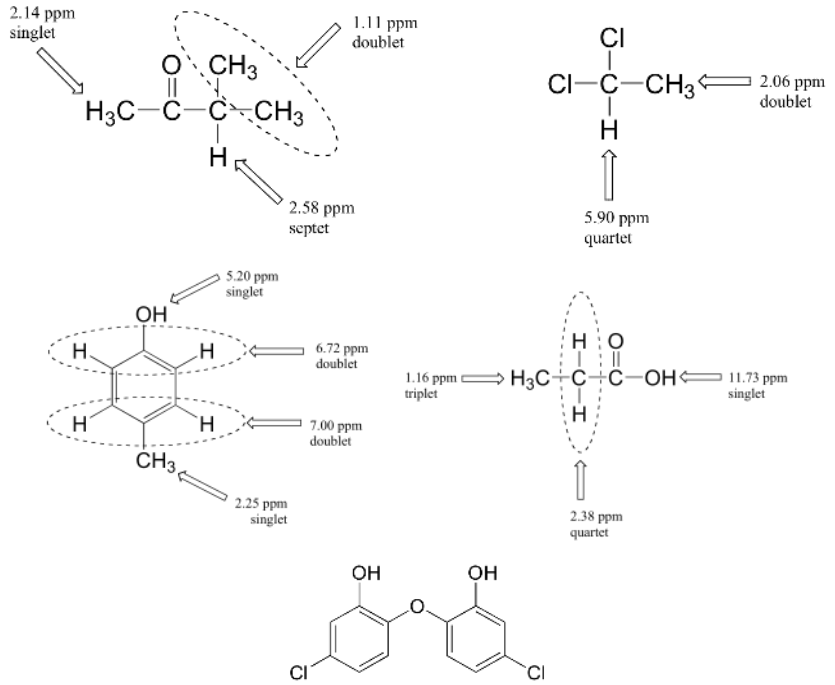


Second, splitting occurs primarily between hydrogens that are separated by three bonds. This is why the H_a hydrogens in ethyl acetate form a singlet– the nearest hydrogen neighbors are five bonds away, too far for coupling to occur.



Occasionally we will see four-bond and even 5-bond splitting, but in these cases the magnetic influence of one set of hydrogens on the other set is much more subtle than what we typically see in three-bond splitting (more details about how we quantify coupling interactions is provided in section 5.5B). Finally, splitting is most noticeable with hydrogens bonded to carbon. Hydrogens that are bonded to heteroatoms (alcohol or amino hydrogens, for example) are coupled weakly - or not at all - to their neighbors. This has to do with the fact that these protons exchange rapidly with solvent or other sample molecules.

Below are a few more examples of chemical shift and splitting pattern information for some relatively simple organic molecules.



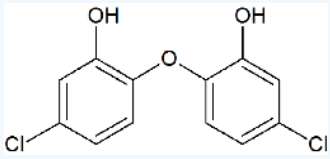
MULTIPLICITY IN PROTON NMR

The number of lines in a peak is always one more (n+1) than the number of hydrogens on the neighboring carbon. This table summarizes coupling patterns that arise when protons have different numbers of neighbors.

# of lines	ratio of lines	term for peak	# of neighbors
1	-	singlet	0
2	1:1	doublet	1
3	1:2:1	triplet	2
4	1:3:3:1	quartet	3
5	1:4:6:4:1	quintet	4
6	1:5:10:10:5:1	sextet	5
7	1:6:15:20:15:6:1	septet	6
8	1:7:21:35:35:21:7:1	octet	7
9	1:8:28:56:70:56:28:8:1	nonet	8

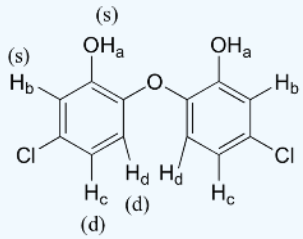
EXAMPLE 13.11.2

How many proton signals would you expect to see in the ^{1}H-NMR spectrum of the structure shown? For each of the proton signals, predict the splitting pattern. Assume that you see only 3-bond coupling.



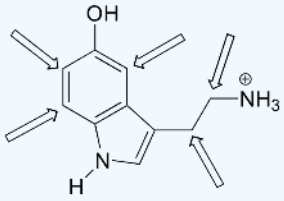
Answer

Because of the symmetry in the molecule, there are only four proton signals. Predicted splitting is indicated.



EXAMPLE 13.11.3

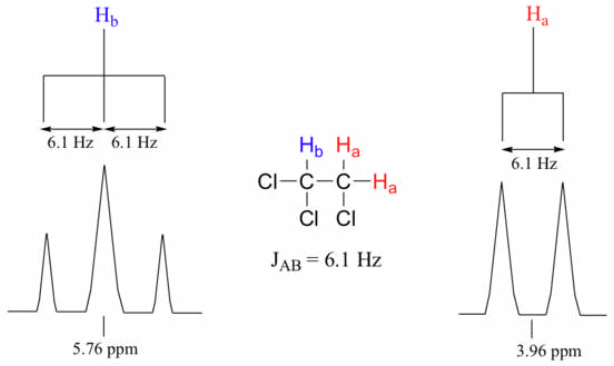
Predict the splitting pattern for the ^{1}H-NMR signals corresponding to the protons at the locations indicated by arrows (the structure is that of the neurotransmitter serotonin).



Solutions

COUPLING CONSTANTS

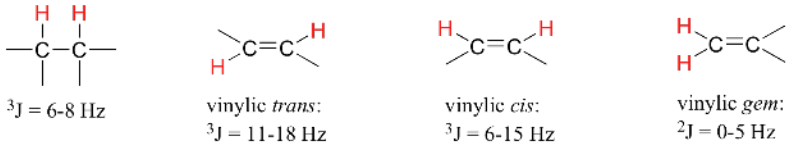
Chemists quantify the spin-spin coupling effect using something called the **coupling constant**, which is abbreviated with the capital letter *J*. The coupling constant is simply the difference, expressed in Hz, between two adjacent sub-peaks in a split signal. For our doublet in the 1,1,2-trichloroethane spectrum, for example, the two subpeaks are separated by 6.1 Hz, and thus we write $^3J_{a\text{-}b}$ = 6.1 Hz.



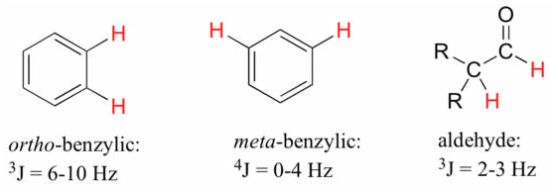
The superscript 3 tells us that this is a three-bond coupling interaction, and the a-b subscript tells us that we are talking about coupling between H_a and H_b. Unlike the chemical shift value, *the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR magnet*. This is because the strength of the magnetic moment of a neighboring proton, which is the source of the spin-spin coupling phenomenon, does *not* depend on the applied field strength.

When we look closely at the triplet signal in 1,1,2-trichloroethane, we see that the coupling constant - the `gap` between subpeaks - is 6.1 Hz, the same as for the doublet. This is an important concept! The coupling constant $^3J_{a\text{-}b}$ quantifies the magnetic interaction between the H_a and H_b hydrogen sets, and *this interaction is of the same magnitude in either direction*. In other words, H_a influences H_b to the same extent that H_b influences H_a. When looking at more complex NMR spectra, this idea of **reciprocal coupling constants** can be very helpful in identifying the coupling relationships between proton sets.

Coupling constants between proton sets on neighboring sp^3-hybridized carbons is typically in the region of 6-8 Hz. With protons bound to sp^2-hybridized carbons, coupling constants can range from 0 Hz (no coupling at all) to 18 Hz, depending on the bonding arrangement.



For vinylic hydrogens in a *trans* configuration, we see coupling constants in the range of ^3J = 11-18 Hz, while *cis* hydrogens couple in the ^3J = 6-15 Hz range. The 2-bond coupling between hydrogens bound to the same alkene carbon (referred to as geminal hydrogens) is very fine, generally 5 Hz or lower. *Ortho* hydrogens on a benzene ring couple at 6-10 Hz, while 4-bond coupling of up to 4 Hz is sometimes seen between *meta* hydrogens.

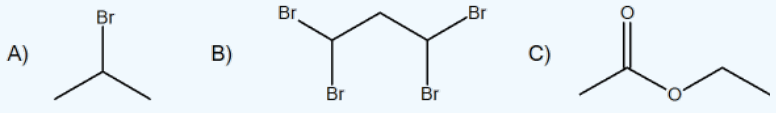


Fine (2-3 Hz) coupling is often seen between an aldehyde proton and a three-bond neighbor. Table 4 lists typical constant values.

> Remember, chemically equivalent protons do not couple with one another to give spin-spin splitting.

? EXERCISE 13.5.1

Predict the splitting patterns of the following molecules:

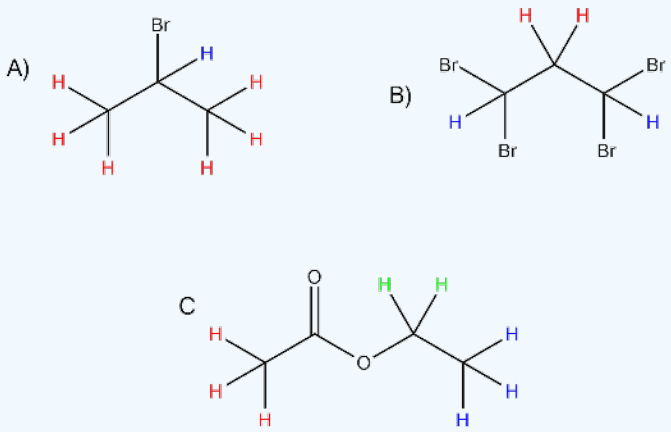


Answer

a. H: Doublet. H: Septet

b. H: Doublet, H: Triplet

c. H: Singlet, H: Quartet, H: Triplet

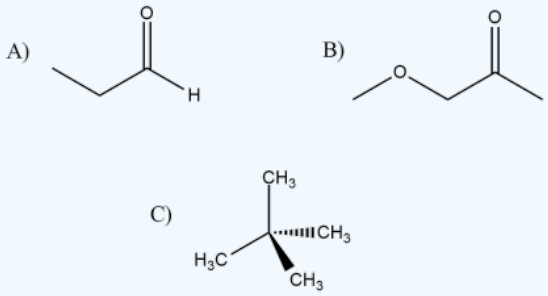


EXERCISE 13.5.2

Draw the following according to the criteria given.

a. C_3H_5O; two triplet, 1 doublet
b. $C_4H_8O_2$; three singlets
c. C_5H_{12}; one singlet

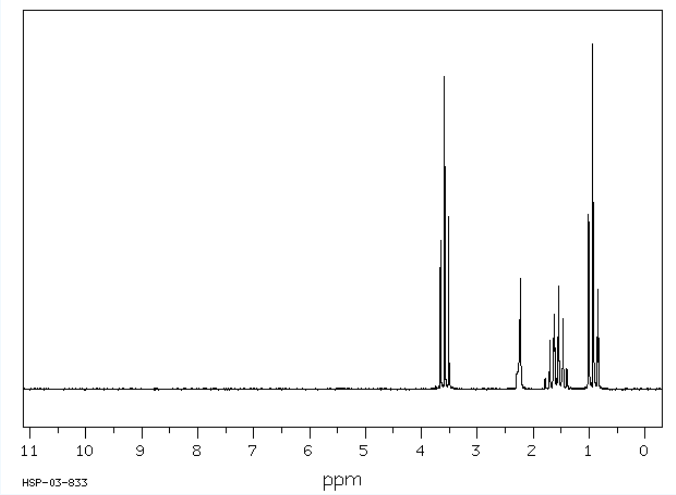
Answer



These are just some drawings, more may be possible.

EXERCISE 13.5.3

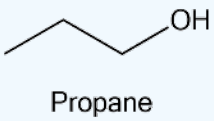
The following spectrum is for C_3H_8O. Determine the structure.



A triplet; B singlet; C sextet; D triplet

Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 3 December 2016)

Answer



Propane

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13.6: ^{1}H NMR SPECTROSCOPY AND PROTON EQUIVALENCE

OBJECTIVES

After completing this section, you should be able to

- identify those protons which are equivalent in a given chemical structure.
- use the ^{1}H NMR spectrum of a simple organic compound to determine the number of equivalent sets of protons present.

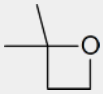
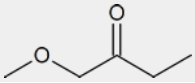
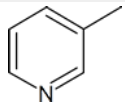
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

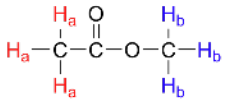
- diastereotopic
- enantiotopic
- homotopic

STUDY NOTES

It is important at this stage to be able to identify equivalent protons in any organic compound given the structure of that compound. Once you know the number of different groups of equivalent protons in a compound, you can predict the number (before coupling) and relative strength of signals. Look at the following examples and make sure you understand how the number and intensity ratio of signals are derived from the structure shown.

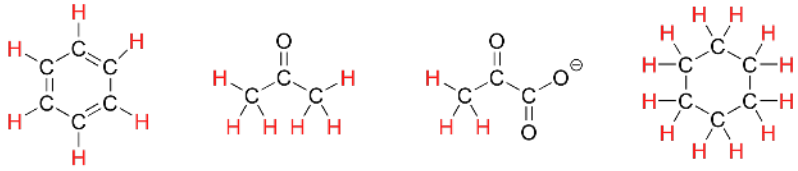
Structure	Number of Signals	Ratio of Signals	
CH3OCH2CH2Br	3	A : B : C	3 : 2 : 2
	1		
	3	A : B : C	2 : 2 : 6 (or 1 : 1 : 3)
	3	A : B : C	2 : 4 : 2 (or 1 : 2 : 1)
	4	A : B : C : D	3 : 2 : 2 : 3
	5	A : B : C : D : E	3 : 1 : 1 : 1 : 1

Proton equivalence in proton NMR refers to the concept that not all hydrogen atoms in a molecule produce distinct signals in the NMR spectrum. Instead, chemically equivalent protons, meaning those that occupy identical environments within a molecule, yield the same NMR signal. This concept is essential for interpreting NMR spectra accurately. Chemical equivalence is determined by the molecular structure and symmetry of a molecule. If all protons in all organic molecules had the same resonance frequency in an external magnetic field of a given strength, the information in the previous paragraph would be interesting from a theoretical standpoint, but would not be terribly useful to organic chemists. Fortunately for us, however, resonance frequencies are not uniform for all protons in a molecule. *In an external magnetic field of a given strength, protons in different locations in a molecule have different resonance frequencies, because they are in non-identical electronic environments.* In methyl acetate, for example, there are two 'sets' of protons. The three protons labeled H_a have a different - and easily distinguishable – resonance frequency than the three H_b protons, because the two sets of protons are in non-identical environments: they are, in other words, chemically nonequivalent.



On the other hand, the three H_a protons are all in the same electronic environment, and are chemically equivalent to one another. They have identical resonance frequencies. The same can be said for the three H_b protons. These protons are considered to be homotopic. Homotopic protons are chemically identical, so electronically equivalent, thus show up as identical NMR absorptions.

The ability to recognize chemical equivalency and nonequivalency among atoms in a molecule will be central to understanding NMR. In each of the molecules below, all protons are chemically equivalent, and therefore will have the same resonance frequency in an NMR experiment.



benzene acetone pyruvate cyclohexane

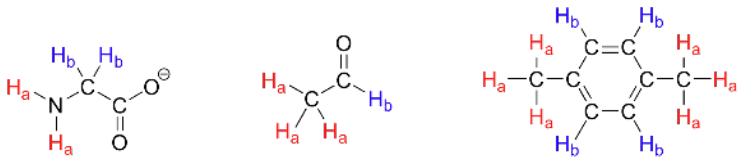
You might expect that the equatorial and axial hydrogens in cyclohexane would be non-equivalent, and would have different resonance frequencies. In fact, an axial hydrogen *is* in a different electronic environment than an equatorial hydrogen. Remember, though, that the molecule rotates rapidly between its two chair conformations, meaning that any given hydrogen is rapidly moving back and forth between equatorial and axial positions. It turns out that, except at extremely low temperatures, this rotational motion occurs on a time scale that is much faster than the time scale of an NMR experiment.



ring-flip process is *fast* compared to the NMR time-scale

In this sense, NMR is like a camera that takes photographs of a rapidly moving object with a slow shutter speed - the result is a blurred image. In NMR terms, this means that all 12 protons in cyclohexane are equivalent.

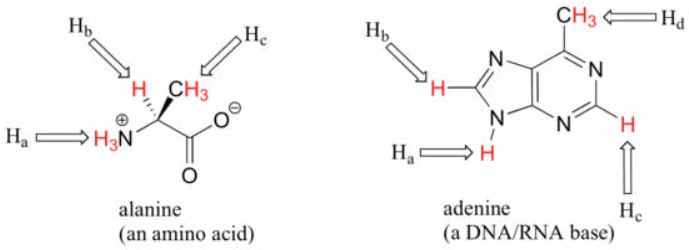
Each the molecules in the next figure contains *two* sets of protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



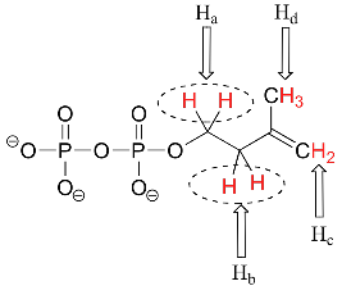
glycine acetaldehyde *para*-xylene

Notice how the symmetry of *para*-xylene results in there being only two different sets of protons.

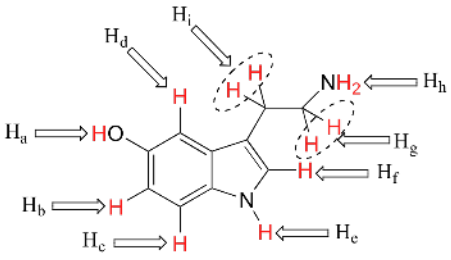
Most organic molecules have several sets of protons in different chemical environments, and each set, in theory, will have a different resonance frequency in ^{1}H-NMR spectroscopy.



alanine (an amino acid) adenine (a DNA/RNA base)

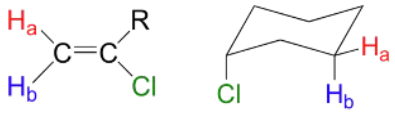


isopentenyl diphosphate
(a lipid building block)

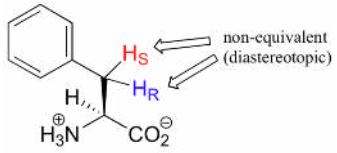


seratonin (a neurotransmitter)

When stereochemistry is taken into account, the issue of equivalence vs nonequivalence in NMR starts to get a little more complicated. It should be fairly intuitive that hydrogens on different sides of asymmetric ring structures and double bonds are in different electronic environments, and thus are non-equivalent and have different resonance frequencies. In the alkene and cyclohexene structures below, for example, H_a is *trans* to the chlorine substituent, while H_b is *cis* to chlorine.

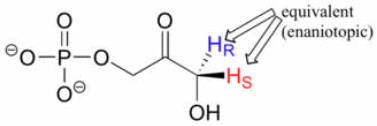


What is not so intuitive is that diastereotopic hydrogens (section 3.10) on chiral molecules are also non-equivalent:

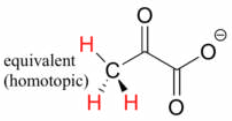


phenylalanine

However, enantiotopic and homotopic hydrogens are chemically equivalent. To determine if protons are homotopic or enantiotopic, you can do a thought experiment by replacing one H with X followed by the other H by X. In pyruvate below, if you replace any of the Hs with an X, then you would get the same molecule. These protons are homotopic. In dihydroxyacetone phosphate, this is not quite the case. If you exchange H_R for X, then you would create a stereocenter with R configuration. If you exchange H_S for X, then you would create a stereocenter with S configuration. The two "new molecules" would have the relationship of being enantiomers. Therefore H_R and H_S are enantiotopic protons. The only way these protons will show up different under NMR experimental conditions would be if you used a solvent that was chiral. Since most common solvents are all achiral, the enantiotopic protons are NMR equivalent and will show up as if they were the same proton.



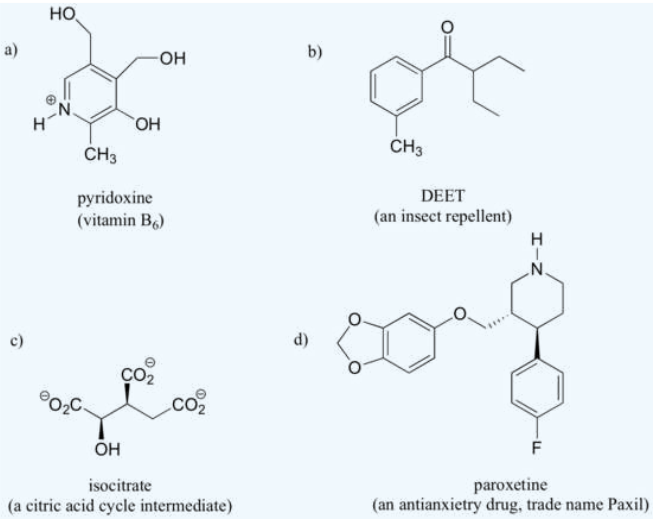
dihydroxyacetone
phosphate



pyruvate

EXAMPLE 13.6.1

How many different sets of protons do the following molecules contain? (count diastereotopic protons as non-equivalent).



Solution

EXERCISE 13.6.1

How many non-equivalent hydrogen are in the following molecules; how many different signals will you see in a H^1 NMR spectrum.

a. $CH_3CH_2CH_2Br$
b. $CH_3OCH_2C(CH_3)_3$
c. Ethyl Benzene
d. 2-methyl-1-hexene

Answer

A. 3; B. 3; C. 5; D. 7

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13.7: MORE COMPLEX SPIN-SPIN SPLITTING PATTERNS

OBJECTIVES

After completing this section, you should be able to

- explain how multiple coupling can give rise to complex-looking ^{1}H NMR spectra.
- predict the splitting pattern expected in the ^{1}H NMR spectrum of an organic compound in which multiple coupling is possible.
- interpret ^{1}H NMR spectra in which multiple coupling is evident.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

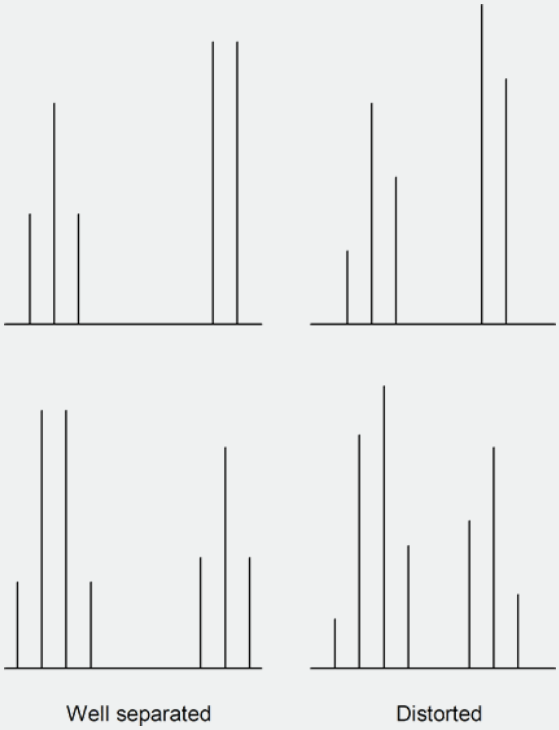
- tree diagram

STUDY NOTES

We saw the effects of spin-spin coupling on the appearance of a ^{1}H NMR signal. These effects can be further complicated when that signal is coupled to several different protons. For example, $BrCH_2CH_2CH_2Cl$ would produce three signals. The hydrogens at C_1 and C_3 would each be triplets because of coupling to the two hydrogens on C_2. However, the hydrogen on C_2 "sees" two different sets of neighboring hydrogens, and would therefore produce a triplet of triplets.

Another effect that can complicate a spectrum is the "closeness" of signals. If signals accidently overlap they can be difficult to identify. In the example above, we expected a triplet of triplets. However, if the coupling is identical (or almost identical) between the hydrogens on C_2 and the hydrogens on both C_1 and C_3, one would observe a quintet in the ^{1}H NMR spectrum. [You can try this yourself by drawing a tree diagram of a triplet of triplets assuming, first, different coupling constants, and then, identical coupling constants.] Keep this point in mind when interpreting real ^{1}H NMR spectra.

Also, when multiplets are well separated, they form patterns. However, when multiplets approach each other in the spectrum they sometimes become distorted. Usually, the inner peaks become larger than the outer peaks. Note the following examples:



Aromatic ring protons quite commonly have overlapping signals and multiplet distortions. Sometimes you cannot distinguish between individual signals, and one or more messy multiplets often appear in the aromatic region.

It is much easier to rationalize the observed ^{1}H NMR spectrum of a known compound than it is to determine the structure of an unknown compound from its ^{1}H NMR spectrum. However, rationalizations can be a useful learning technique as you try to improve your proficiency in spectral interpretation. Remember that when a chemist tries to interpret the ^{1}H NMR spectrum of an unknown compound, he or she usually has additional information available to make the task easier. For example, the chemist will almost certainly have an infrared spectrum of the compound and possibly a mass spectrum too. Details of how the compound was synthesized may be available, together with some indication of its chemical properties, its physical properties, or both.

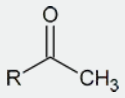
In examinations, you will be given a range of information (IR, MS, UV data and empirical formulae) to aid you with your structural determination using ^{1}H NMR spectroscopy. For example, you may be asked to determine the structure of $C_6H_{12}O$ given the following spectra:

Infrared spectrum: 3000 cm^{-1} and 1720 cm^{-1} absorptions are both strong

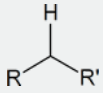
^{1}H NMR

δ (ppm)	Protons	Multiplicity
0.87	6	doublet
1.72	1	broad multiplet
2.00	3	singlet
2.18	2	doublet

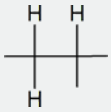
To answer this question, you note that the infrared spectrum of $C_6H_{12}O$ shows **C–H** stretching (3000 cm^{-1}) and **C–O** stretching (1720 cm^{-1}). Now you have to piece together the information from the ^{1}H NMR spectrum. Notice the singlet with three protons at 2.00 ppm. This signal indicates a methyl group that is not coupled to other protons. It could possibly mean the presence of a methyl ketone functional group.



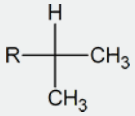
The signal at 1.72 ppm is a broad multiplet, suggesting that a carbon with a single proton is beside carbons with several different protons.



The doublet signal at 2.18 ppm implies that a **–CH_2–** group is attached to a carbon having only one proton.

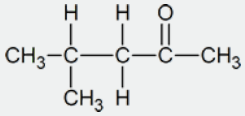


The six protons showing a doublet at 0.87 ppm indicate two equivalent methyl groups attached to a carbon with one proton.



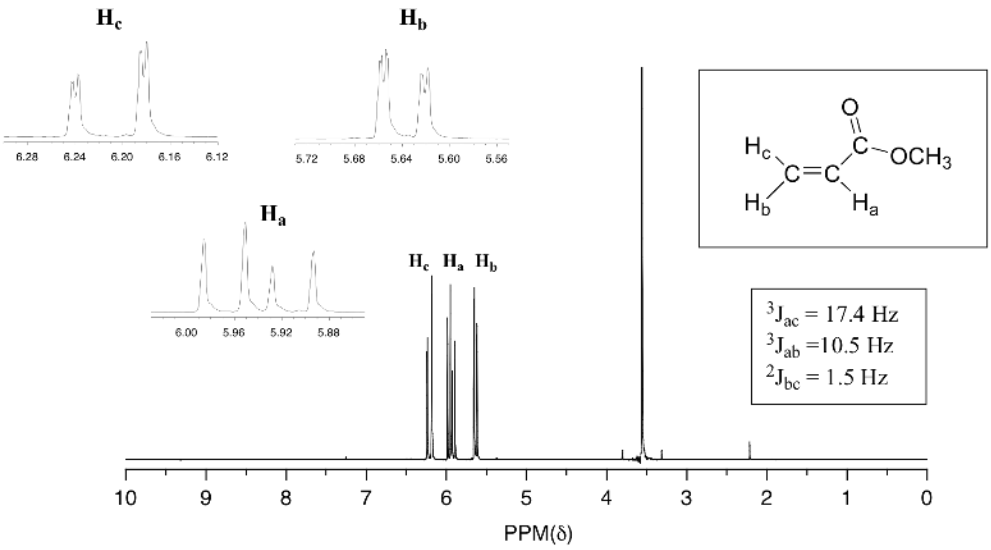
Whenever you see a signal in the 0.7-1.3 ppm range that is a multiplet of three protons (3, 6, 9) it is most likely caused by equivalent methyl groups.

Using trial and error, and with the above observations, you should come up with the correct structure.

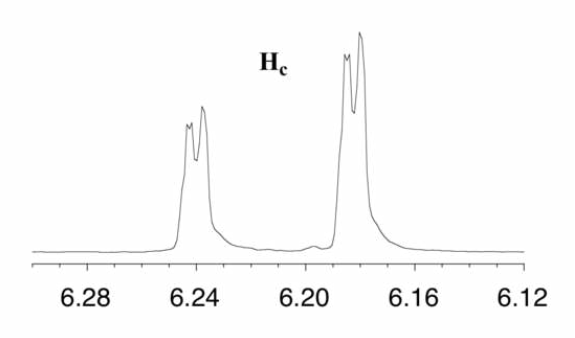


COMPLEX COUPLING

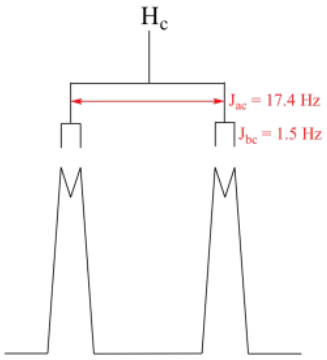
In all of the examples of spin-spin coupling that we have seen so far, the observed splitting has resulted from the coupling of one set of hydrogens to *just one* neighboring set of hydrogens. When a set of hydrogens is coupled to *two or more* sets of nonequivalent neighbors, the result is a phenomenon called **complex coupling**. A good illustration is provided by the ^{1}H-NMR spectrum of methyl acrylate:



First, let's first consider the H_c signal, which is centered at 6.21 ppm. Here is a closer look:

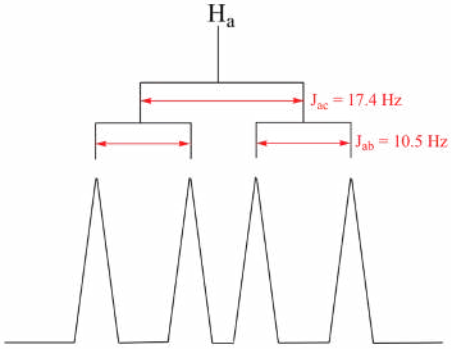


With this enlargement, it becomes evident that the Hc signal is actually composed of four sub-peaks. Why is this? H_c is coupled to both H_a and H_b , but with *two different coupling constants*. Once again, a splitting diagram (or tree diagram) can help us to understand what we are seeing. H_a is *trans* to H_c across the double bond, and splits the H_c signal into a doublet with a coupling constant of $^3J_{ac}$ = 17.4 Hz. In addition, each of these H_c doublet sub-peaks is split again by H_b (*geminal* coupling) into two more doublets, each with a much smaller coupling constant of $^2J_{bc}$ = 1.5 Hz.

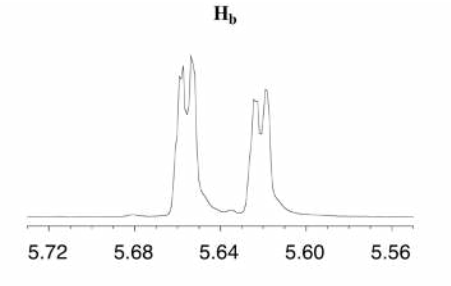


The result of this `double splitting` is a pattern referred to as a **doublet of doublets**, abbreviated `**dd**`.

The signal for H_a at 5.95 ppm is also a doublet of doublets, with coupling constants $^3J_{ac}$= 17.4 Hz and $^3J_{ab}$ = 10.5 Hz.



The signal for H_b at 5.64 ppm is split into a doublet by H_a, a *cis* coupling with $^3J_{ab}$ = 10.4 Hz. Each of the resulting sub-peaks is split again by H_c, with the same *geminal* coupling constant $^2J_{bc}$ = 1.5 Hz that we saw previously when we looked at the H_c signal. The overall result is again a doublet of doublets, this time with the two `sub-doublets` spaced slightly closer due to the smaller coupling constant for the *cis* interaction. Here is a blow-up of the actual $H_b$signal:



EXAMPLE 13.7.1

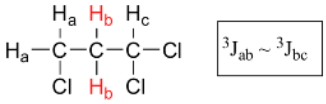
Construct a splitting diagram for the H_b signal in the ^{1}H-NMR spectrum of methyl acrylate. Show the chemical shift value for each sub-peak, expressed in Hz (assume that the resonance frequency of TMS is exactly 300 MHz).

Solution

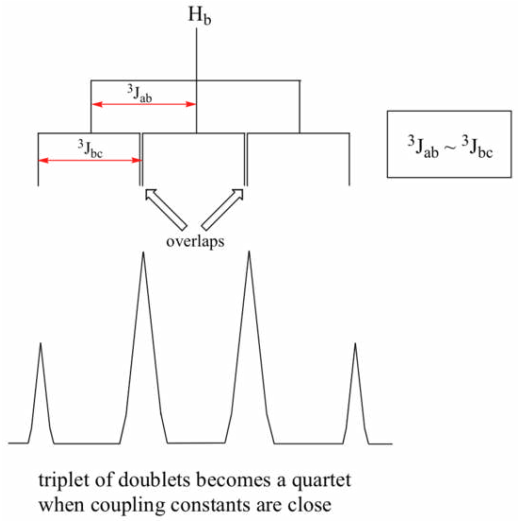
NOTE

When constructing a splitting diagram to analyze complex coupling patterns, it is usually easier to show the larger splitting first, followed by the finer splitting (although the reverse would give the same end result).

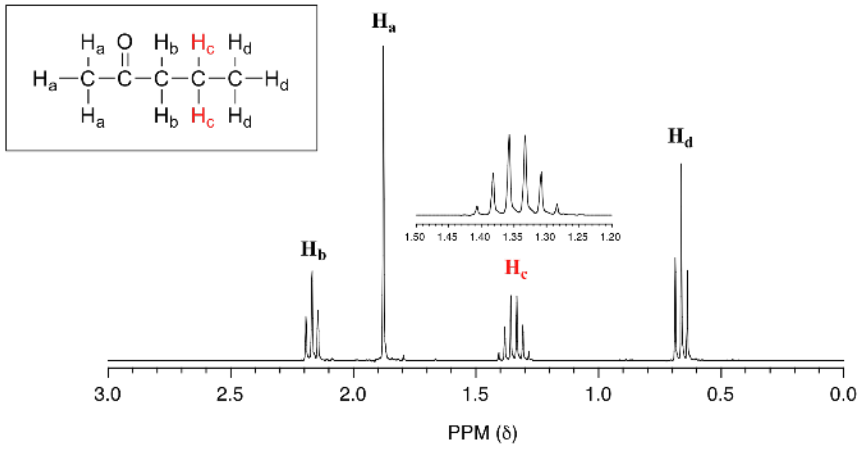
When a proton is coupled to two different neighboring proton sets with identical or very close coupling constants, the splitting pattern that emerges often appears to follow the simple `$n$ + 1 rule` of non-complex splitting. In the spectrum of 1,1,3-trichloropropane, for example, we would expect the signal for H_b to be split into a triplet by H_a, and again into doublets by H_c, resulting in a 'triplet of doublets'.



H_a and H_c are not equivalent (their chemical shifts are different), but it turns out that $^3J_{ab}$ is very close to $^3J_{bc}$. If we perform a splitting diagram analysis for H_b, we see that, due to the overlap of sub-peaks, the signal appears to be a quartet, and for all intents and purposes follows the n + 1 rule.

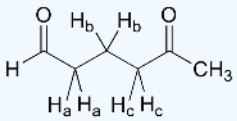


For similar reasons, the H_c peak in the spectrum of 2-pentanone appears as a sextet, split by the five combined H_b and H_d protons. Technically, this 'sextet' could be considered to be a 'triplet of quartets' with overlapping sub-peaks.



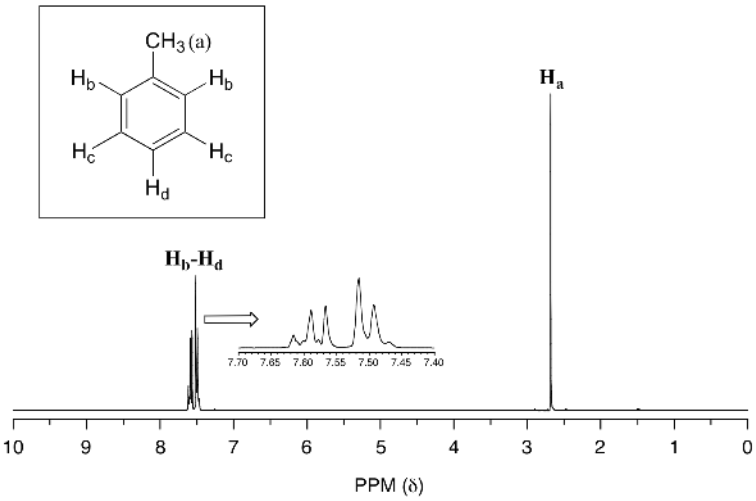
EXAMPLE 13.7.2

What splitting pattern would you expect for the signal corresponding to H_b in the molecule below? Assume that $J_{ab} \sim J_{bc}$. Draw a splitting diagram for this signal, and determine the relative integration values of each subpeak.



Solution

In many cases, it is difficult to fully analyze a complex splitting pattern. In the spectrum of toluene, for example, if we consider only 3-bond coupling we would expect the signal for H_b to be a doublet, H_d a triplet, and H_c a triplet.



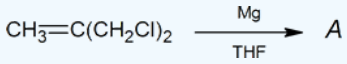
In practice, however, all three aromatic proton groups have very similar chemical shifts and their signals overlap substantially, making such detailed analysis difficult. In this case, we would refer to the aromatic part of the spectrum as a **multiplet**.

When we start trying to analyze complex splitting patterns in larger molecules, we gain an appreciation for why scientists are willing to pay large sums of money (hundreds of thousands of dollars) for higher-field NMR instruments. Quite simply, the stronger our magnet is, the more resolution we get in our spectrum. In a 100 MHz instrument (with a magnet of approximately 2.4 Tesla field strength), the 12 ppm frequency 'window' in which we can observe proton signals is 1200 Hz wide. In a 500 MHz (~12 Tesla) instrument, however, the window is 6000 Hz - five times wider. In this sense, NMR instruments are like digital cameras and HDTVs: better resolution means more information and clearer pictures (and higher price tags!)

? EXERCISE 13.7.1

Draw the structures of compound given the information.

An unknown compound *A* was prepared as follows:



Mass spectrum

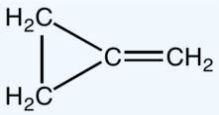
base peak *m*/*e* = 39

parent peak *m*/*e* = 54

^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
1.0	2	triplet
5.4	1	quintet

Answer



? EXERCISE 13.7.2

Draw the structures of compound given the information.

Unknown compound *B* has the molecular formula $C_7H_6O_2$.

Infrared spectrum

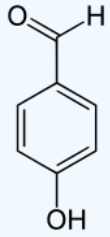
3200 cm^{-1} (broad) and 1747 cm^{-1} (strong) absorptions

^{1}H NMR spectrum

δ (ppm)	Protons
6.9	2
7.4	2
9.8	1
10.9	1

Hint: Aromatic ring currents deshield all proton signals just outside the ring.

Answer



EXERCISE 13.7.3

Draw the structures of compound given the information.

Unknown compound *C* shows no evidence of unsaturation and contains only carbon and hydrogen.

Mass spectrum

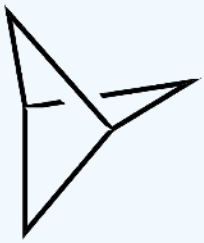
parent peak *m*/*e* = 68

^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
1.84	3	triplet
2.45	1	septet

Hint: Think three dimensionally!

Answer



EXERCISE 13.7.4

Draw the structures of compound given the information.

Unknown compound *D* ($C_{15}H_{14}O$) has the following spectral properties.

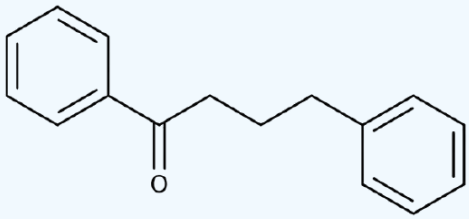
INFRARED SPECTRUM

3010 cm^{-1} (medium)
1715 cm^{-1} (strong)
1610 cm^{-1} (strong)
1500 cm^{-1} (strong)

^{1}H NMR spectrum

δ (ppm)	Relative Area	Multiplicity
3.00	2	triplet
3.07	2	triplet
7.1-7.9	10	Multiplets

Answer



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13.8: USES OF ^{1}H NMR SPECTROSCOPY

OBJECTIVE

After completing this section, you should be able to use data from ^{1}H NMR spectra to distinguish between two (or more) possible structures for an unknown organic compound.

There will be cases in which you already know what the structure might be. In these cases:

- You should draw attention to pieces of data that most strongly support your expected structure. This approach will demonstrate evaluative understanding of the data; that means you can look at data and decide what parts are more crucial than others.
- You should also draw attention to negative results: that is, peaks that might be there if this spectrum matched another, possible structure, but that are in fact missing.

One of the most complicated problems to deal with is the analysis of a mixture. This situation is not uncommon when students run reactions in lab and analyse the data.

- Sometimes the spectra show a little starting material mixed in with the product.
- Sometimes solvents show up in the spectrum.
- As you might expect, the minor component usually shows up as smaller peaks in the spectrum. If there are fewer molecules present, then there are usually fewer protons to absorb in the spectrum.
- In this case, you should probably make two completely separate sets of data tables for your analysis, one for each compound, or else one for the main compound and one for impurities.

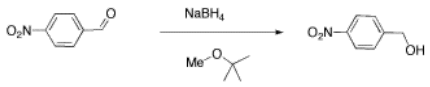
Remember that integration ratios are really only meaningful within a single compound. If your NMR sample contains some benzene (C_6H_6) and some acetone (CH_3COCH_3), and there is a peak at 7.15 that integrates to 1 proton and a peak at 2.10 ppm integrating to 6 protons, it might mean there are 6 protons in acetone and 1 in benzene, but you can tell that isn't true by looking at the structure. There must be six times as many acetone molecules as benzene molecules in the sample.

There are six protons in the benzene, and they should all show up near 7 ppm. There are six protons in acetone, and they should all show up near 2 ppm. Assuming that small integral of 1H for the benzene is really supposed to be 6H, then the large integral of 6H for the acetone must also represent six times as many hydrogens, too. It would be 36 H. There are only six hydrogens in acetone, so it must represent six times as many acetone molecules as there are benzenes.

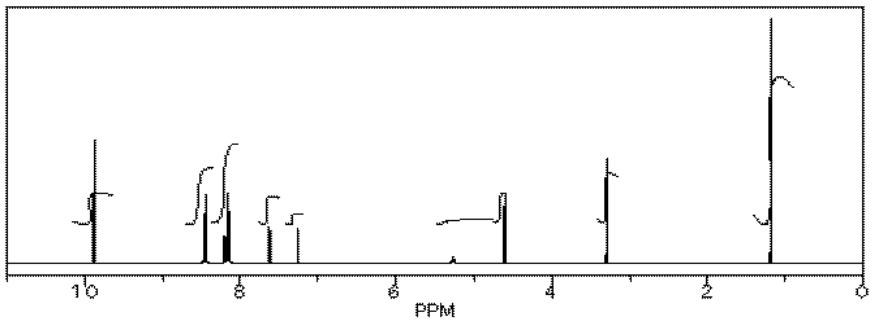
Similarly, if you have decided that you can identify two sets of peaks in the ^{1}H spectrum, analysing them in different tables makes it easy to keep the integration analysis completely separate too ; 1 H in one table will not be the same size integral as 1 H in the other table unless the concentrations of the two compounds in the sample are the same.

However, comparing the ratio of two integrals for two different compounds can give you the ratio of the two compounds in solution, just as we could determine the ratio of benzene to acetone in the mixture described above.

We will look at two examples of sample mixtures that could arise in lab. Results like these are pretty common events in the labIn the first example, a student tried to carry out the following reaction, a borohydride reduction of an aldehyde. The borohydride should give a hydride anion to the C=O carbon; washing with water should then supply a proton to the oxygen, giving an alcohol.

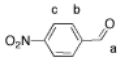
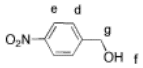
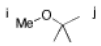


Her reaction produced the following spectrum.



(simulated data)

From this data, she produced the table below.

	shift	integration	int(n)	internal ratio	multiplicity	part structure	assignment
a	9.9 ppm	11 mm	2H	1H	singlet		
b	8.5 ppm	23 mm	4H	2H	doublet		 1
c	8.1 ppm	(20 mm?)	4H	2H	doublet		
d	8.2 ppm	(10 mm?)	2H	2H	doublet		
e	7.6 ppm	9 mm	2H	2H	doublet		 2
f	5.3 ppm	2 mm	0.4H	<1H	singlet	OH	
g	4.7 ppm	12 mm	2H	2H	singlet		
h	7.2 ppm	4 mm	0.8H	1H	singlet	$CHCl_3$	
i	3.3 ppm	8 mm	1.5H	3H	singlet		
j	1.2 ppm	24 mm	4.5H	9H	singlet		
			23.4H total				

Ratio of reactant **1** to product **2** is 2:1 based on peaks at 9.9 and 4.7 ppm (2H / 1H) : (2H / 2H); the reaction is 33% complete [2 / (2+1)]

Ratio of product **2** to TBME is 2:1 based on peaks at 4.7 and 3.3 ppm (2H / 2H) : (1.5H / 3H); the ratio of **1**:**2**:TBME is 2:1:0.5, so the sample is 57% **1** [2/(2+1+0.5)], 29% **2** and 14% TBME.

Notice how she calculated that ratio. She found a peak in molecule 1, the aldehyde, that she was pretty sure corresponded to the aldehydic hydrogen, the H attached to the C=O; in other words, the CH=O. She found another peak from molecule 2, the alcohol, that she was pretty sure represented the two hydrogens on the carbon attached to oxygen, the CH_2-O.

The integrals for those two peaks are equal. They are both 2H in her table. However, she notes that within each molecule, the first integral really represents 1H and the second represents 2H. That means there must be twice as many of molecule 1 as there are molecule 2. That way, there would be 2 x CH=O, and its integral would be the same as the 1 x CH_2-O in the other molecule.

One way to approach this kind of problem is to:

- choose one peak from each of the two compounds you want to compare.
- decide how many hydrogens each peak is supposed to represent in a molecule. Is it supposed to be a CH_2, a CH, a CH_3?
- divide the integral value for that peak by that number of hydrogens it is supposed to represent in a molecule.
- compare the two answers (integral A / ideal # H) vs (integral B / ideal # H).
- the ratio of those two answers is the ratio of the two molecules in the sample.

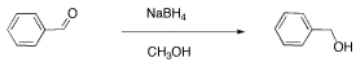
So there is twice as much aldehyde as alcohol in the mixture. In terms of these two compounds alone, she has 33% alcohol and 66% aldehyde. That's (1/(1+2)) x100% for the alcohol, and (2/(1+2)) x100% for the aldehyde. That calculation just represents the amount of individual component divided by the total of the components she wants to compare.

There are a number of things to take note of here.

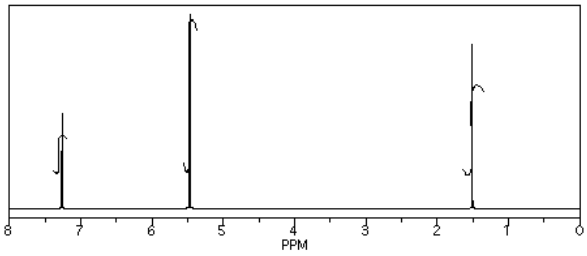
- Her reaction really didn't work very well. She still has majority starting material, not product.
- She will get a good grade on this lab. Although the experiment didn't work well, she has good data, and she has analyzed it very clearly.
- She has separated her data table into different sections for different compounds. Sometimes that makes it easier to analyze things.
- She has noted the actual integral data (she may have measured the integral with a ruler) and also converted it into a more convenient ratio, based on the integral for a peak that she felt certain about.
- She went one step further, and indicated the internal integration ratio within each individual compound.

- She calculated the % completion of the reaction using the integral data for the reactant and product, and she made clear what part of the data she used for that calculation. A similar procedure could be done if a student were just trying to separate two components in a mixture rather than carry out a reaction.
- She also calculated the overall purity of the mixture, including a solvent impurity that she failed to remove.
- However, $CHCl_3$ is not included in her analysis of purity. $CHCl_3$ really isn't part of her sample; it was just present in the NMR solvent, so it doesn't represent anything in the material she ended up with at the end of lab.

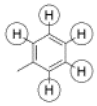
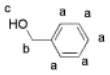
Another student carried out a similar reaction, shown below. He also finished the reaction by washing with water, but because methanol is soluble in water, he had to extract his product out of the water. He chose to use dichloromethane for that purpose.



He obtained the following data.



From this data, he constructed the following table.

	shift	integration	int(n)	multiplicity	partial structure	assignment
a	7.3 ppm	16 mm	5H	singlet		
b	5.4 ppm	64 mm	2H	singlet		
c	1.6 ppm	37 mm	1H	singlet	OH	

There are some things to learn about this table, too.

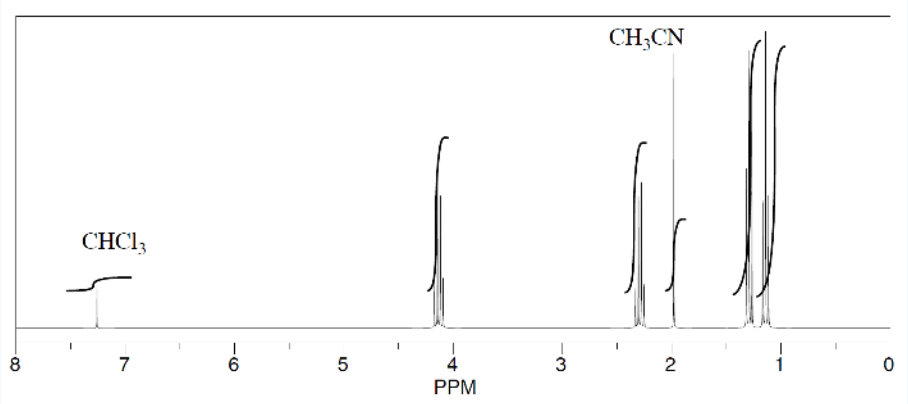
- Does the integration ratio really match the integral data? Or is this just wishful thinking?
- This table might reflect what he wants to see in the data. But what else could be in the data?
- $CHCl_3$ is often seen in NMR spectra if $CDCl_3$ is used for the NMR sample. It's there, at 7.2 ppm.
- "Leftover" or residual solvent is very common in real lab data. There it is, CH_2Cl_2 from the extraction, at 5.4 ppm.
- What about water? Sometimes people don't dry their solutions properly before evaporating the solvent. There is probably water around 1.5 to 1.6 ppm here.

This student might not get a very good grade; the sample does not even show up in the spectrum, so he lost it somewhere. But his analysis is also poor, so he will really get a terrible grade.

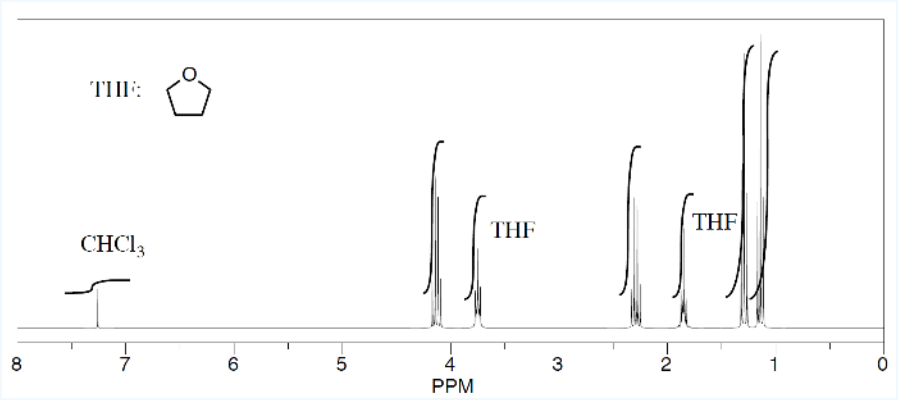
EXAMPLE 13.8.1

Three students performed a synthesis of a fragrant ester, ethyl propanoate, $CH_3CH_2CO_2CH_2CH_3$. During their reactions, they each used a different solvent. The students were able to see peaks in the NMR spectrum for ethyl propanoate, as well as peaks for chloroform ($CHCl_3$, in the $CDCl_3$ they used to make their NMR samples).

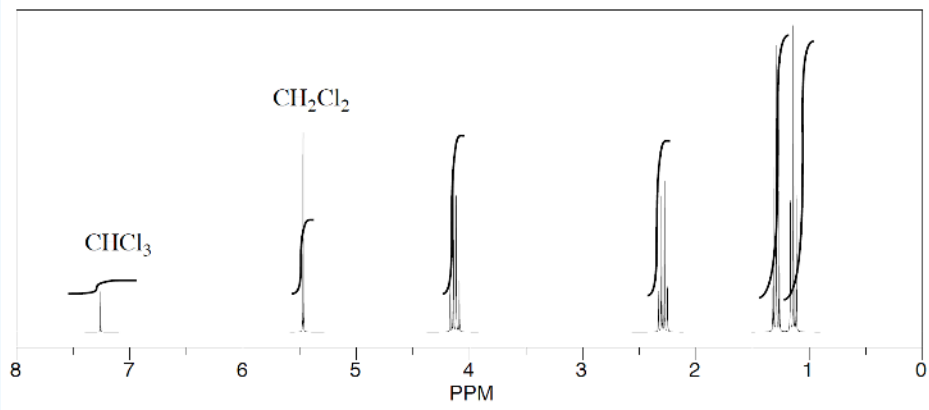
First student's spectrum:



Second student's spectrum:



Third student's spectrum:

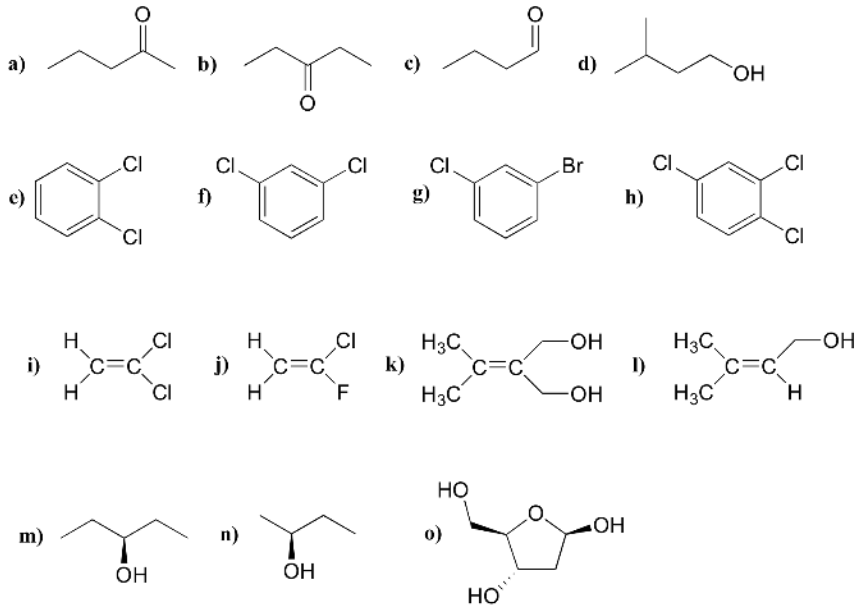


They were also able to determine that they had some leftover solvent in their samples by consulting a useful table of solvent impurities in NMR (which they found in Goldberg et. al., Organometallics 2010, 29, 2176-2179).

1. What is the ratio of leftover solvent to ethyl propanoate in each sample?
2. What is the percent of each sample that is leftover solvent

ADDITIONAL NMR EXAMPLES

For each molecule, predict the number of signals in the ^{1}H-NMR and the ^{13}C-NMR spectra (do not count split peaks - eg. a quartet counts as only one signal). Assume that diastereotopic groups are non-equivalent.

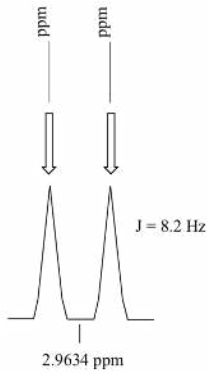


P5.2: For each of the 20 common amino acids, predict the number of signals in the proton-decoupled ^{13}C-NMR spectrum.

P5.3: Calculate the chemical shift value (expressed in Hz, to one decimal place) of each sub-peak on the ^{1}H-NMR doublet signal below. Do this for:

a) a spectrum obtained on a 300 MHz instrument

b) a spectrum obtained on a 100 MHz instrument



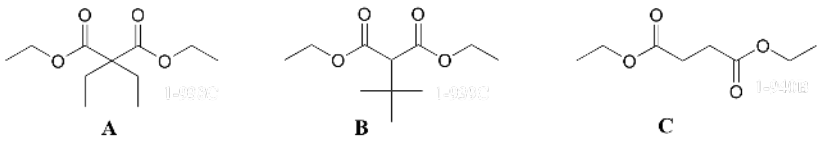
P5.4: Consider a quartet signal in an ^{1}H-NMR spectrum obtained on a 300 MHz instrument. The chemical shift is recorded as 1.7562 ppm, and the coupling constant is J = 7.6 Hz. What is the chemical shift, expressed to the nearest 0.1 Hz, of the furthest downfield sub-peak in the quartet? What is the resonance frequency (again expressed in Hz) of this sub-peak?)

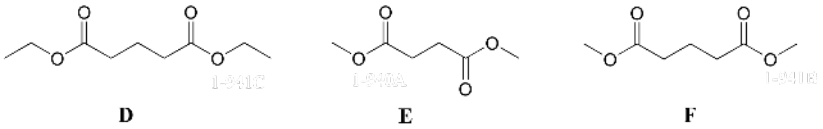
P5.5: One easily recognizable splitting pattern for the aromatic proton signals from disubstituted benzene structures is a pair of doublets. Does this pattern indicate *ortho*, *meta*, or *para* substitution?

P5.6 : Match spectra below to their corresponding structures A-F.

Structures:

https://chem.libretexts.org/@go/page/31544





Spectrum 1

δ	splitting	integration
4.13	q	2
2.45	t	2
1.94	quintet	1
1.27	t	3

Spectrum 2

δ	splitting	integration
3.68	s	3
2.99	t	2
1.95	quintet	1

Spectrum 3

δ	splitting	integration
4.14	q	1
2.62	s	1
1.26	t	1.5

Spectrum 4

δ	splitting	integration
4.14	q	4
3.22	s	1
1.27	t	6
1.13	s	9

Spectrum 5

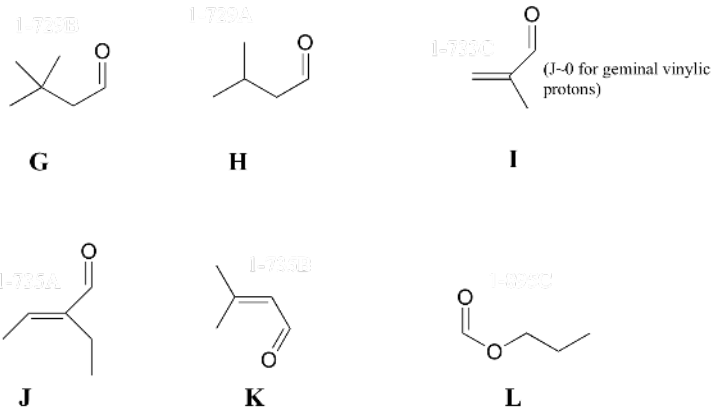
δ	splitting	integration
4.18	q	1
1.92	q	1
1.23	t	1.5
0.81	t	1.5

Spectrum 6

δ	splitting	integration
3.69	s	1.5
2.63	s	1

P5.7: Match spectra 7-12 below to their corresponding structures G-L .

Structures:



Spectrum 7:

δ	splitting	integration
9.96	d	1
5.88	d	1
2.17	s	3
1.98	s	3

Spectrum 8:

δ	splitting	integration
9.36	s	1
6.55	q	1
2.26	q	2
1.99	d	3
0.96	t	3

Spectrum 9:

δ	splitting	integration
9.57	s	1
6.30	s	1
6.00	s	1
1.84	s	3

Spectrum 10:

δ	splitting	integration
9.83	t	1
2.27	d	2
1.07	s	9

Spectrum 11:

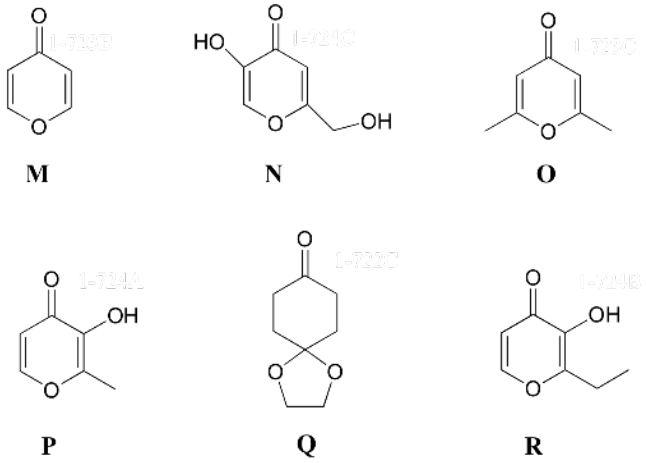
δ	splitting	integration
9.75	t	1
2.30	dd	2
2.21	m	1
0.98	d	6

Spectrum 12:

δ	splitting	integration
8.08	s	1
4.13	t	2
1.70	m	2
0.96	t	3

P5.8: Match the ^{1}H-NMR spectra 13-18 below to their corresponding structures M-R .

Structures:



Spectrum 13:

δ	splitting	integration
8.15	d	1
6.33	d	1

Spectrum 14: 1-723C (structure O)

δ	splitting	integration
6.05	s	1
2.24	s	3

Spectrum 15:

δ	splitting	integration
8.57	s (b)	1
7.89	d	1
6.30	d	1
2.28	s	3

Spectrum 16:

δ	splitting	integration
9.05	s (b)	1
8.03	s	1
6.34	s	1
5.68	s (b)	1
4.31	s	2

Spectrum 17:

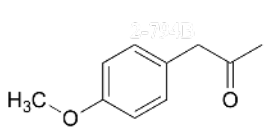
δ	splitting	integration
7.76	d	1
7.57	s (b)	1
6.44	d	1
2.78	q	2
1.25	t	3

Spectrum 18:

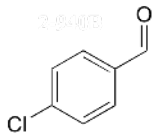
δ	splitting	integration
4.03	s	1
2.51	t	1
2.02	t	1

P5.9: Match the ^{1}H-NMR spectra 19-24 below to their corresponding structures S-X.

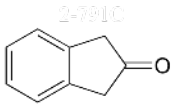
Structures:



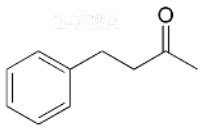
S



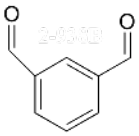
T



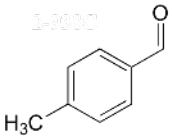
U



V



W



X

Spectrum 19:

δ	splitting	integration
9.94	s	1
7.77	d	2
7.31	d	2
2.43	s	3

Spectrum 20:

δ	splitting	integration
10.14	s	2
8.38	s	1
8.17	d	2
7.75	t	1

Spectrum 21:

δ	splitting	integration
9.98	s	1
7.81	d	2
7.50	d	2

Spectrum 22:

δ	splitting	integration
7.15-7.29	m	2.5
2.86	t	1
2.73	t	1
2.12	s	1.5

Spectrum 23:

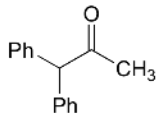
δ	splitting	integration
7.10	d	1
6.86	d	1
3.78	s	1.5
3.61	s	1
2.12	s	1.5

Spectrum 24:

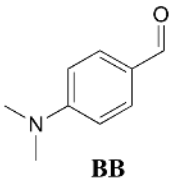
δ	splitting	integration
7.23-7.30	m	1
3.53	s	1

P5.10: Match the ^{1}H-NMR spectra 25-30 below to their corresponding structures AA-FF.

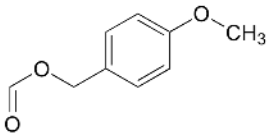
Structures:



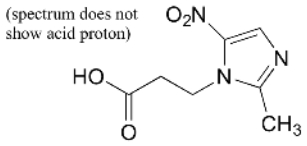
AA



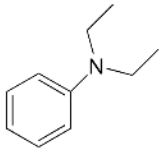
BB



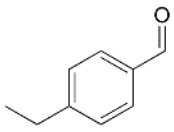
CC



DD



EE



FF

Spectrum 25:

δ	splitting	integration
9.96	s	1
7.79	d	2
7.33	d	2
2.72	q	2
1.24	t	3

Spectrum 26:

δ	splitting	integration
9.73	s	1
7.71	d	2
6.68	d	2
3.06	s	6

Spectrum 27:

δ	splitting	integration
7.20-7.35	m	10
5.12	s	1
2.22	s	3

Spectrum 28:

δ	splitting	integration
8.08	s	1
7.29	d	2
6.87	d	2
5.11	s	2
3.78	s	3

Spectrum 29:

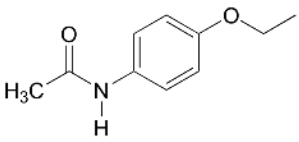
δ	splitting	integration
7.18	d	1
6.65	m	1.5
3.2	q	2
1.13	t	3

Spectrum 30:

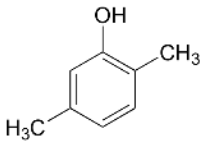
δ	splitting	integration
8.32	s	1
4.19	t	2
2.83	t	2
2.40	s	3

P5.11: Match the ^{1}H-NMR spectra 31-36 below to their corresponding structures GG-LL

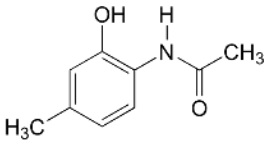
Structures:



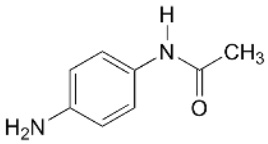
GG



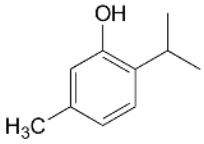
HH



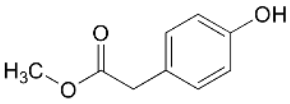
II



JJ



KK



LL

Spectrum 31:

δ	splitting	integration
6.98	d	1
6.64	d	1
6.54	s	1
4.95	s	1
2.23	s	3
2.17	s	3

Spectrum 32:

δ	splitting	integration
7.08	d	1
6.72	d	1
6.53	s	1
4.81	s	1
3.15	7-tet	1
2.24	s	3
1.22	d	6

Spectrum 33:

δ	splitting	integration
7.08	d	2
6.71	d	2
6.54	s	1
3.69	s	3
3.54	s	2

Spectrum 34:

δ	splitting	integration
9.63	s	1
7.45	d	2
6.77	d	2
3.95	q	2
2.05	s	3
1.33	t	3

Spectrum 35:

δ	splitting	integration
9.49	s	1
7.20	d	2
6.49	d	2
4.82	s	2
1.963	s	3

Spectrum 36:

δ	splitting	integration
9.58	s(b)	1
9.31	s	1
7.36	d	1
6.67	s	1
6.55	d	1
2.21	s	3
2.11	s	3

P5.12: Use the NMR data given to deduce structures.

a) Molecular formula: C_5H_8O

^{1}H-NMR:

δ	splitting	integration
9.56	s	1
6.25	d (J~1 Hz)	1
5.99	d (J~1 Hz)	1
2.27	q	2
1.18	t	3

^{13}C-NMR

δ	DEPT
194.60	CH
151.77	C
132.99	CH_2
20.91	CH_2
11.92	CH_3

b) Molecular formula: $C_7H_{14}O_2$

^{1}H-NMR:

δ	splitting	integration
3.85	d	2
2.32	q	2
1.93	m	1
1.14	t	3
0.94	d	6

^{13}C-NMR

δ	DEPT
174.47	C
70.41	CH_2
27.77	CH
27.64	CH_2
19.09	CH_3
9.21	CH_3

c) Molecular formula: $C_5H_{12}O$

^{1}H-NMR:

δ	splitting	integration
3.38	s	2H
2.17	s	1H
0.91	s	9H

^{13}C-NMR

δ	DEPT
73.35	CH_2
32.61	C
26.04	CH_3

d) Molecular formula: $C_{10}H_{12}O$

^{1}H-NMR:

δ	splitting	integration
7.18-7.35	m	2.5
3.66	s	1
2.44	q	1
1.01	t	1.5

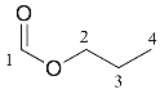
^{13}C-NMR

δ	DEPT
208.79	C
134.43	C
129.31	CH
128.61	CH
126.86	CH
49.77	CH_2
35.16	CH_2
7.75	CH_3

P5.13:

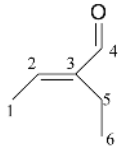
^{13}C-NMR data is given for the molecules shown below. Complete the peak assignment column of each NMR data table.

a)



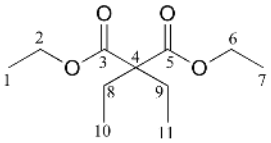
δ	DEPT	carbon #
161.12	CH	
65.54	CH_2	
21.98	CH_2	
10.31	CH_3	

b)



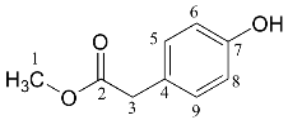
δ	DEPT	carbon #
194.72	C	
149.10	C	
146.33	CH	
16.93	CH_2	
14.47	CH_3	
12.93	CH_3	

c)



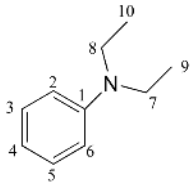
δ	DEPT	carbon #
171.76	C	
60.87	CH_2	
58.36	C	
24.66	CH_2	
14.14	CH_3	
8.35	CH_3	

d)



δ	DEPT	carbon #
173.45	C	
155.01	C	
130.34	CH	
125.34	C	
115.56	CH	
52.27	CH_3	
40.27	CH_2	

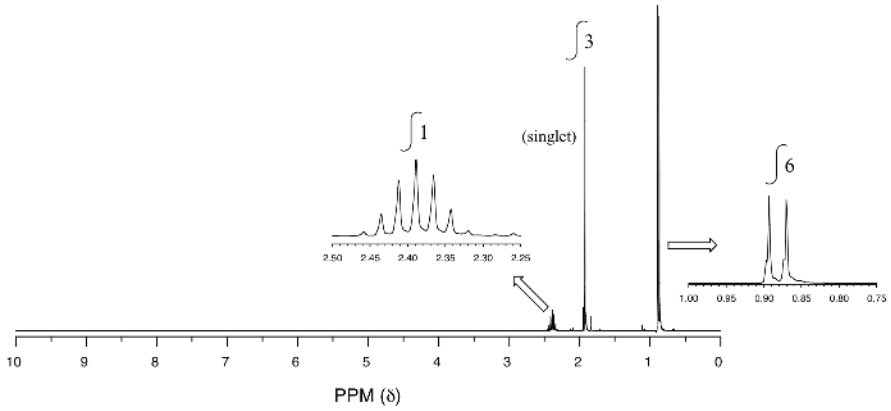
e)



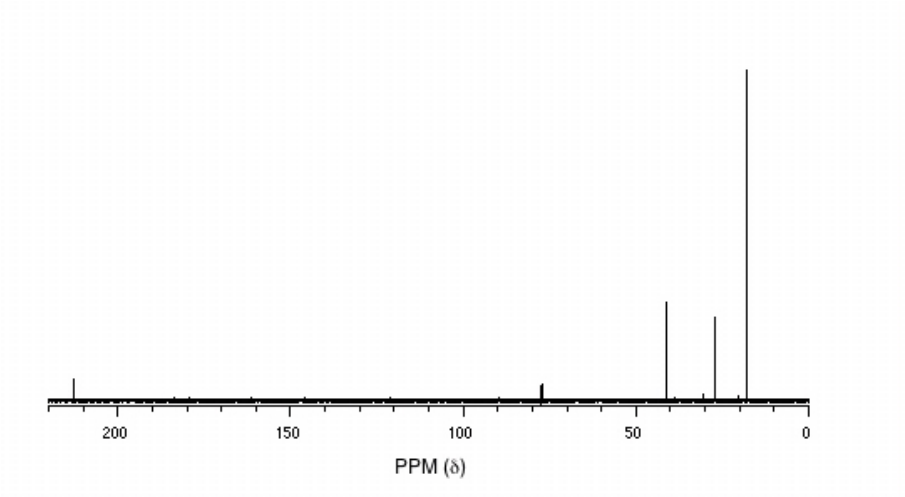
δ	DEPT	carbon #
147.79	C	
129.18	CH	
115.36	CH	
111.89	CH	
44.29	CH_2	
12.57	CH_3	

P5.14: You obtain the following data for an unknown sample. Deduce its structure.

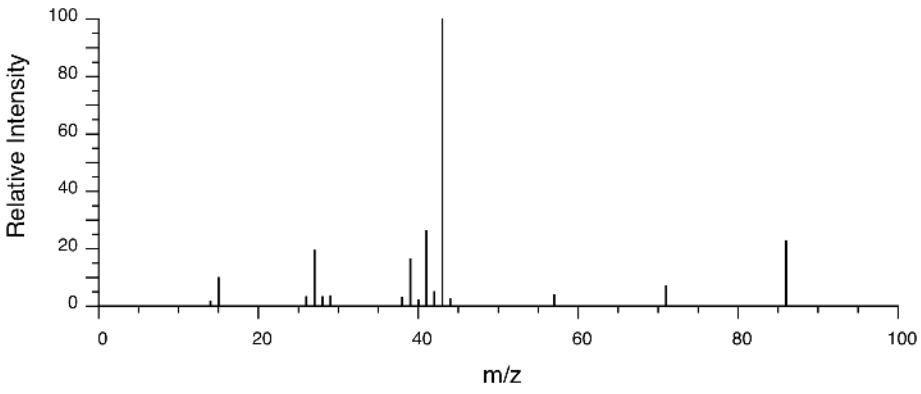
^{1}H-NMR:



^{13}C-NMR:



Mass Spectrometry:



P5.15: You take a ^{1}H-NMR spectrum of a sample that comes from a bottle of 1-bromopropane. However, you suspect that the bottle might be contaminated with 2-bromopropane. The NMR spectrum shows the following peaks:

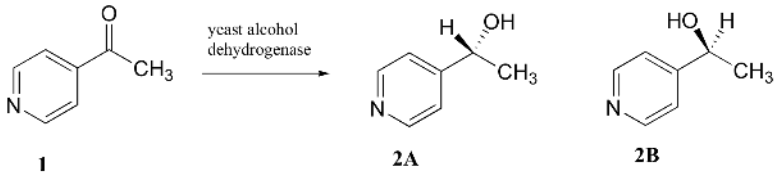
δ	splitting	integration
4.3	septet	0.0735
3.4	triplet	0.661
1.9	sextet	0.665
1.7	doublet	0.441
1.0	triplet	1.00

How badly is the bottle contaminated? Specifically, what percent of the molecules in the bottle are 2-bromopropane?

Challenge problems

C5.1: All of the ^{13}C-NMR spectra shown in this chapter include a signal due to $CDCl_3$, the solvent used in each case. Explain the splitting pattern for this signal.

C5.2: Researchers wanted to investigate a reaction which can be catalyzed by the enzyme alcohol dehydrogenase in yeast. They treated 4'-acylpyridine (1) with living yeast, and isolated the alcohol product(s) (some combination of 2A and 2B).

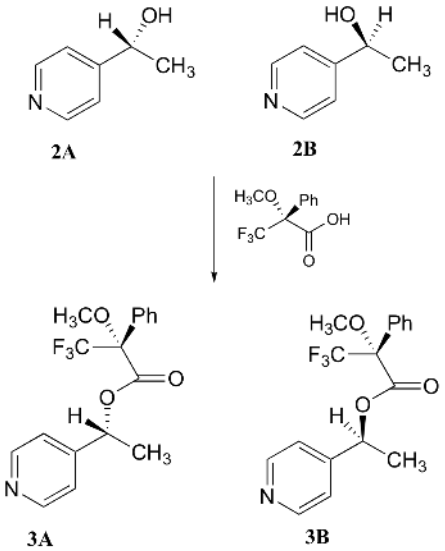


1 **2A** **2B**

a) Will the products 2A and 2B have identical or different ^{1}H-NMR spectra? Explain.

b) Suggest a ^{1}H-NMR experiment that could be used to determine what percent of starting material (1) got turned into product (2A and 2B).

c) With purified 2A/2B, the researchers carried out the subsequent reaction shown below to make 3A and 3B, known as 'Mosher's esters'. Do 3A and 3B have identical or different ^{1}H-NMR spectra? Explain.



2A **2B** **3A** **3B**

d) Explain, very specifically, how the researchers could use ^{1}H-NMR to determine the relative amounts of 2A and 2B formed in the reaction catalyzed by yeast enzyme.

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13.9: ^{13}C NMR SPECTROSCOPY - SIGNAL AVERAGING AND FT-NMR

OBJECTIVES

After completing this section, you should be able to

- Understand why the nuclei C NMR looks at is ^{13}C and not ^{12}C.
- Know why more scans are needed in ^{13}C NMR than ^{1}H NMR.

Most of what we have learned about ^{1}H-NMR spectroscopy also applies to ^{13}C-NMR, although there are several important differences.

SIGNAL STRENGTH IN ^{13}C-NMR SPECTROSCOPY

The ^{12}C isotope of carbon - which accounts for more than 98% of the carbons in organic molecules - does not have a nuclear magnetic moment, and thus is NMR-inactive. Fortunately for organic chemists, however, the ^{13}C isotope, which accounts for 1.1% of the remaining carbon atoms in nature, has a magnetic moment just like protons.

The magnetic moment of a ^{13}C nucleus is much weaker than that of a proton, meaning that NMR signals from ^{13}C nuclei are inherently much weaker than proton signals. This, combined with the low natural abundance of ^{13}C, means that it is much more difficult to observe carbon signals and there is a much lower signal-to-noise ratio than in ^{1}H NMR. Therefore, more concentrated samples are required to generate a useful spectrum, and often the data from hundreds of scans must be averaged in order to bring the signal-to-noise ratio down to acceptable levels. This type of **signal averaging** works since background noise in a spectrum is typically random while the signal caused by the ^{13}C nuclei is not. Therefore if the spectra from multiple scans is averaged, the noise gets closer to 0 while the signal stays the same, increasing the signal-to-noise ratio.

FOURIER TRANSFORM (FT) NMR

Earlier versions of NMR instruments used variable magnetic fields which required recording of each signal in the spectrum sequentially which is called continuous wave (CW) NMR. The **Fourier Transform** allows recording of all signals simultaneously by introducing a short pulse of all RF frequencies that cause resonance for a given nucleus. This complex signal is then manipulated through complex mathematical processing that creates an NMR spectrum that looks similar to a CW spectrum, but in much less time.

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13.10: CHARACTERISTICS OF ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

- Determine the number of distinct C atoms in a molecule.
- Use the chemical shifts table to determine functional groups present in a molecule.
- Assign a chemical shift to each carbon in a given molecule.

THE BASICS OF ^{13}C-NMR SPECTROSCOPY

Unlike ^{1}H-NMR signals, the area under a ^{13}C-NMR signal cannot be used to determine the number of carbons to which it corresponds. This is because the signals for some types of carbons are inherently weaker than for other types – peaks corresponding to carbonyl carbons, for example, are much smaller than those for methyl or methylene (CH_2) peaks. Peak integration is generally not useful in ^{13}C-NMR spectroscopy, except when investigating molecules that have been enriched with ^{13}C isotope.

The resonance frequencies of ^{13}C nuclei are lower than those of protons in the same applied field - in a 7.05 Tesla instrument, protons resonate at about 300 MHz, while carbons resonate at about 75 MHz. This is fortunate, as it allows us to look at ^{13}C signals using a completely separate 'window' of radio frequencies. This means you will only see the ^{13}C nuclei in a ^{13}C NMR experiment like in the ^{1}H NMR experiments we just looked at, we only saw hydrogens. Just like in ^{1}H-NMR, the standard used in ^{13}C-NMR experiments to define the 0 ppm point is tetramethylsilane (TMS), although of course in ^{13}C-NMR it is the signal from the four equivalent *carbons* in TMS that serves as the standard. Chemical shifts for ^{13}C nuclei in organic molecules are spread out over a much wider range than for protons – up to 200 ppm for ^{13}C compared to 12 ppm for protons (see Table 3 for a list of typical ^{13}C-NMR chemical shifts). This is also fortunate, because it means that the signal from each carbon in a compound can almost always be seen as a distinct peak, without the overlapping that often plagues ^{1}H-NMR spectra. The chemical shift of a ^{13}C nucleus is influenced by essentially the same factors that influence a proton's chemical shift: bonds to electronegative atoms and diamagnetic anisotropy effects tend to shift signals downfield (higher resonance frequency). In addition, sp^2 hybridization results in a large downfield shift. The ^{13}C-NMR signals for carbonyl carbons are generally the furthest downfield (170-220 ppm), due to both sp^2 hybridization and to the double bond to oxygen.

EXAMPLE 13.10.1

a. How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 5.1?
b. How many sets of non-equivalent carbons are there in:
   - toluene
   - 2-pentanone
   - para-xylene
   - triclosan

(all structures are shown earlier in this chapter)

Solution

a

a) 8 signals (each carbon is different)

b) 11 signals (the two enantiotopic CH_2CH_3 groups are NMR-equivalent)

c) 6 signals (each carbon is different)

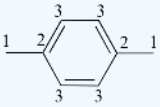
d) 16 signals (the fluorobenzene group only contributes 4 signals due to symmetry)

b

a) 5 signals

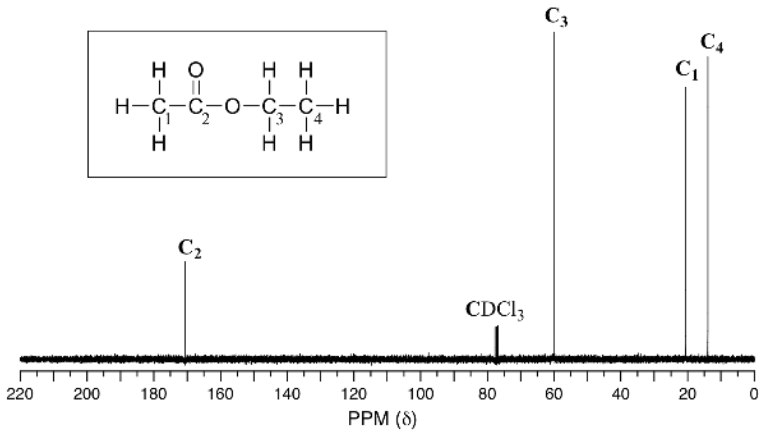
b) 5 signals

c) 3 signals

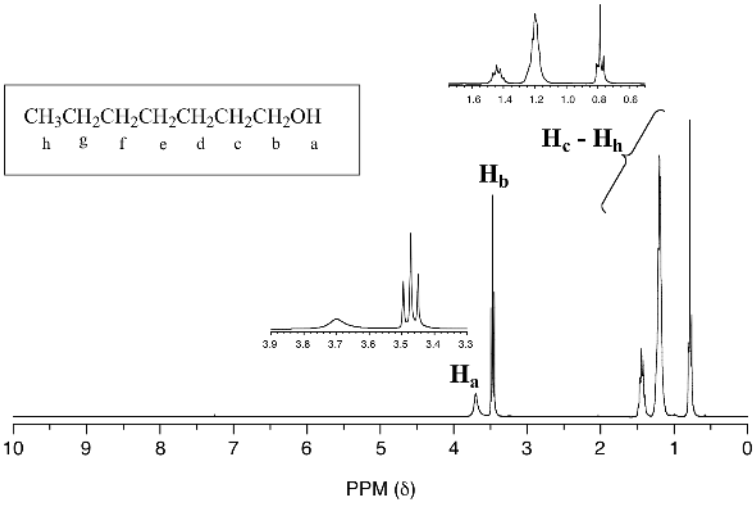


d) 6 signals

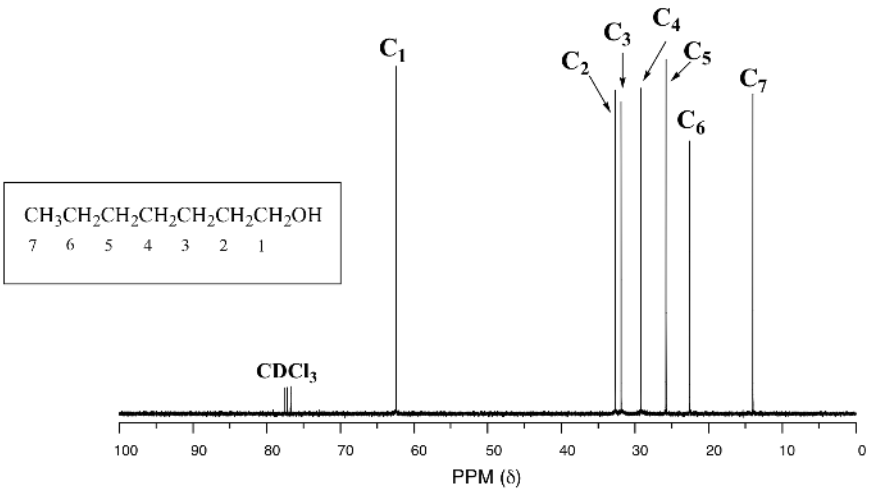
Because of the low natural abundance of ^{13}C nuclei, it is very unlikely to find two ^{13}C atoms near each other in the same molecule, and thus *we do not see spin-spin coupling between neighboring carbons in a ^{13}C-NMR spectrum*. There is, however, **heteronuclear coupling** between ^{13}C carbons and the hydrogens to which they are bound. Carbon-proton coupling constants are very large, on the order of 100 – 250 Hz. For clarity, chemists generally use a technique called **broadband decoupling**, which essentially 'turns off' C-H coupling, resulting in a spectrum in which all carbon signals are singlets. Below is the proton-decoupled^{13}C-NMR spectrum of ethyl acetate, showing the expected four signals, one for each of the carbons.



One of the greatest advantages of ^{13}C-NMR compared to ^{1}H-NMR is the breadth of the spectrum - recall that carbons resonate from 0-220 ppm relative to the TMS standard, as opposed to only 0-12 ppm for protons. Because of this, ^{13}C signals rarely overlap, and we can almost always distinguish separate peaks for each carbon, even in a relatively large compound containing carbons in very similar environments. In the proton spectrum of 1-heptanol, for example, only the signals for the alcohol proton (H_a) and the two protons on the adjacent carbon (H_b) are easily analyzed. The other proton signals overlap, making analysis difficult.



In the ^{13}C spectrum of the same molecule, however, we can easily distinguish each carbon signal, and we know from this data that our sample has seven non-equivalent carbons. (Notice also that, as we would expect, the chemical shifts of the carbons get progressively smaller as they get farther away from the deshielding oxygen.)



This property of ^{13}C-NMR makes it very helpful in the elucidation of larger, more complex structures.

^{13}C NMR CHEMICAL SHIFTS

The Carbon NMR is used for determining functional groups using characteristic shift values. ^{13}C chemical shifts are greatly affected by electronegative effects. If a H atom in an alkane is replaced by substituent X, electronegative atoms (O, N, halogen), ^{13}C signals for nearby carbons shift downfield (left; increase in ppm) with the effect diminishing with distance from the electron withdrawing group. Figure 13.11.1 shows typical ^{13}C chemical shift regions of the major chemical class.

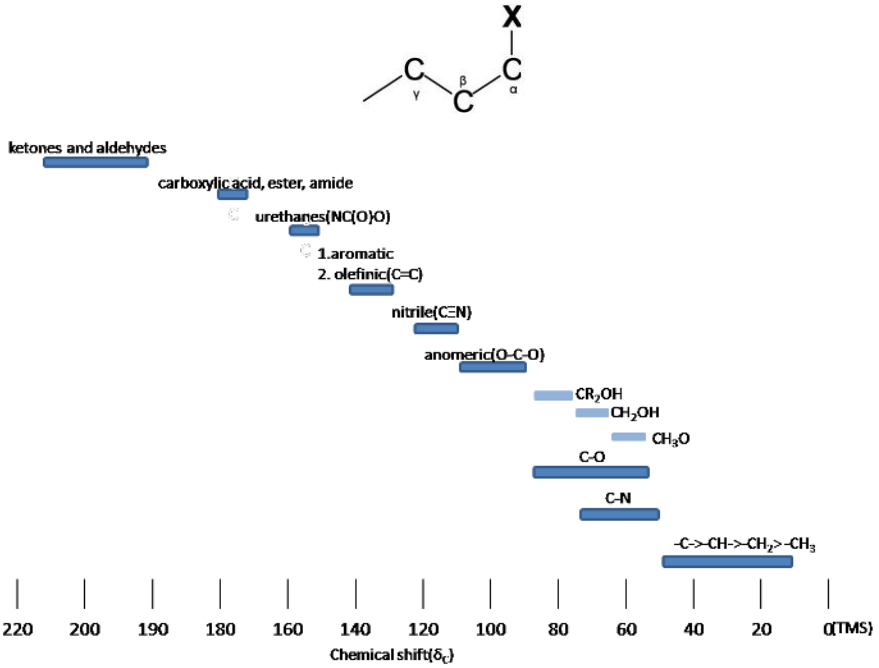


Figure **13.10.1**: ^{13}C Chemical shift range for organic compound

SPIN-SPIN SPLITTING

Comparing the ^{1}H NMR, there is a big difference thing in the ^{13}C NMR. The ^{13}C-^{13}Cspin-spin splitting rarely exit between adjacent carbons because ^{13}C is naturally lower abundant (1.1%)

- **^{13}C-^{1}H Spin coupling**: ^{13}C-^{1}H Spin coupling provides useful information about the number of protons attached a carbon atom. In case of one bond coupling ($^{1}J_{CH}$), -CH, -CH_2, and CH_3 have respectively doublet, triplet, quartets for the ^{13}C resonances in the spectrum. However, ^{13}C-^{1}H Spin coupling has an disadvantage for ^{13}C spectrum interpretation. ^{13}C-^{1}H Spin coupling is hard to analyze and reveal structure due to a forest of overlapping peaks that result from 100% abundance of ^{1}H.
- **Decoupling**: Decoupling is the process of removing ^{13}C-^{1}H coupling interaction to simplify a spectrum and identify which pair of nuclei is involved in the J coupling. The decoupling ^{13}C spectra shows only one peak(singlet) for each unique carbon in

the molecule (Fig 13.11.2). Decoupling is performed by irradiating at the frequency of one proton with continuous low-power RF.

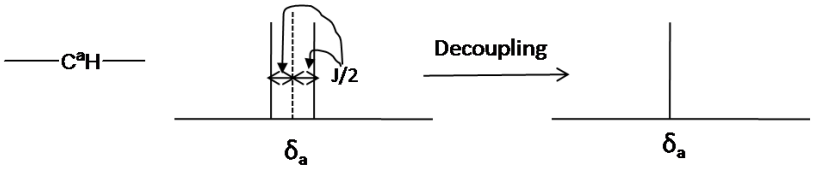


Figure **13.10.2**: Decoupling in the ^{13}C NMR

SUMMARY

^{13}C NMR (Carbon-13 Nuclear Magnetic Resonance) Spectroscopy is a powerful analytical technique used to study the structure and connectivity of organic molecules. Unlike proton NMR, which detects hydrogen nuclei, ^{13}C NMR specifically targets the carbon nuclei within a molecule. In ^{13}C NMR spectroscopy, carbon atoms resonate at characteristic frequencies based on their local chemical environment, which is influenced by neighboring atoms and functional groups. These resonances appear as peaks in the NMR spectrum, providing valuable information about the types of carbon atoms present and their surroundings. By analyzing the chemical shifts, intensities, and coupling patterns of these peaks, chemists can deduce crucial structural details such as the number and types of carbon atoms, their connectivity, and the presence of certain functional groups. This information is essential for determining the molecular structure and understanding chemical properties and reactivities.

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13.11: DEPT ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

- Understand why the peaks do not have splitting like in ^{1}H NMR.
- Using DEPT, distinguish whether a methyl (CH_3), methylene (CH_2), methine (CH) or quarternary C is present in the molecule and how many.
- Propose a structure based on ^{13}C spectral data.

DEPT (Distortionless Enhancement by Polarization Transfer) ^{13}C NMR Spectroscopy is a powerful technique used in organic chemistry to elucidate the structure of organic molecules. Unlike traditional ^{13}C NMR spectroscopy, which provides only basic information about carbon environments, DEPT enhances signals from specific types of carbon atoms, allowing for more detailed analysis. DEPT works by selectively enhancing signals from three types of carbon atoms: methyl (CH_3), methylene (CH_2), and quaternary carbons (C with no attached hydrogens). This enhancement is achieved through a series of pulse sequences that manipulate the nuclear spins of carbon atoms, resulting in distinct peaks in the NMR spectrum corresponding to each carbon type.

DEPT experiments are used for distinguishing between a CH_3 group (methyl), a CH_2 group (methylene), and a CH group (methine). The proton pulse is set at 45°, 90°, or 135° in the three separate experiments. The different pulses depend on the number of protons attached to a carbon atom. Figure **13.11.1** is an example about DEPT spectrum of n-isobutlybutrate.

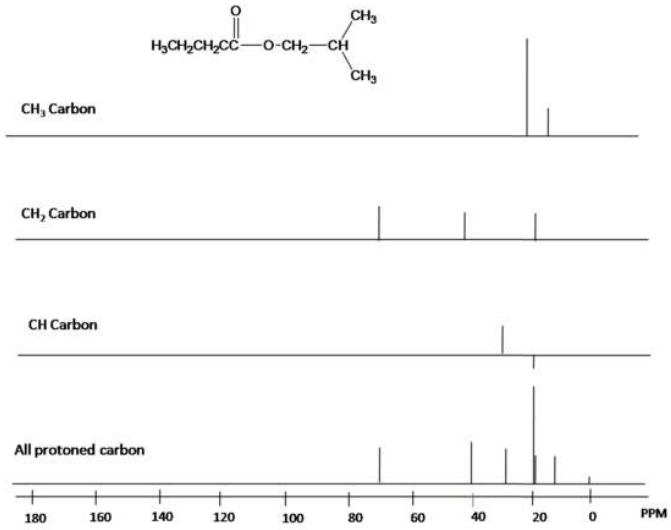


Figure **13.11.1**: DEPT spectrum of n-isobutlybutrate.

While broadband decoupling results in a much simpler spectrum, useful information about the presence of neighboring protons is lost. However, another modern NMR technique called DEPT (Distortionless Enhancement by Polarization Transfer) allows us to determine how many hydrogens are bound to each carbon. For example, a DEPT experiment tells us that the signal at 171 ppm in the ethyl acetate spectrum is a quaternary carbon (no hydrogens bound, in this case a carbonyl carbon), that the 61 ppm signal is from a methylene (CH_2) carbon, and that the 21 ppm and 14 ppm signals are both methyl (CH_3) carbons. The details of the DEPT experiment are beyond the scope of this text, but DEPT information will often be provided along with ^{13}C spectral data in examples and problems.

Below are two more examples of ^{13}C NMR spectra of simple organic molecules, along with the type of substitution for that carbon which was obtained from a DEPT experiment.

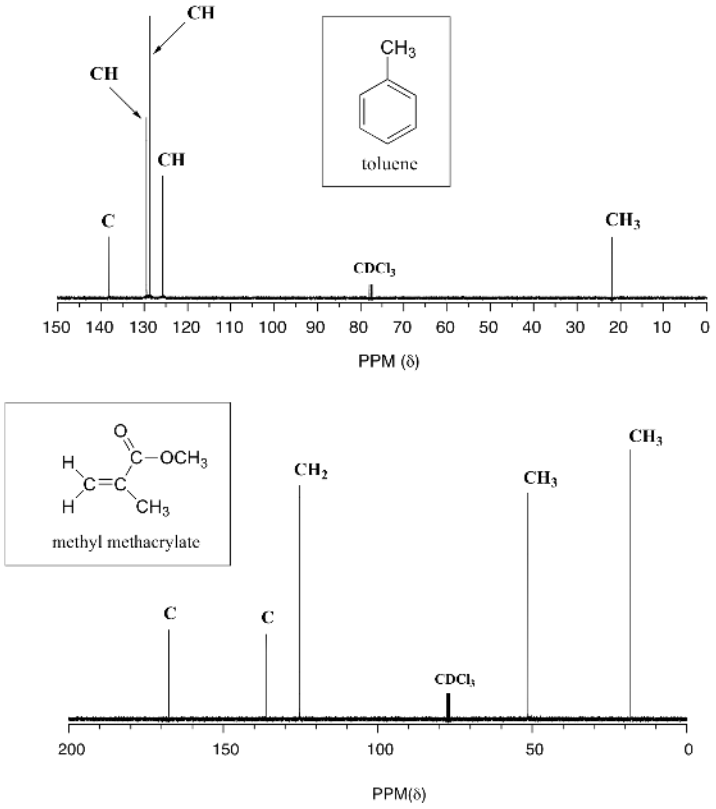
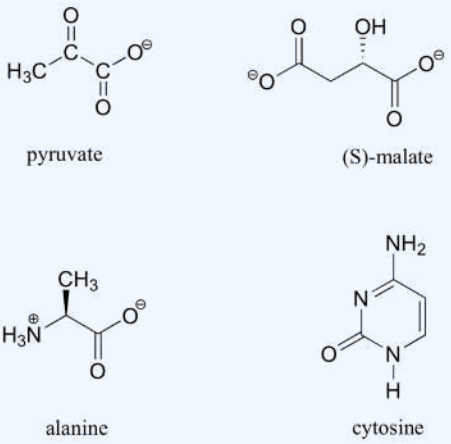


Figure **13.11.2**: ^{13}C NMR spectra of toluene (left) and meth methacryalate (right)

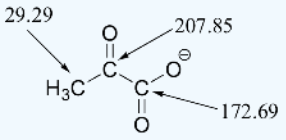
EXERCISE 13.11.1

^{13}C-NMR (and DEPT) data for some common biomolecules are shown below (data are from the Aldrich Library of ^{1}H and ^{13}C NMR). Match the NMR data to the correct structure, and make complete peak assignments.

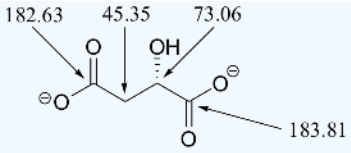
- spectrum a: 168.10 ppm (C), 159.91 ppm (C), 144.05 ppm (CH), 95.79 ppm (CH)
- spectrum b: 207.85 ppm (C), 172.69 ppm (C), 29.29 ppm (CH_3)
- spectrum c: 178.54 ppm (C), 53.25 ppm (CH), 18.95 ppm (CH_3)
- spectrum d: 183.81 ppm (C), 182. 63 ppm (C), 73.06 ppm (CH), 45.35 ppm (CH_2)



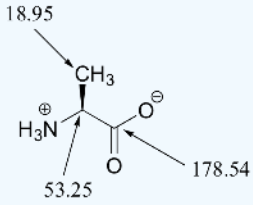
Answer



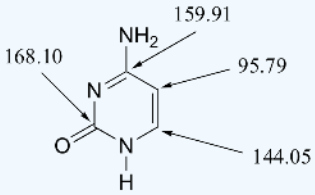
pyruvate: spectrum b



(S)-malate: spectrum d



alanine (spectrum c)



cytosine (spectrum a)

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13.12: USES OF ^{13}C NMR SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to use data from ^{13}C NMR spectra to distinguish between two (or more) possible structures for an unknown organic compound.

FEATURES OF A ^{13}C NMR SPECTRUM

Butane shows two different peaks in the ^{13}C NMR spectrum, below. Note that: the chemical shifts of these peaks are not very different from methane. The carbons in butane are in a similar environment to the one in methane.

- there are two distinct carbons in butane: the methyl, or CH_3, carbon, and the methylene, or CH_2, carbon.
- the methyl carbon absorbs slightly upfield, or at lower shift, around 10 ppm.
- the methylene carbon absorbs at slightly downfield, or at higher shift, around 20 ppm.
- other factors being equal, methylene carbons show up at slightly higher shift than methyl carbons.

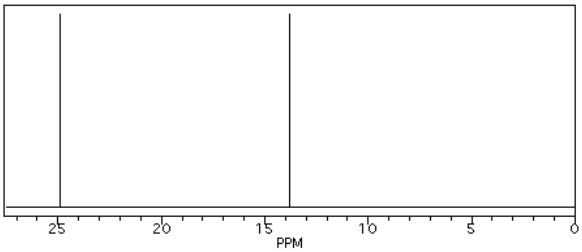


Figure **13.12.1**. *Simulated ^{13}C NMR spectrum of butane (showing only the upfield portion of the spectrum).*

In the ^{13}C NMR spectrum of pentane (below), you can see three different peaks, even though pentane just contains methyl carbons and methylene carbons like butane. As far as the NMR spectrometer is concerned, pentane contains three different kinds of carbon, in three different environments. That result comes from symmetry.

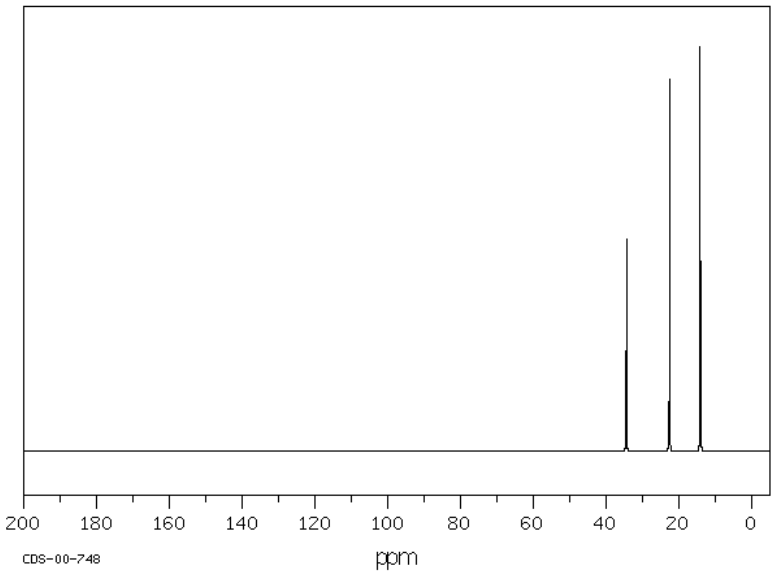


Figure **13.12.2**.*^{13}C NMR spectrum of pentane. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 15 August 2008)*

Symmetry is an important factor in spectroscopy. Nature says:

- atoms that are symmetry-inequivalent can absorb at different shifts.
- atoms that are symmetry-equivalent must absorb at the same shift.

To learn about symmetry, take a model of pentane and do the following:

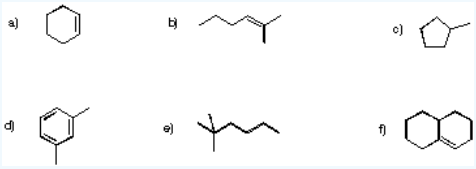
- make sure the model is twisted into the most symmetric shape possible: a nice "W"

- make sure the model is twisted into the most symmetric shape possible: a nice "W".
- choose one of the methyl carbons to focus on.
- rotate the model 180 degrees so that you are looking at the same "W" but from the other side.
- note that the methyl you were focusing on has simply switched places with the other methyl group. These two carbons are symmetry-equivalent via two-fold rotation.

By the same process, you can see that the second and fourth carbons along the chain are also symmetry-equivalent. However, the middle carbon is not; it never switches places with the other carbons if you rotate the model. There are three different sets of inequivalent carbons; these three groups are not the same as each other according to symmetry.

EXAMPLE 13.12.1

Determine how many inequivalent carbons there are in each of the following compounds. How many peaks do you expect in each ^{13}C NMR spectrum?



Practically speaking, there is only so much room in the spectrum from one end to the other. At some point, peaks can get so crowded together that you can't distinguish one from another. You might expect to see ten different peaks in eicosane, a twenty-carbon alkane chain, but when you look at the spectrum you can only see seven different peaks. That may be frustrating, because the experiment does not seem to agree with your expectation. However, you will be using a number of methods together to minimize the problem of misleading data.

Solution

a) Three inequivalent carbons/three peaks. There is a plane of symmetry that bisects the cyclohexene horizontally. The three different carbons are one of the alkene (C1), the CH_2 next to alkene (C3) and C4.

b) Six inequivalent carbons/six peaks. The two methyl groups attached to the alkene are identical.

c) Four inequivalent carbons/four peaks. This molecule has a plane of symmetry through the molecule, including the methyl group. The two carbons adjacent to the methyl group are equivalent (C2 and C5). C3 and C4 are also equivalent.

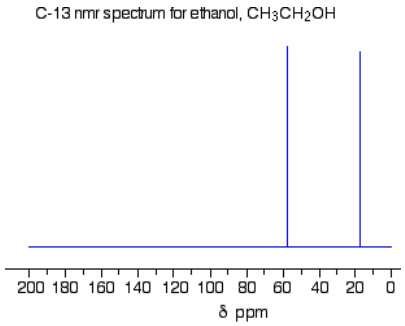
d) Five inequivalent carbons/five peaks. This molecule has a plane of symmetry that passes through the ring carbon between the two methyl groups. The two methyl carbons are identical. The two ring carbons with the methyl groups attached are identical (C1 and C3). C4 and C6 are also equivalent.

e) Six inequivalent carbons/six peaks. The three methyl groups at the end of the molecule are equivalent.

f) Ten inequivalent carbons/ten peaks. There is no symmetry for the carbons in this molecule.

THE ^{13}C NMR SPECTRUM FOR ETHANOL

This is a simple example of a ^{13}C NMR spectrum. Don't worry about the scale for now - we'll look at that in a minute.



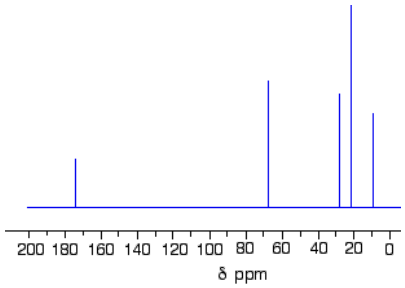
NOTE

Note: The NMR spectra on this page have been produced from graphs taken from the Spectral Data Base System for Organic Compounds (SDBS) at the National Institute of Materials and Chemical Research in Japan.

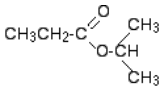
There are two peaks because there are two different environments for the carbons. The carbon in the CH_3 group is attached to 3 hydrogens and a carbon. The carbon in the CH_2 group is attached to 2 hydrogens, a carbon and an oxygen. The two lines are in different places in the NMR spectrum because they need different external magnetic fields to bring them in to resonance at a particular radio frequency.

THE ^{13}C NMR SPECTRUM FOR A MORE COMPLICATED COMPOUND

This is the ^{13}C NMR spectrum for 1-methylethyl propanoate (also known as isopropyl propanoate or isopropyl propionate).



This time there are 5 lines in the spectrum. That means that there must be 5 different environments for the carbon atoms in the compound. Is that reasonable from the structure?



If you count the carbon atoms, there are 6 of them. So why only 5 lines? In this case, two of the carbons are in exactly the same environment. They are attached to exactly the same things. Look at the two CH_3 groups on the right-hand side of the molecule.

You might reasonably ask why the carbon in the CH_3 on the left is not also in the same environment. Just like the ones on the right, the carbon is attached to 3 hydrogens and another carbon. But the similarity is not exact - you have to chase the similarity along the rest of the molecule as well to be sure.

The carbon in the left-hand CH_3 group is attached to a carbon atom which in turn is attached to a carbon with two oxygens on it - and so on down the molecule. That's not exactly the same environment as the carbons in the right-hand CH_3 groups. They are attached to a carbon which is attached to a single oxygen - and so on down the molecule. We'll look at this spectrum again in detail on the next page - and look at some more similar examples as well. This all gets easier the more examples you look at.

For now, all you need to realize is that each line in a ^{13}C NMR spectrum recognizes a carbon atom in one particular environment in the compound. If two (or more) carbon atoms in a compound have exactly the same environment, they will be represented by a single line.

NOTE

You might wonder why all this works, since only about 1% of carbon atoms are ^{13}C. These are the only ones picked up by this form of NMR. If you had a single molecule of ethanol, then the chances are only about 1 in 50 of there being one ^{13}C atom in it, and only about 1 in 10,000 of both being ^{13}C.

But you have got to remember that you will be working with a sample containing huge numbers of molecules. The instrument can pick up the magnetic effect of the ^{13}C nuclei in the carbon of the CH_3 group and the carbon of the CH_2 group even if they are in separate molecules. There's no need for them to be in the same one.

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13.S: STRUCTURE DETERMINATION - NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

13.1 Nuclear Magnetic Resonance Spectroscopy

- An applied magnetic field orients nuclei from random to aligned with or against the field. The nuclei absorb EM radiation of a frequency with energy that matches this energy gap.

13.2 The Nature of NMR Absorptions

- Nuclei in an applied field can align with the magnetic field (+1/2) or against the magnetic field (-1/2). The difference in the energy of these two states is the resonant frequency of that atom.
- To allow comparison between NMR spectra from instruments of differing field strength, the x-axis is reported as chemical shift, rather than frequency.
- **Chemical shift** is defined as the frequency of absorbance (in Hz) divided by the resonant frequency of the instrument (in MHz), thus the units are PPM (parts per million).
- Tetramethylsilane is used as a standard reference with its **chemical shift** set to 0 PPM (since these protons are highly shielded).
- Higher **chemical shifts** are called downfield, while lower shifts are called upfield.
- Nearby electrons shield the nuclei from the induced magnetic field, thus reducing their chemical shift. Atoms of higher electronegativity pull some of this electron density away from the nuclei causing increased **chemical shift**. This is called **deshielding**.

13.3 The Chemical Shift

- Pi electrons in a compound generate their own magnetic field that influences shielding of nearby atoms. This is most clearly exemplified by benzene protons that are highly deshielded (chemical shifts of 6.5-8 PPM).
- Protons that are involved in hydrogen bonding have variable chemical shifts and often do not absorb at one specific frequency, leading to broader peaks.

13.4 Chemical Shifts in ^{1}H NMR Spectroscopy

- Chemical shifts of protons are shifted upfield (higher ppm) by electronegative groups attached to the same carbon (and to a lesser effect when attached to nearby carbons).
- Aromatic protons appear between 6.5 and 8 ppm.
- Chemical shifts of O-H and N-H bonds vary with temperature and concentration.

13.5 Integration of ^{1}H NMR Absorptions - Proton Counting

- The are under a ^{1}H NMR signal is proportional to the number of hydrogens that caused the signal.

13.6 Spin-Spin Splitting in ^{1}H NMR Spectra

- ^{1}H signals are split into multiple peaks by neighboring H atoms whose spins can add to or subtract from the magnetic field.
- Spin-spin coupling yields n+1 peaks where n is the number of neighboring protons.
- Multiplets formed from spin-spin splitting follow specific symmetry based on the number of neighboring protons.
- The distance between peaks in a signal are called coupling constants.

13.7 ^{1}H NMR Spectroscopy and Proton Equivalence

- Equivalent protons (protons in identical electrical environments) only give 1 signal.
- To determine the number of ^{1}H NMR signals expected, symmetry of a molecule needs to be examined to find equivalent protons.
- Protons with different stereochemistry are not equivalent.
- Protons on chiral molecules that are diastereotopic (would create a diastereomer if replaced) are not equivalent.

13.8 More Complex Spin-Spin Splitting Patterns

- ^{1}H NMR signals can overlap making interpretation more difficult.
- Signals can distort where the peaks are not completely symmetrical in shape.
- When neighboring protons are nonequivalent, the coupling constant can be different leading to complex sets of peaks.
- Some complex multiplets can be identified such as a doublet of doublets, but others cannot and are referred to as multiplets.

13.9 Uses of ^{1}H NMR Spectroscopy

- ^{1}H NMR can help identify components of a mixture or determine which product was formed in a reaction.

13.10 ^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR

- NMR signals for ^{13}C NMR are much weaker than for ^{1}H, requiring higher sample concentration and averaging of many scans (hundreds or even thousands).
- **Signal averaging** increases signal-to-noise ratio when running multiple scans in NMR.
- **Fourier Transform** NMR allows the entire spectrum to be acquired at once, rather than one frequency at a time.

13.11 Characteristics of ^{13}C NMR Spectroscopy

- Chemical shifts for ^{13}C NMR are spread over a wider range of frequencies (0-200 ppm).
- Carbons with sp^2 hybridization are shifted far downfield
- Since it is exceptionally rare to have two ^{13}C atoms adjacent to one another, there is no spin-spin coupling in ^{13}C NMR.
- Coupling constants between carbons and hydrogens are large and make interpretation of ^{13}C NMR spectra difficult, so most spectra are run using broadband decoupling. This leads to all signals in ^{13}C NMR appearing as singlets.

13.12 DEPT ^{13}C NMR Spectroscopy

- ^{13}C NMR DEPT experiments are used to identify the number of attached hydrogens each carbon has.

13.13 Uses of ^{13}C NMR Spectroscopy

SKILLS TO MASTER

- Skill 13.1 Interpretation of ^{1}H NMR Spectra.
- Skill 13.2 Interpretation of ^{13}C NMR Spectra.

MEMORIZATION TASKS (MT)

MT 13.1 Memorize chemical shifts patterns in ^{1}H NMR.

MT 13.2 Memorize spin-spin splitting patterns

MT 13.3 Memorize chemical shift patterns in ^{13}C NMR.

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CHAPTER OVERVIEW

14: CONJUGATED COMPOUNDS AND ULTRAVIOLET SPECTROSCOPY

LEARNING OBJECTIVES

After you have completed Chapter 14, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the reactions discussed, along with those from previous chapters, when designing multi-step syntheses.
3. use the reactions and concepts discussed to solve road-map problems.
4. use ultraviolet-spectral data, in conjunction with other spectral data, to elucidate the structure of an unknown compound.
5. define, and use in context, the key terms introduced.

You have already studied the chemistry of compounds that contain one carbon-carbon double bond. In this chapter, you will focus your attention on compounds that contain two or more such bonds. In particular you will study the properties of those compounds that contain two carbon-carbon double bonds which are separated by one carbon-carbon single bond. These compounds are called “conjugated dienes.”

To understand the properties exhibited by conjugated dienes, you must first examine their bonding in terms of the molecular orbital theory introduced in Section 1.11. Then, you must learn how the products of a reaction are dependent on both thermodynamic and kinetic considerations. Which of these two factors is the most important can sometimes determine which of two possible products will predominate when a reaction is carried out under specific conditions. Although we shall not make extensive use of ultraviolet spectroscopy, this technique can often provide important information when conjugated compounds are being investigated. In general, ultraviolet spectroscopy is less useful than the other spectroscopic techniques introduced earlier.

14.0: Introduction
14.1: Stability of Conjugated Dienes- Molecular Orbital Theory
14.2: Electrophilic Additions to Conjugated Dienes- Allylic Carbocations
14.3: Kinetic vs. Thermodynamic Control of Reactions
14.4: The Diels-Alder Cycloaddition Reaction
14.5: Characteristics of the Diels-Alder Reaction
14.6: Diene Polymers- Natural and Synthetic Rubbers
14.7: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy
14.8: Interpreting Ultraviolet Spectra- The Effect of Conjugation
14.9: Conjugation, Color, and the Chemistry of Vision
14.S: Conjugated Compounds and Ultraviolet Spectroscopy (Summary)

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14.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to determine whether or not a molecule contains a conjugated system, given its Kekulé, condensed or shorthand formula.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

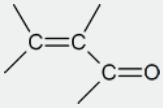
- conjugated diene
- conjugated double bonds
- diene
- enone
- polyene

STUDY NOTES

Conjugated double bonds are double bonds which are separated by one carbon-carbon single bond. Thus the double bonds in butadiene, $\ce{\sf{CH2=CH-CH=CH2}}$, are conjugated, and this compound is an example of a *conjugated diene*.

Just as the term *diene*indicates the presence of two carbon-carbon double bonds in a compound, so the term *polyene* is used to describe compounds containing many carbon-carbon double bonds.

An *enone* is a compound containing a carbon-carbon double bond (ene) and a carbonyl group (one). A conjugated enone contains the structural unit:



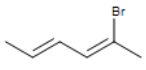
CONJUGATED DIENES

A diene is a hydrocarbon chain that has two double bonds that may or may not be adjacent to each other. This section focuses on the delocalization of π systems by comparing two neighboring double bonds. The arrangements of these double bonds can have varying affects on the compounds reactivity and stability.

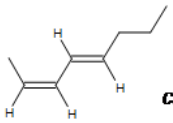
NAMING DIENES

First identify the longest chain containing both carbons with double bonds in the compound. Then give the lowest possible number for the location of the carbons with double bonds and any other functional groups present (remember when naming alkenes that some groups take priority such as alcohols). Do not forget stereochemistry or any other orientation of the double bond such as (E/Z,cis or trans).

Examples:



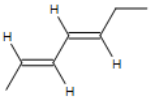
2-Bromo-2,4-hexadiene



***cis*-2-*trans*-4-octadiene**



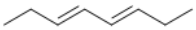
1,3-cyclopentadiene



***trans*-2,4-heptadiene**

CONJUGATED VS. NONCONJUGATED VS. CUMULATED DIENES

Conjugated dienes are two double bonds separated by a single bond



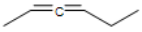
3,5-octadiene

Nonconjugated (Isolated) dienes are two double bonds are separated by more than one single bond.



2,5-heptadiene

Cumulated dienes (allenes) are two double bond connected to a carbon atom.



2,3-hexadiene

The reactivity of these molecules is substantially different from that of alkenes which have isolated C=C. These molecules are thus considered a different class of organic molecule. Conjugated dienes, especially butadiene, are very important materials in the production of rubber, and thus for the tires of our cars.

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14.1: STABILITY OF CONJUGATED DIENES- MOLECULAR ORBITAL THEORY

OBJECTIVES

After completing this section, you should be able to

1. write a reaction sequence to show a convenient method for preparing a given conjugated diene from an alkene, allyl halide, alkyl dihalide or alcohol (diol).
2. identify the reagents needed to prepare a given diene from one of the starting materials listed in Objective 1, above.
3. compare the stabilities of conjugated and non-conjugated dienes, using evidence obtained from hydrogenation experiments.
4. discuss the bonding in a conjugated diene, such as 1,3-butadiene, in terms of the hybridization of the carbon atoms involved.
5. discuss the bonding in 1,3-butadiene in terms of the molecular orbital theory, and draw a molecular orbital for this and similar compounds.

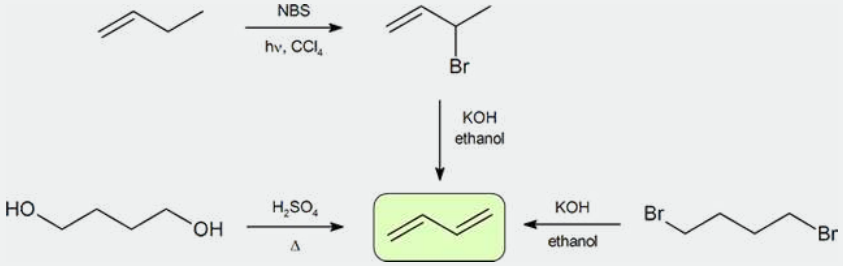
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- delocalized electrons
- node

STUDY NOTES

The two most frequent ways to synthesize conjugated dienes are dehydration of alcohols and dehydrohalogenation of organohalides, which were introduced in the preparation of alkenes (Section 8.1). The following scheme illustrates some of the routes to preparing a conjugated diene.



The formation of synthetic polymers from dienes such as 1,3-butadiene and isoprene is discussed in Section 14.6. Synthetic polymers are large molecules made up of smaller repeating units. You are probably somewhat familiar with a number of these polymers; for example, polyethylene, polypropylene, polystyrene and poly(vinyl chloride).

As the hydrogenation of 1,3-butadiene releases less than the predicted amount of energy, the energy content of 1,3-butadiene must be lower than we might have expected. In other words, 1,3-butadiene is more stable than its formula suggests.

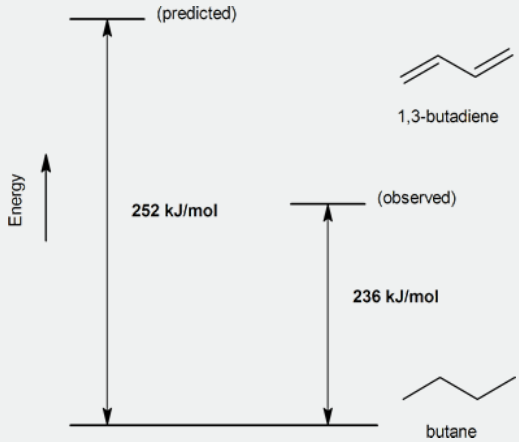


Figure 14.1: Energy diagram for the hydrogenation of 1,3-butadiene (not to scale).

Some university-level general chemistry courses do not introduce the subject of molecular orbitals. If you have taken such a course, or forgotten what is meant by the term "molecular orbital," combine a review of Section 1.11 with your study of this section.

CONJUGATED VS. NON-CONJUGATED DIENES

Dienes are compounds which contain two double bonds. These dienes can be non-conjugated (the two double bonds are separated by at least one sp^3 hybridized atom. Conjugated dienes have the two double bonds separated by a single bond. Conjugated dienes have properties and reactivity which are distinctly different than non-conjugated dienes. Determining if double bonds are conjugated represents an important skill in organic chemistry.



3,5-Octadiene
(Conjugated)



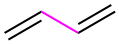
2,5-Octadiene
(Non-Conjugated)



1,3-Cyclohexadiene
(Conjugated)



1,4-Cyclohexadiene
(Non-Conjugated)



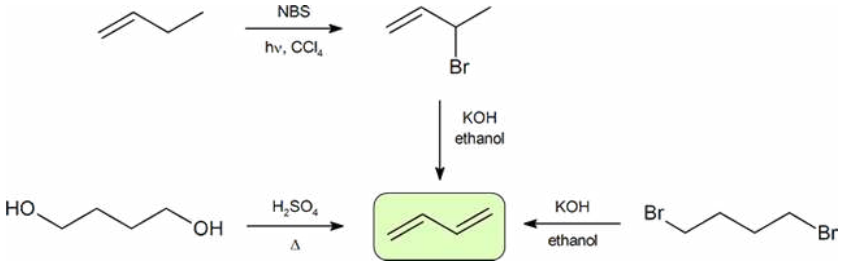
1,3-Butadiene
(Conjugated)



1,4-Pentadiene
(Non-Conjugated)

SYNTHESIS OF DIENES

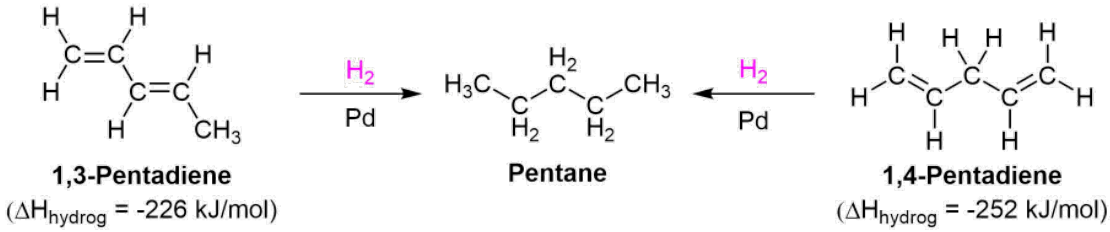
Conjugated dienes can be prepared using many of the methods used for the preparation of alkenes previously discussed (**Sections 11-7, 11-8, 11-9, and 11-10**). A convenient method starts with the free radical halogenation of the allylic carbon of an alkene using NBS. The resulting halide can then be reacted with a strong base to result in E2 elimination and create a diene product. The compound, 1,3-butadiene, is the simplest conjugated diene and has an important use in the synthesis of polymers which will be discussed in **Section 14.6**. Many simple dienes, such as 1,3-butadiene and isoprene, can be prepared industrially by the double dehydration of alcohols and the double dehydrohalogenation of organohalides.



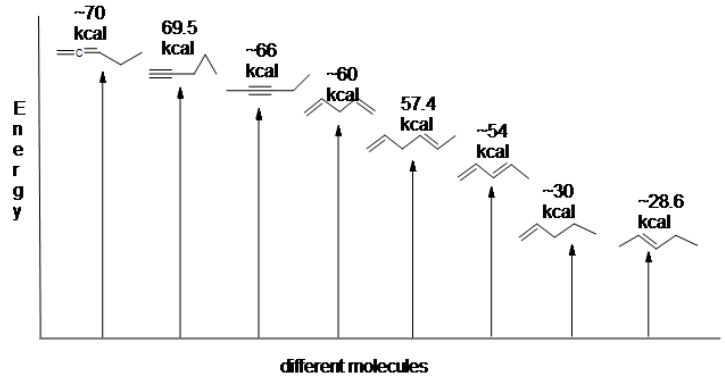
STABILITY OF CONJUGATED DIENES

Conjugated dienes are known to be more stable than non-conjugated dienes as shown by their experimentally determined heats of hydrogenation. In **Section 7-6**, it was shown that as alkenes become more stable, they contain less energy, and therefore release less heat during hydrogenation. Experiments have shown that conjugated dienes have a lower heat of hydrogenation (-226 kJ/mol) than non-conjugated dienes (-251 kJ/mol). Using the differences in heats of hydrogenation the stabilization energy in conjugated dienes can be estimate to be roughly 25 kJ/mol.

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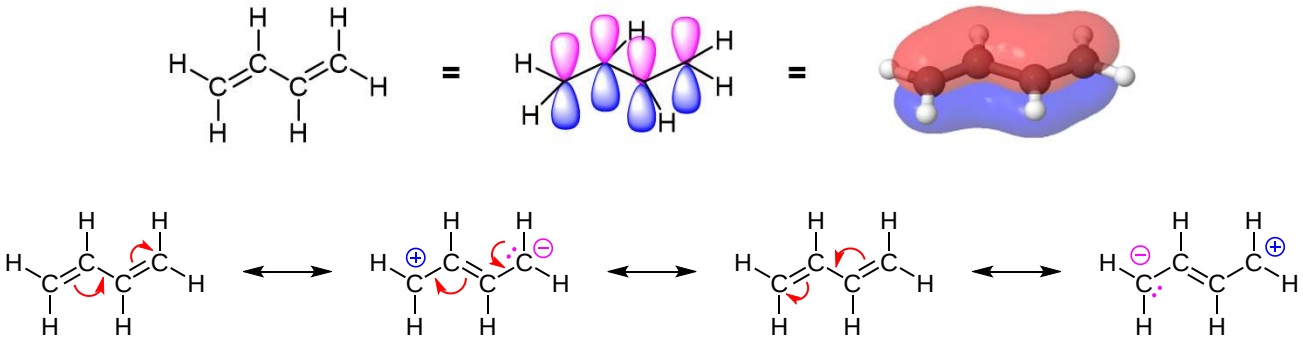


Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

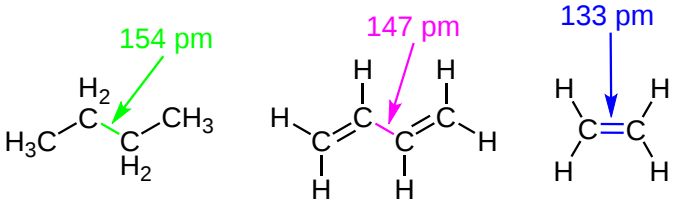


The stabilization of dienes by conjugation is less dramatic than the aromatic stabilization of benzene. Nevertheless, similar resonance and molecular orbital descriptions of conjugation may be written.

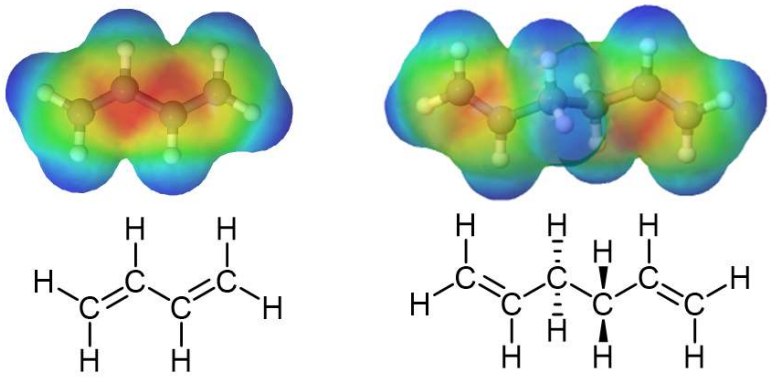
Each alkene carbon in 1,3 dienes are sp^2 hybridized and therefore have one unhybridized *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system which can be represented by the resonance forms shown below. This delocalization of charges stabilizes conjugated diene making them more stable than non-conjugated dienes.



Evidence of conjugation in 1,3 dienes is seen in the single bond being stronger and shorter (147 pm) than an ordinary alkane C-C bond (154 pm). The resonance hybrid of a 1,3-butadiene shows this bond to contain significant double bond character with its bond length being roughly the average of a single and double bond.



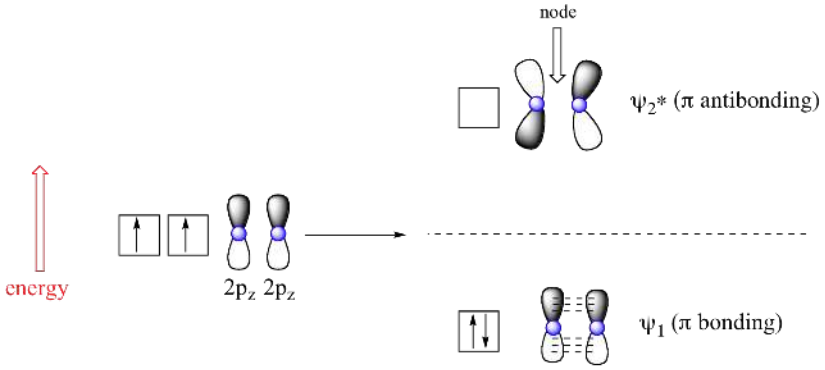
The delocalized electron density of a 1,3 diene can be seen when viewing an electrostatic potential maps. In conjugated dienes, it is observed that the pi electron density overlap (shown in red) is closer together and delocalized in conjugated dienes, while in non-conjugated dienes the pi electron density is located completely on the double bonds.



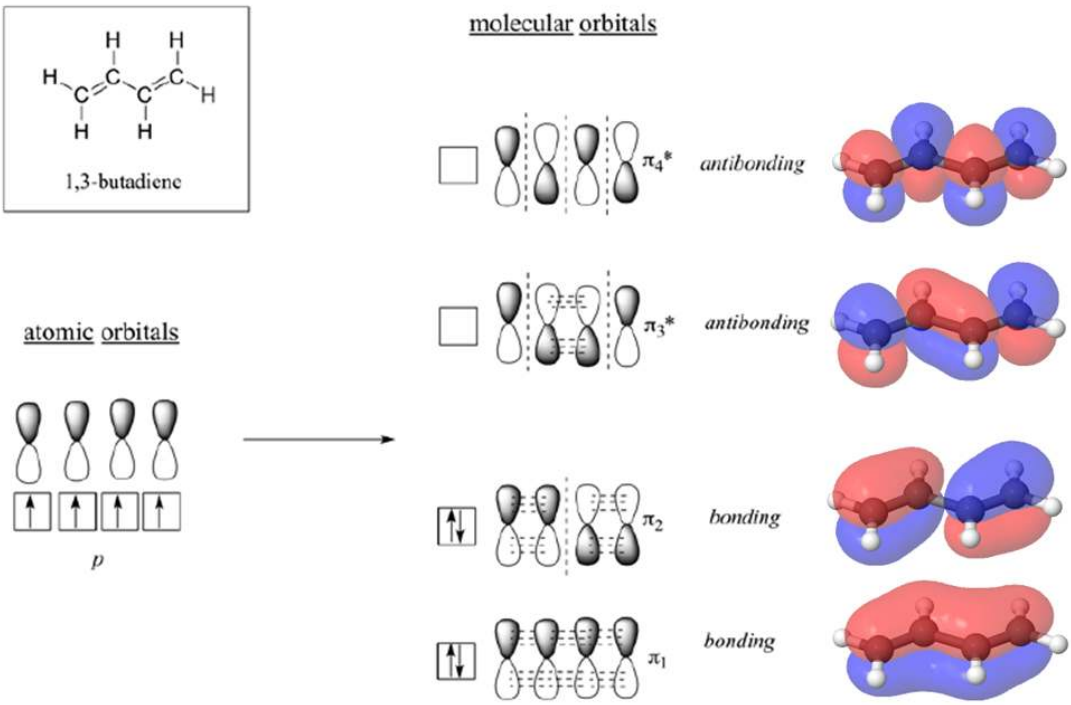
Conjugated **Non-Conjugated**

MOLECULAR ORBITALS OF 1,3 DIENES

According to MO theory discussed in section 1-11, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.



With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two anti-bonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



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14.2: ELECTROPHILIC ADDITIONS TO CONJUGATED DIENES- ALLYLIC CARBOCATIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
2. write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
3. write the mechanism for the addition of one mole equivalent of hydrogen halide to a conjugated diene, and hence account for the formation of 1,2- and 1,4-addition products.
4. explain the stability of allylic carbocations in terms of resonance.
5. draw the resonance contributors for a given allylic carbocation.
6. predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
7. predict which of the possible 1,2- and 1,4-addition products is likely to predominate when one mole equivalent of a hydrogen halide is reacted with a given conjugated diene.
8. use the concept of carbocation stability to explain the ratio of the products obtained when a given conjugated diene is reacted with one mole equivalent of hydrogen halide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

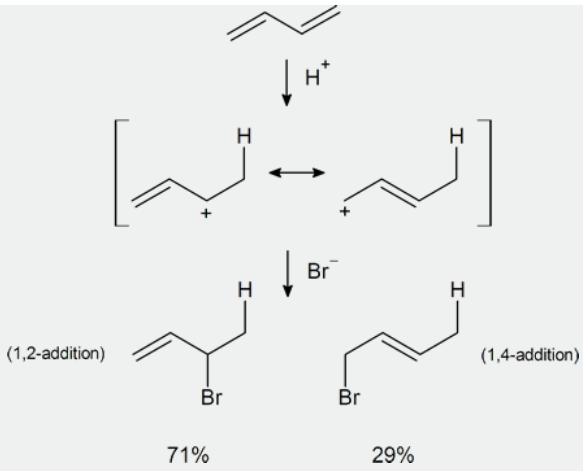
- 1,2-addition
- 1,4-addition

STUDY NOTES

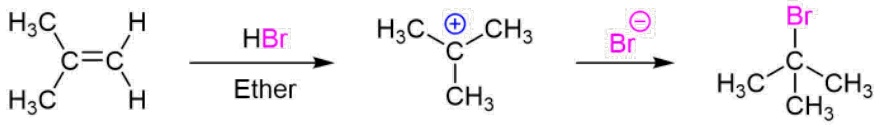
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon atoms. Thus in 1,2- and 1,4-additions to 2,4-hexadiene, the additions actually occur at carbons 2 and 3, and 2 and 5, respectively.

The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov’s rule, where the stability of the carbocation intermediate would increase: primary < secondary < tertiary. With conjugated dienes the allylic carbocation intermediately generated has different resonance forms. The following scheme represents the mechanism for the addition of HBr to 1,3-butadiene (at 0°C). Note the resonance contributors for the allylic carbocation intermediate and that the product resulting from the secondary cation is generated in higher yield than from the primary cation as you might expect from our discussions until now. However, in the next section you will see that the resulting product ratio can be drastically affected by a number of reaction conditions, including temperature.

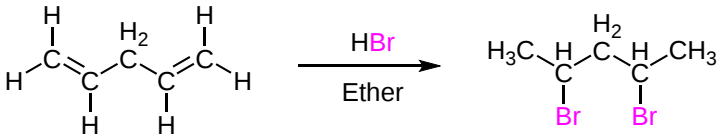


In Section 7.9 we saw that electrophilic addition to a simple alkene would follow Markovnikov's rule. Markovnikov's rule states that for the electrophilic addition of HX, the carbocation intermediate forms on the double bond carbon with the greatest number of alkyl substitutents. Because the stability of carbocation intermediates increases as it number of alky groups increases (primary < secondary < tertiary), this regioselectivity is provided by preferably forming a more stable carbocation intermediate during the reaction. During the electrophilic addition of HBr to 2-methylpropene, the more stable tertiary carbocation intermediate is preferably formed which yields the Markovnikov addition product 2-bromo-2-methylpropane. Formation of 1-bromo-2-methylpropane does not occur because it would require the formation of a less stable primary carbocation intermediate.



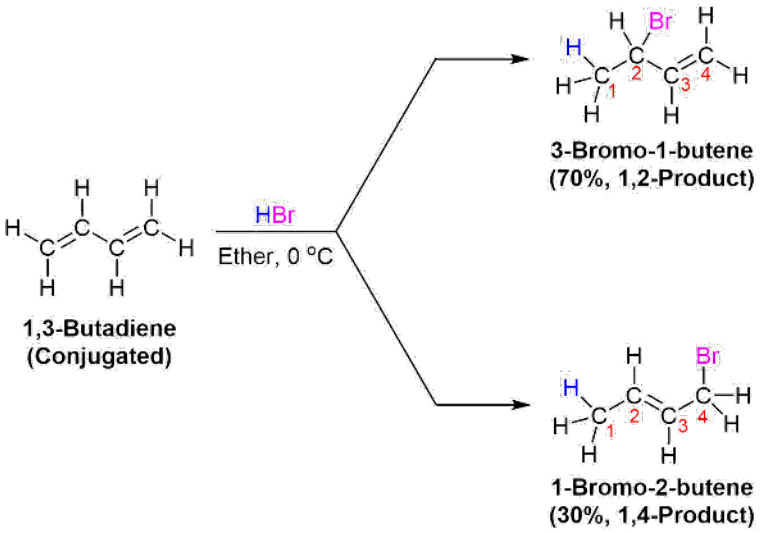
2-Methylpropene | **Tertiary Carbocation** | **2-Bromo-2-Methylpropane (Markovnikov addition product)**

When an electrophilic addition is performed on a non-conjugated diene, the double bonds react in much the same manner as individual alkenes. During the addition of two equivalents of HBr to 1,4-pentadiene, a non-conjugated diene, Markovnikov's rule is still followed producing 2,4-dibromopentane as the product.



1,4-Pentadiene (Non-conjugated) | **2,4-Dibromopentane (Markovnikov addition product)**

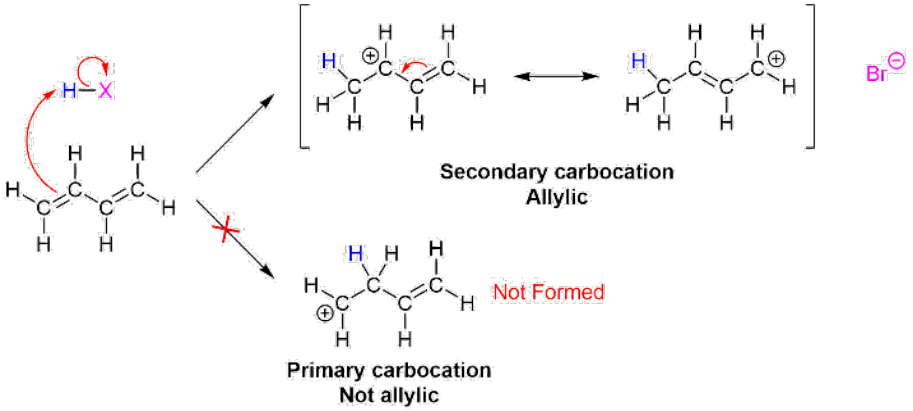
Conjugated dienes undergo the usual reactions of alkenes, such as catalytic hydrogenation, radical additions, and electrophilic additions more readily than most alkenes or dienes that have isolated double bonds. During the electrophilic addition of one equivalent of HX to a conjugated diene, the expected Markovnikov addition product is formed during a process called **1,2-addition**. In addition, an unexpected product is formed from **1,4-addition**, i.e. the halogen bonds at the terminal carbon atoms of a conjugated diene and the remaining double bond shifts to the 2,3-location. Note, the numbers (1 and 4) refer to which of the four carbons making up the conjugated diene the H and Br are bonded to in the products and are not used for the compounds IUPAC nomenclature. Although there are various methods for effecting the relative ratio of 1,2 and 1,4 addition products during the electrophilic addition to a conjugated diene, a mixture of these products is almost always produced. When one equivalent HBr undergoes electrophilic addition to 1,3-butadiene, 1,2 addition provides the expected Markovnikov product 3-bromo-1-butene in a 70% yield. This process is called a 1,2 addition because the hydrogen from HBr (labeled blue) bonds to the first carbon of the diene and the bromine from HBr bonds to the second carbon of the diene. The compound 1-bromo-2-butene is also produced in a 30% yield during the reaction as product of 1,4 addition. Here the hydrogen of HBr bonds to the first carbon of the diene and the Br bonds to the fourth carbon of the diene.



THE MECHANISM FOR ELECTROPHILIC ADDITION OF HBR TO A CONJUGATED DIENE

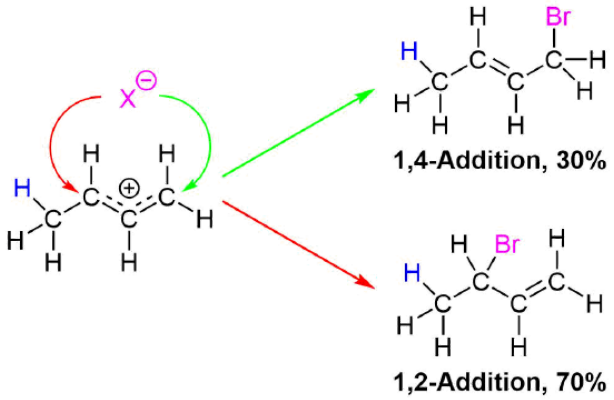
Regardless if the 1,2 or 1,4 addition product is formed, the first step of the mechanism is the protonation of one of the double bonds. In the same manner as the electrophilic addition of HX to an alkene, the protonation occurs regioselectively to give the more stable carbocation. In the case of a conjugated diene, the more stable cation is not only secondary, but also *allylic*, and therefore enjoys the stabilization created from the positive charge being distributed over two carbons by resonance. The resonance hybrid of the allylic carbocation intermediate can be depicted by two resonance forms (shown below) both of which have a full positive charge.

STEP 1)



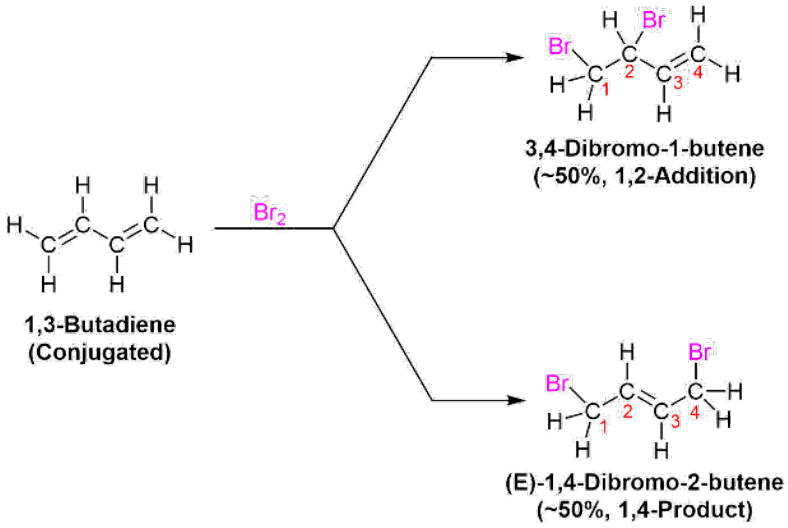
**ST
EP
2)**

This allylic carbocation, more properly denoted as the resonance hybrid shown below, has two carbons which have significant positive charge. The halide ion can attack either carbon. Attacking the central carbon, adjacent to the site of protonation, leads to the the 1,2-addition product. Attacking the terminal carbon, distant from the site of protonation, leads to the 1,4 addition product.



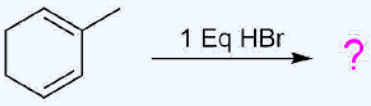
OTHER ELECTROPHILIC ADDITIONS

Formation of both 1,2- and 1,4-addition products occurs not only with hydrogen halides, but also with other electrophiles such as the halogens (X_2). The electrophilic addition of bromine to 1,3-butadiene is an example. As shown below, a roughly 50:50 mixture of 3,4-dibromo-1-butene (the expected 1,2 addition product) and 1,4-dibromo-2-butene (the 1,4 addition product) is obtained. The double bond of the 1,4 addition product is primarily formed as the (E) isomer.



✔ WORKED EXAMPLE 14.2.1

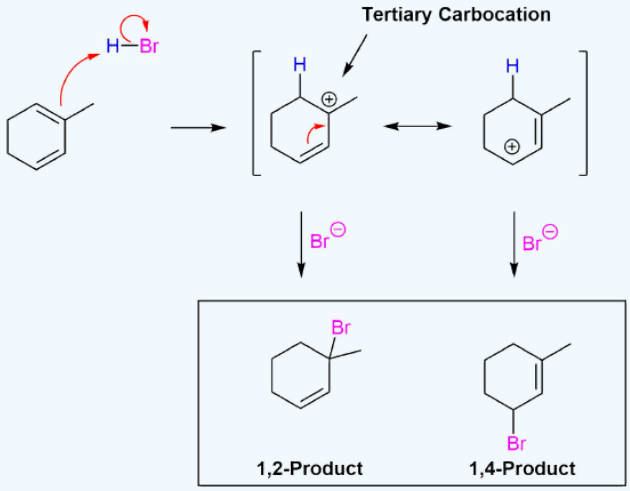
Give the expected products from the following reaction. Show both 1,2 and 1,4 addition products.



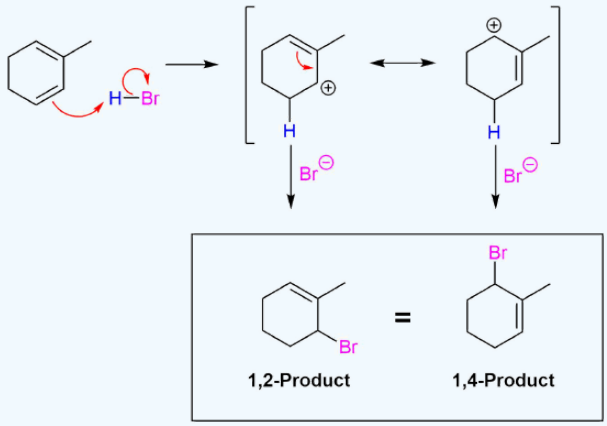
Solution

For this example the two double bonds in the diene are not equivalent and must be considered separately. Each double bond of the reactant has the possibility of forming a 1,2 and a 1,4 addition product so the reaction has the possibility of forming four product. Protonate each double bond separately and draw out the resonance forms of the allylic carbocation intermediate created. Then react each resonance form with Br- to create the two possible products. Repeat this process with the second double bond to create the four possible product. Lastly, look for symmetry in the products to see if any are same molecule. Also, consider the stability of each carbocation created during this process. The most stable carbocation will generally product the favored product of the reaction.

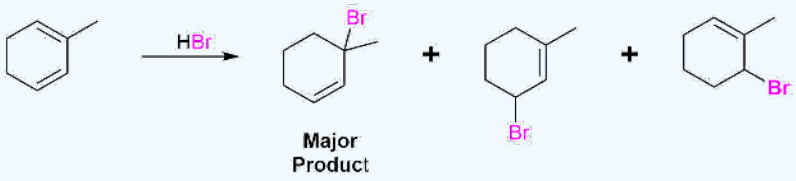
Addition to the first double bond creates a resonance form with a tertiary carbocation intermediate. Due to the stability of the tertiary carbocation this product will most likely go one to be the preferred product of this reaction.



Addition to the second double bond creates a symmetrical compound so only one product is formed.



Over the reaction proposed would be expected to form three products.

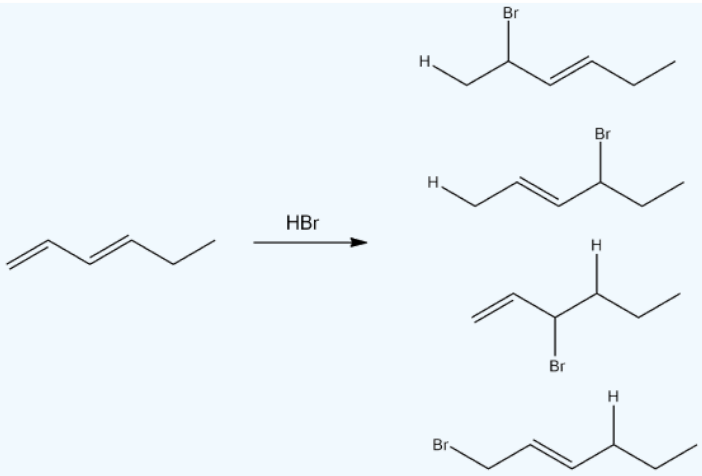


EXERCISE 14.2.1

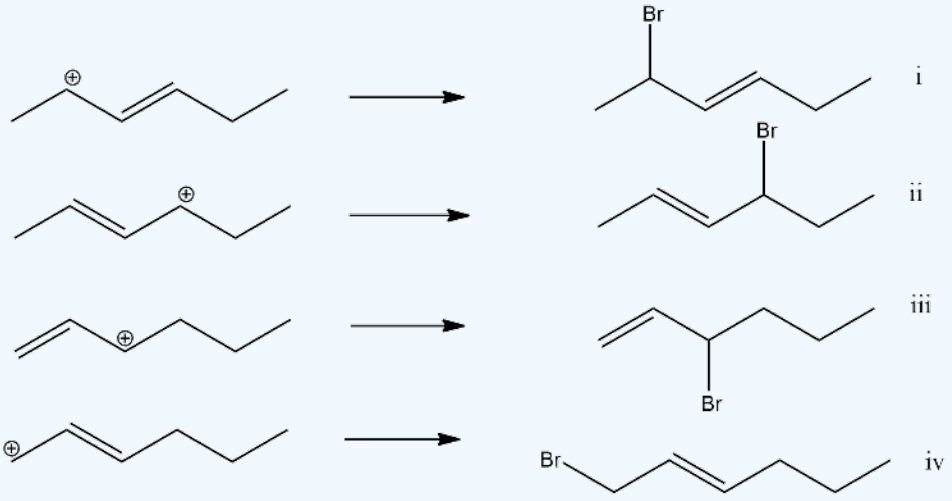
1. Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.
2. Look at the previous addition reaction of HBr with a diene. Consider the transition states, predict which of them would be the major products and which will be the minor.
3. Write out the products of 1,2 addition and 1,4- addition of HBr to 1,3-cyclohexadiene.
4. What is unusual about the products of 1,2- and 1,4- addition of HX to an unsubstituted cyclic 1,3-diene?
5. Write out the products of 1,2 addition and 1,4- addition of Br2 to 1,3-cyclohexadiene.

Answer

1)



2) The products i-iii all show a secondary cation intermediate which is more stable than primary. Therefore those would be major products and the iv product would be the minor product.

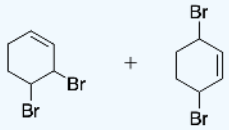


3) The same product will result from 1,2 and 1,4 addition.



4) Addition of the HX to unsubstituted cycloalka-1,3-dienes in either 1,2- or 1,4- manner gives the same product because of symmetry.

5) Both 1,2 and 1,4 products will form.



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- **14.3: Kinetic vs. Thermodynamic Control of Reactions** by Dietmar Kennepohl, Natasha Singh, Orthocresol (StackExchange), Steven Farmer is licensed CC BY-SA 4.0.

14.3: KINETIC VS. THERMODYNAMIC CONTROL OF REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. explain the difference between thermodynamic and kinetic control of a chemical reaction; for example, the reaction of a conjugated diene with one equivalent of hydrogen halide.
2. draw a reaction energy diagram for a reaction which can result in both a thermodynamically controlled product and a kinetically controlled product.
3. explain how reaction conditions can determine the product ratio in a reaction in which there is competition between thermodynamic and kinetic control.

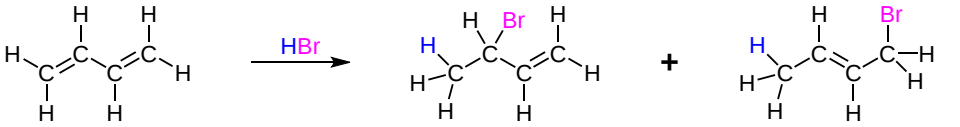
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- kinetic control
- thermodynamic control

Like non-conjugated dienes, conjugated dienes are subject to attack by electrophiles. In fact, conjugated dienes experience relatively greater kinetic reactivity when reacted with electrophiles than non-conjugated dienes do. The reaction mechanism is similar to other electrophilic addition reactions to alkenes (Section 7.9). During the electrophilic addition of HBr to a 1,3-butadiene, However, there are two possible outcomes once the carbocation intermediate is formed. The allyl carbocation is stabilized by resonance structures that vary in the position of the carbocation. This allows the bromide ion to add to either of these carbons resulting in the formation 1,2 and 1,4 addition products. When this reaction is run at a temperature of 0 ºC or lower, the 1,2 addition product dominates. However, if the same reaction is run at 40 ºC the 1,4 addition product dominates.

The reaction of one equivalent of hydrogen bromide with 1,3-butadiene yields different product ratios under different reaction conditions and is a classic example of the concept of **thermodynamic** versus **kinetic** control of a reaction.



1,3-Butadiene **1,2-Addition Product** **1,4-Addition Product**

At -80 ºC:	80%	20%	**Kinetic Control**
At 0 ºC:	70%	30%	**Kinetic Control**
At 40 ºC:	15%	85%	**Thermodynamic Control**
At 60 ºC:	10%	90%	**Thermodynamic Control**

At lower temperatures the formation of the 1,2 and 1,4 addition products are irreversible and thus do not reach equilibrium. When a reaction is irreversible the major product is determined by the relative reaction rates and not by thermodynamic stability. Of the two products, the formation of the 1,2 addition product has a higher rate of reaction and forms faster making it the major product. The reaction product which forms with a higher rate of reaction is called the **Kinetic Product** and when the kinetic product dominates, the reaction is said to be under **Kinetic Control**.

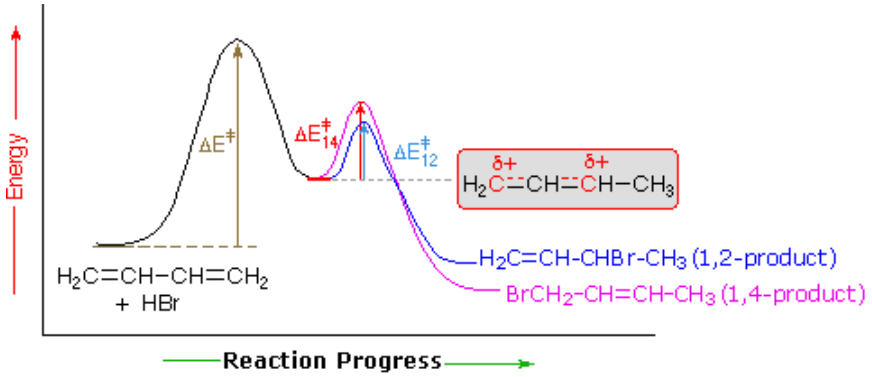
At higher temperatures the reaction to form both products becomes reversible and a reaction equilibrium is reached. When a reaction is reversible the major product is determined by thermodynamic stability. The 1,4 addition product is more stable and becomes the major product under these reaction conditions. The more stable product is called the **Thermodynamic Product** and when the thermodynamic product dominates, the reaction is said to be under **Thermodynamic Control**.

The 1,4 addition product is more stable because it has an internal, disubstituted double bond, and we know that as a general rule that the thermodynamic stability of an alkene increases with increasing substitution. So, when compared to the terminal, monosubstituted alkene of the 1,2 addition product, the 1,4 addition product is expected to be more stable.

> *A simple definition is that the kinetic product is the product that is formed faster, and the thermodynamic product is the product that is more stable. This is precisely what is happening here. The kinetic product is 3-bromobut-1-ene, and the thermodynamic product is 1-bromobut-2-ene (specifically, the trans isomer).*

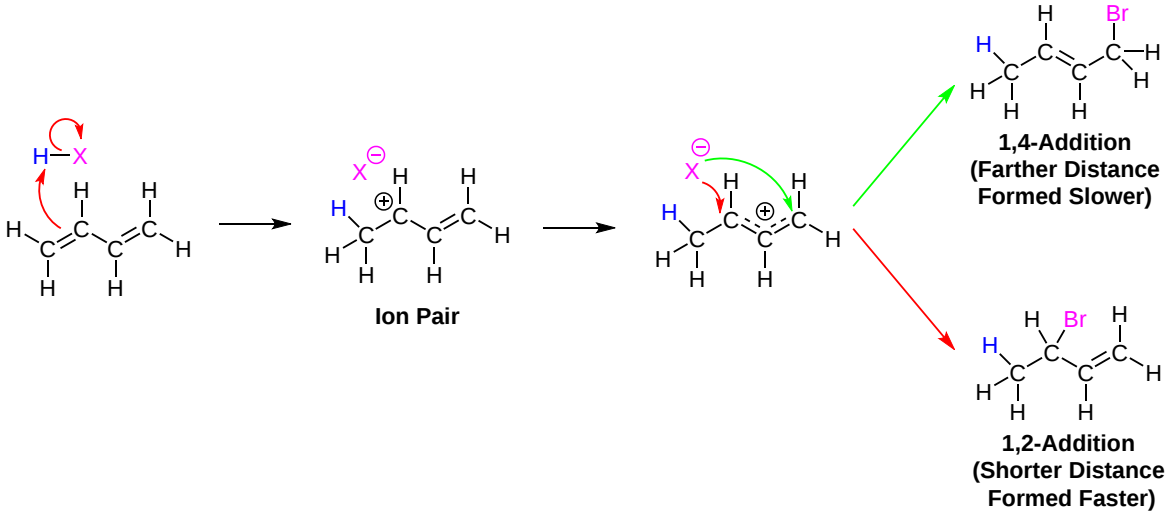
An explanation for the temperature influence is shown in the following energy diagram for the addition of HBr to 1,3-butadiene. The initial step in which a proton bonds to carbon #1 is the **rate determining step**, as indicated by the large activation energy (light gray arrow). The second faster step is the **product determining step**, and there are two reaction paths (colored blue for 1,2-addition and magenta for 1,4-addition).

At elevated temperatures, the products are more likely to have enough energy to overcome the reverse activation barrier for the second step allowing regeneration of the carbocation intermediate. Under these conditions, this step of the mechanism will be reversible and an equilibrium will be established. Since the system is no longer limited by temperature, the system will minimize its Gibbs free energy, which is the thermodynamic criterion for chemical equilibrium. This places the reaction under *thermodynamic control* and the most thermodynamically stable molecule, the 1,4 addition product, will be predominantly formed.



If the reaction temperature is kept sufficiently *low*, the products will not have enough energy to overcome the reverse activation barrier to regenerate the carbocation intermediate making this step of the mechanism effectively irreversible. This reaction is under kinetic control meaning the product which forms faster, the kinetic product, will predominate.

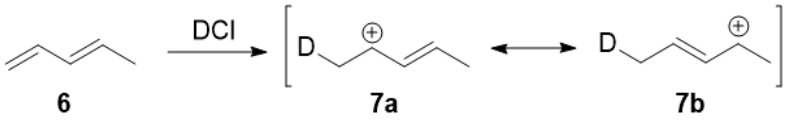
Of the two reaction pathways, the 1,2-addition has a smaller activation energy and would be expected to have a higher reaction rate than the 1,4-addition. The high reaction rate for 1,2-addition can be attributed to the formation of an ion pair during the reaction mechanism. This means that, after a double bond is protonated, the halide counterion remains in close proximity to the carbocation generated. Immediately following dissociation of HX, the chloride ion is going to be much closer to C−2 than it is to C−4, and therefore attack at C−2 is much faster. This ion pair mechanism is a pre-exponential constant effects that is attributed to the proximity and frequency of collision rather than a activation barrier effect.



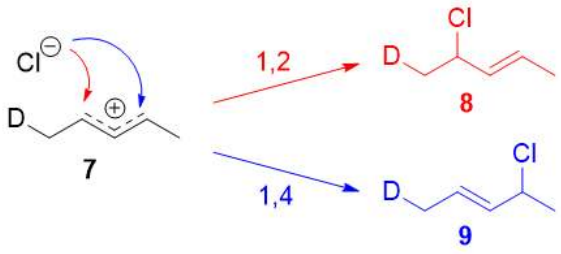
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EXPERIMENTAL EVIDENCE FOR THE ION-PAIR MECHANISM

In 1979, Nordlander *et al.* carried out a similar investigation on the addition of DCl (deuterated hydrochloric acid) to a different substrate, 1,3-pentadiene. This experiment was ingenious, because it was designed to proceed via an almost symmetrical intermediate:



Resonance forms **7a** and **7b** are both allylic and secondary. There is a very minor difference in their stabilities arising from the different hyperconjugative ability of C-D *vs* C-H bonds, but in any case, it is not very large. Therefore, if we adopt the explanation in the previous section, one would expect there not to be any major *kinetic* pathway, and both 1,2- and 1,4-addition products (**8** and **9**) would theoretically be formed roughly equally.



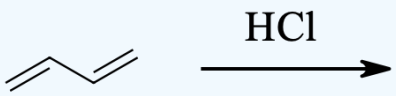
Instead, it was found that the 1,2-addition product was favored over the 1,4-addition product. For example, at -78°C in the absence of solvent, there was a roughly (75:25) ratio of 1,2- to 1,4-addition products. Clearly, there is a factor that favors 1,2-addition that does not depend on the electrophilicity of the carbon being attacked! The authors attributed this effect to an *ion pair* mechanism. This means that, after the double bond is protonated (deuterated in this case), the chloride counterion remains in close proximity to the carbocation generated. Immediately following dissociation of DCl, the chloride ion is going to be much closer to *C-2* than it is to *C-4*, and therefore attack at *C-2* is much faster. In fact, normal electrophilic addition of HX to conjugated alkenes in polar solvents can also proceed via similar ion pair mechanisms. This is reflected by the greater proportion of *syn* addition products to such substrates.

? EXERCISE 14.3.1

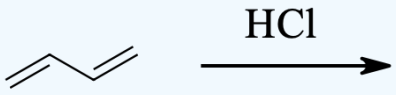
1) Why is the 1,4-addition product the thermodynamically more stable product?

2) Addition of 1 equivalent of bromine to 2,4-hexadiene at 0 degrees C gives 4,5-dibromo-2-hexene plus an isomer. What is the structure of that isomer?

3) The kinetically controlled product in the below reaction is:



4) For the reaction above, which product is the result of 1,4-addition?



5) What would be the major product of the addition of HBr to 2,3-dimethyl-1,3-cyclohexadiene under thermodynamic conditions?

6) Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction. Also, Predict why the 1,4 adduct is the major product in this reaction compared to the 1,2.

Answer

1) The 1,4- product is more thermodynamically stable because there are two alkyl groups on each side of the double bond and more substituted alkenes are more stable.

2) 2,5-Dibromo-3-hexene

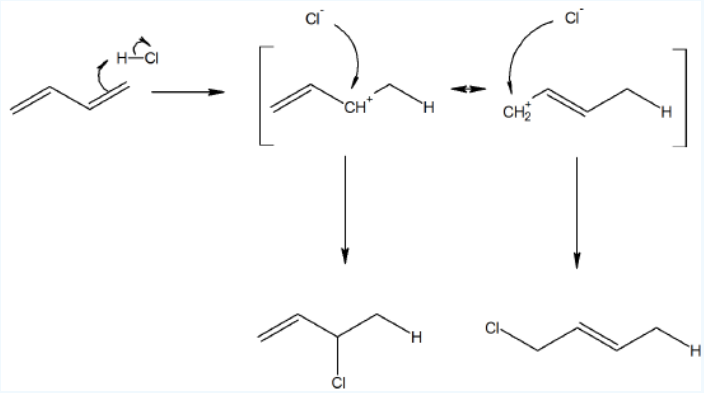
3) 3-Chloro-1-butene

4) 1-Chloro-2-butene

5)



6)



Even though the cation would prefer to be in a secondary position in the transition state, the final product is less stable with a terminal alkene. Therefore the major product will be the 1,4 adduct.

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14.4: THE DIELS-ALDER CYCLOADDITION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent a typical Diels-Alder reaction.
2. draw the structure of the product formed when a given conjugated diene reacts with a given dienophile in a Diels-Alder reaction.
3. identify the diene and dienophile that must be used to prepare a given compound by a Diels-Alder reaction.
4. explain the general mechanism of the Diels-Alder reaction, without necessarily being able to describe it in detail.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Diels-Alder cycloaddition
- pericyclic reaction

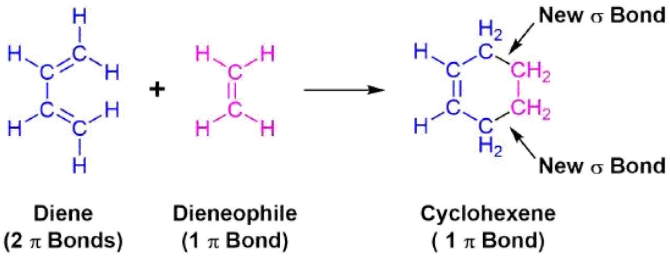
STUDY NOTES

The Diels-Alder reaction is an example of an organic chemical reaction which does not proceed by either a polar or a free radical pathway, but rather a pericyclic reaction.

Although we do not expect you to be able to provide a detailed account of the mechanism of this reaction, you should learn enough about the Diels-Alder reaction to fulfillthe objectives stated above. You will find it useful to contrast the mechanism of the Diels-Alder reaction with the polar and radical mechanisms studied earlier.

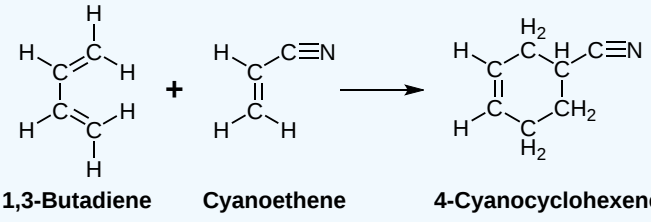
The unique character of conjugated dienes manifests itself dramatically in the **Diels-Alder Cycloaddition Reaction**. The Diels-Alder reaction is an important and widely used synthetic method for making six-membered rings. In the Diels-Alder reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. During the reaction, two pi-bonds are converted to two sigma-bonds. The Diels-Alder cycloaddition is classified as a pericyclic process. Pericyclic reactions involve the redistribution of bonding electrons in a single step mechanism and will be discussed in greater detail in **Chapter 30**. In particular, the Diels-alder reaction is called a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

GENERAL REACTION



An example of the Diels-Alder reaction is the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) to form 4-cyanocyclohexene.

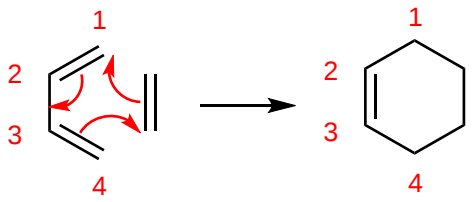
EXAMPLE 14.4.1



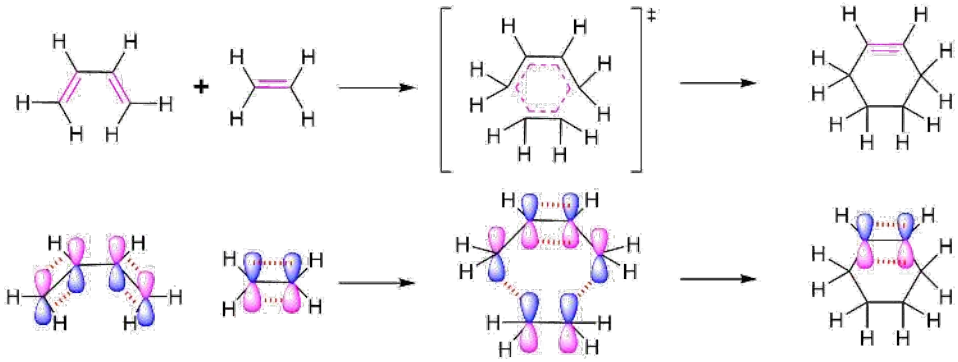
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MECHANISM

All of the electron rearrangements of the Diels-Alder reaction take place once in a single mechanistic step. During this step carbons 1 and 4 of the diene and both alkene carbons of the dienophile, rehybridize from sp^2 to sp^3 and electrons rearrange to create two new sigma bonds in the cyclic product. Carbons 2 and 3 of the diene remain sp^2 hybridized and form a new pi bond in the product.

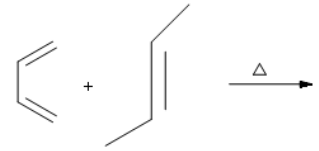


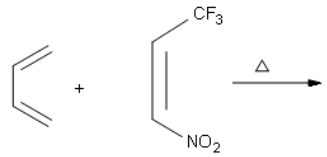
The mechanism occurs through a cyclic transition state in which there is head-on overlap of two p orbitals on carbons 1 and 4 of the diene with the two p orbitals from the alkene of the dienophile to form two new sigma bonds in the cyclohexene product. The remaining two p orbitals from the diene overlap to form the new pi bond.

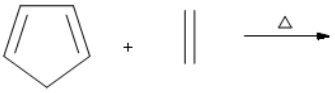


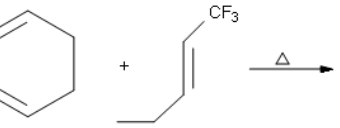
PROBLEMS

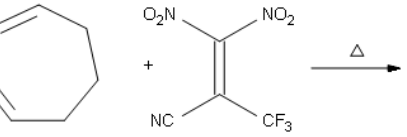
1. 

2. 

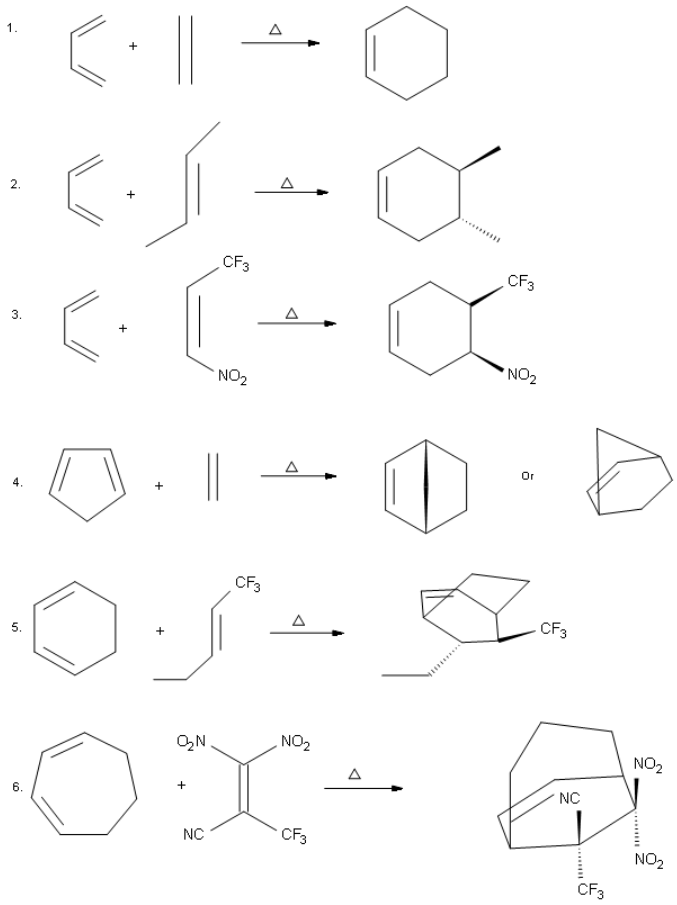
3. 

4. 

5. 

6. 

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14.5: CHARACTERISTICS OF THE DIELS-ALDER REACTION

OBJECTIVES

After completing this section, you should be able to

1. determine whether or not a given compound would behave as a reactive dienophile in a Diels-Alder reaction.
2. predict the stereochemistry of the product obtained from the reaction of a given diene with a given dienophile.
3. recognize that in order to undergo a Diels-Alder reaction, a diene must be able to assume an*s*-cis geometry, and determine whether or not a given diene can assume this geometry.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- dienophile
- dimerization

STUDY NOTES

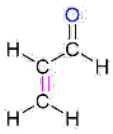
Make sure that you understand that the *s*-cis and *s*-trans forms of a diene such as 1,3-butadiene are conformers, not isomers. Note that some textbooks can confuse the issue further by referring to a compound such as (2Z, 4Z)-hexadiene as cis, cis-2,4-hexadiene, and saying that the most stable form of this compound is its *s*-trans conformer!

In fulfilling Objective 2, above, you must recognize that the Diels-Alder reaction is stereospecific.

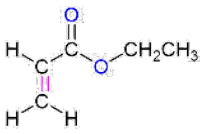
Finally, note reaction **B** in the reading shows 1,3-cyclopentadiene reacting with another molecule of 1,3-cyclopentadiene. When the same compound acts as both diene and dienophile in a Diels-Alder reaction to couple it is a dimerization.

THE DIENOPHILE

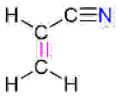
In general, Diels-Alder reactions proceed fastest with electron-withdrawing groups on the dienophile (diene lover). Ethylene reacts slowly while **propenal, ethyl propenoate, and other molecules shown below** are highly reactive in a Diels-Alder reaction.



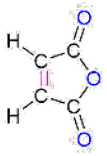
Prepenal
(Acrolein)



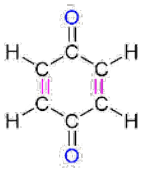
Ethyl propenoate
(Ethyl acrylate)



Propenenitrile
(Acrylonitrile)

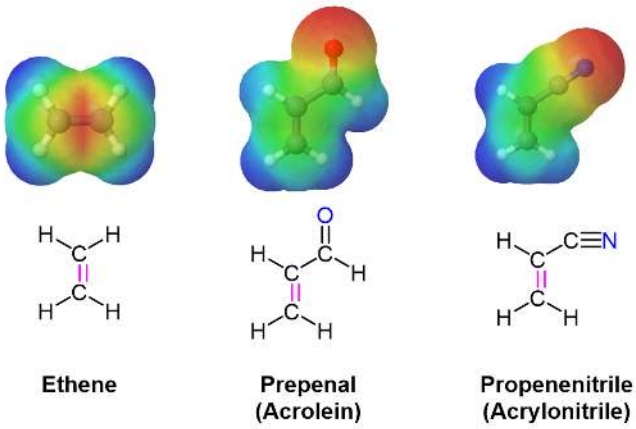


Maleic anhydride



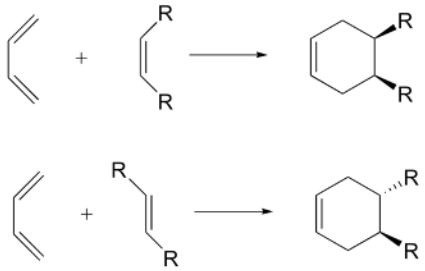
Benzoquinone

In much the same manner as electron-withdrawing substituents on a benzene ring, these are typically a double or triple bond in conjugation with the double bond in the dienophile. A resonance form can be drawn which places a positive charge in the dienophile double bond. This results in the double bond being less electron rich (greater electron density shown in Red/Orange) than ethylene. Electrostatic potential maps show that the electron-withdrawing groups pull electron density away from the double bond.

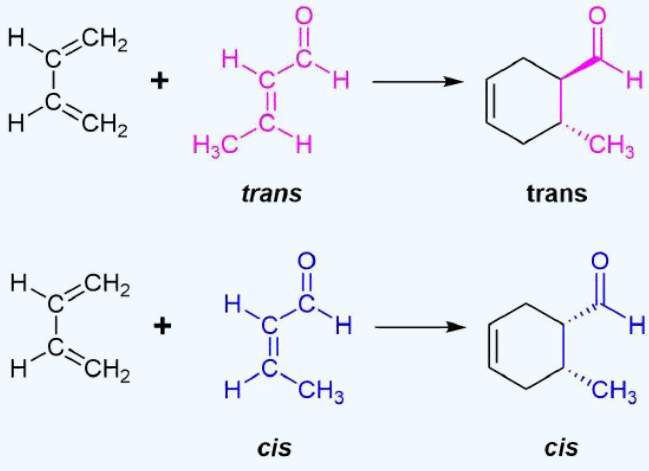


STEREOCHEMISTRY OF DIELS-ALDER (DIENOPHILE)

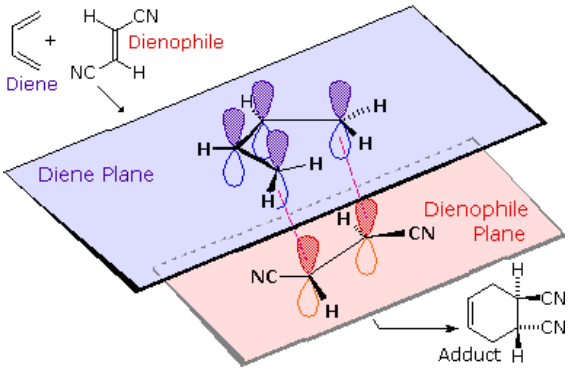
The Diels-Alder reaction is enormously useful for synthetic organic chemists, not only because ring-forming reactions are useful in general but also because in many cases multiple new stereocenters are formed, and the reaction is inherently stereospecific. During a Diels-Alder reaction the stereochemistry of the dienophile is retained in the product. A *cis* dienophile will generate a cyclohexene ring with *cis (syn)* substitution on the two carbons from the dienophile. Likewise a *trans* dienophile will generate a cyclohexene ring with *trans (anti)* substitution on these two carbon.



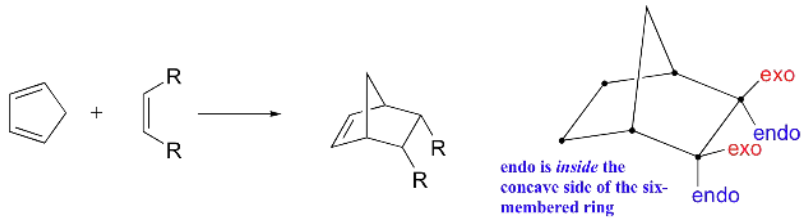
EXAMPLE 14.5.1



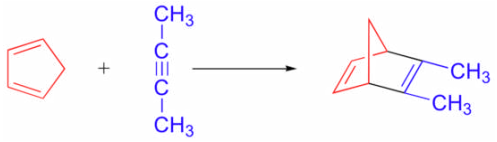
The retention of stereochemistry is due to the planar nature of both reactants and that the forming process is **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the concerted nature of the Diels-Alder mechanism. The drawing below illustrates this fact for the reaction of 1,3-butadiene with (E)-dicyanoethene. The trans relationship of the cyano groups in the dienophile is preserved in the six-membered ring of the adduct.



Another facet of the stereochemical retention of the dienophile is that only the endo product, rather than the alternative exo product, is formed. The words *endo* and *exo* are used to indicate relative stereochemistry when referring to bicyclic structures like substituted norbornanes. The endo position on a bicyclic structure refers to the position that is *inside* the concave shape of the larger (six-membered) ring. As you might predict, the **exo position** refers to the *outside* position. Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**. Preference of the endo position is also a facet of the suprafacial nature of the Diels-Alder reaction. The orbital overlap required for the reaction is greater when the dienophile lies directly underneath the diene.

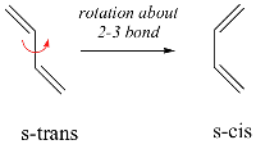


Alkynes can also serve as dienophiles in Diels-Alder reactions:

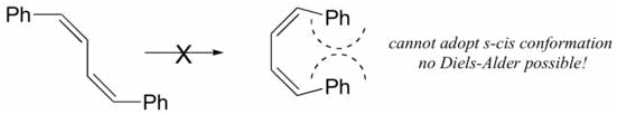


THE DIENE

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups). The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cis conformation in order for the end carbon atoms (#1 & #4) to bond simultaneously to the dienophile. For many acyclic dienes the s-trans conformer is more stable than the s-cis conformer (due to steric crowding of the end groups), but the two are generally in rapid equilibrium, permitting the use of all but the most hindered dienes as reactants in Diels-Alder reactions.



For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.

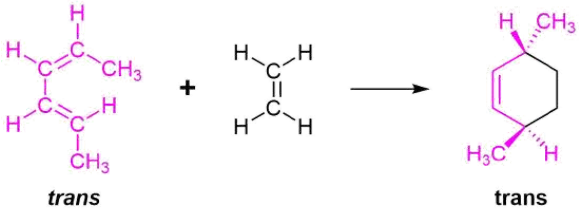


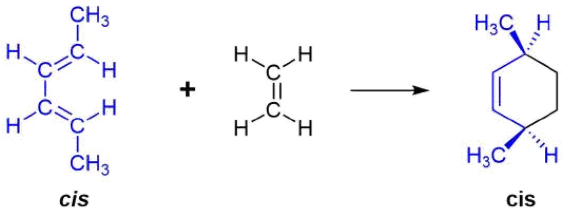
Cyclic dienes, on the other hand, are 'locked' in the s-cis conformation, and are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:



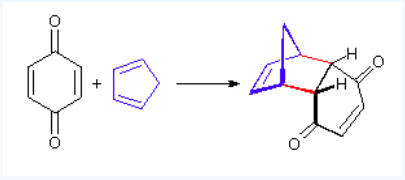
STEREOCHEMISTRY OF DIELS-ALDER (DIENE)

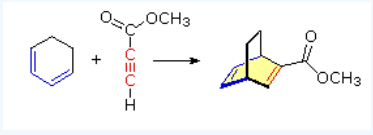
The 1 and 4 Carbons in the diene have the possibility of forming two new stereocenters in the cyclohexene product. Similarly to the effects of dienophile stereochemistry, the positioning of substituents on the 1 and 4 carbons in the diene determine the stereochemistry in the product. The diene substituents can be thought of as being either cis (both facing in or both facing out) or trans and the stereochemistry is retained to form a cis or trans cyclohexene product.

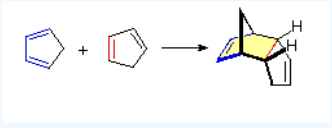


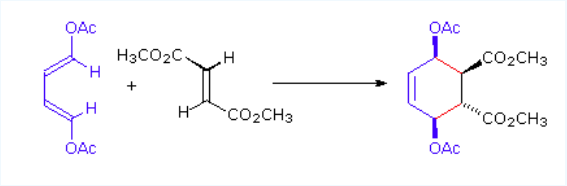


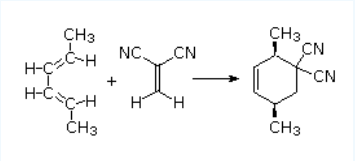
EXAMPLES 14.5.1

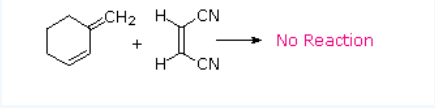










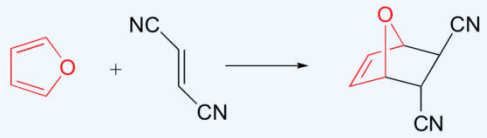


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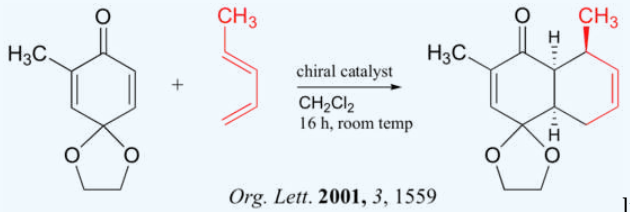
THE ESSENTIAL CHARACTERISTICS OF THE DIELS-ALDER CYCLOADDITION REACTION:

i. The reaction always creates a new six-membered ring.
ii. The diene component must be able to assume an s-cis conformation.
iii. Electron withdrawing groups on the dienophile facilitate reaction.
iv. Electron donating groups on the diene facilitate reaction.
v. Steric hindrance at the bonding sites may inhibit or prevent reaction.
vi. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

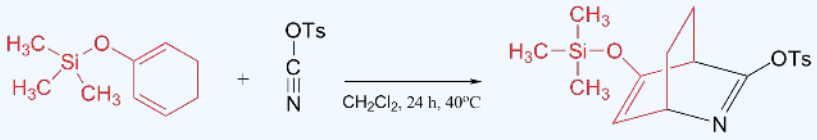
EXAMPLES 14.5.2



J. Med. Chem. **2008,** *51*, 424 link



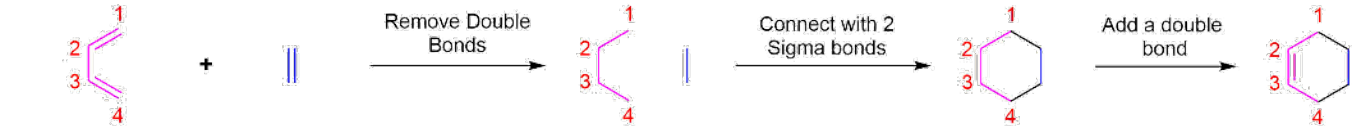
Org. Lett. **2001,** *3*, 1559 link



J. Org. Chem. **2003,** *68*, 8256 link

PREDICTING THE PRODUCT OF A DIELS-ALDER REACTION

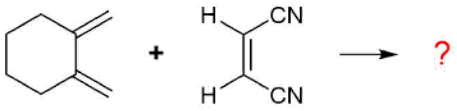
Start by rotating the diene until it is in the s-cis conformation then point it towards the double bond of the dienophile. Remove the double bonds present in the diene and dieneophile. Connect carbons 1 and 4 of the the diene to a carbon in the dienophile double bond using a sigma bond to create a six-membered ring. Create a double bond between carbons 2 and 3 of diene.



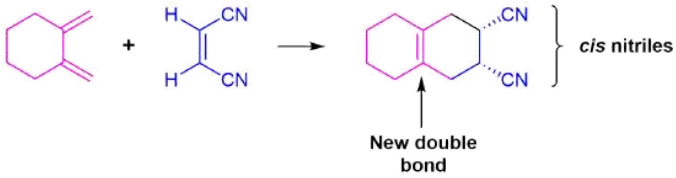
Determine if any substituents attached to either the double bond of the dieneophile or carbons 1 and 4 of the diene have a *cis*/*trans* conformation. If so make sure the substituents have the same configuration in the cycloalkene product.



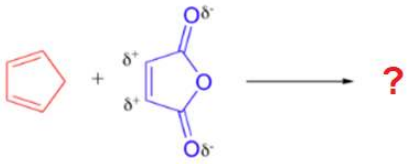
Predict the product of the following reaction:



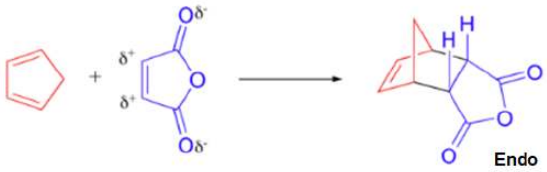
The diene is locked into an s-cis configuration which will promote the reaction. The ring portion of the diene will act as electron donating groups which will also promote the reaction. Because the diene already contained a ring the product will be bicyclic. The dienophile has two nitriles attached to it both of which are electron withdrawing. Since the two nitriles in the dieneophile are *cis* to each other the the two nitriles will be cis to each other in the product.



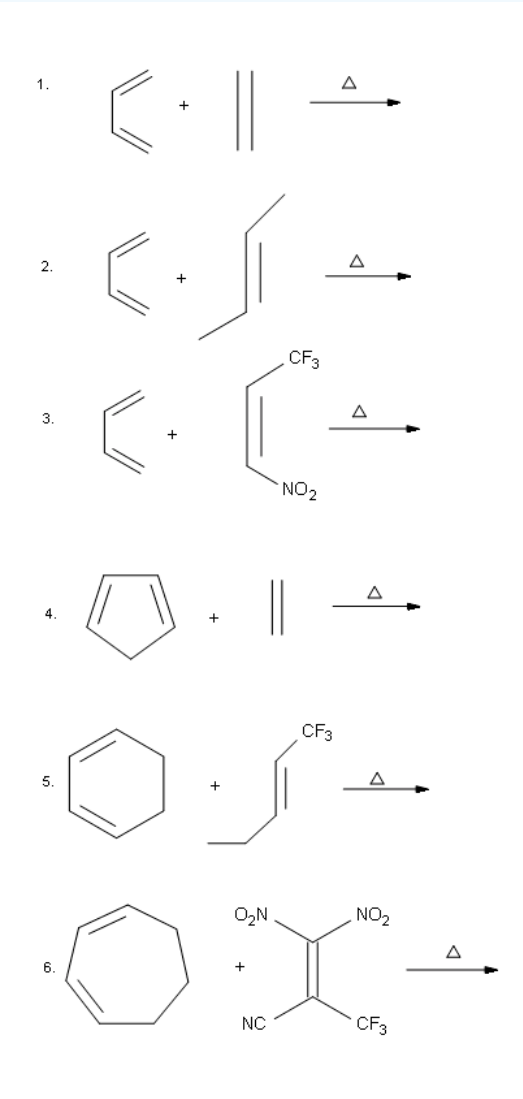
Predict the product of the following reaction:



A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride. Cyclopentadiene is held in the required s-cis configuration so it will make a good diene for a Diels-Alder reaction. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for attack by the pi electrons in the diene. Since it is part of a ring, the double bond of maleic anhydride is in a cis configuration so the cyclohexene ring will also have a cis configuration. Lastly, the product will prefer the endo position.

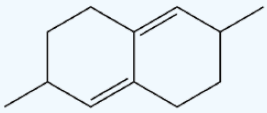


EXERCISE 14.5.1

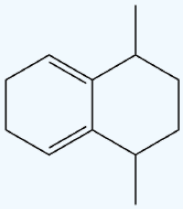


7) Of the following dienes, which are S-trans and which are s-cis? Of those that are s-trans, are they able to rotate to become s-cis?

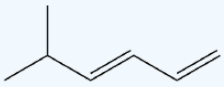
A)



B)

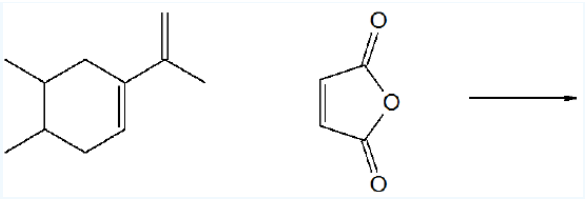


C)

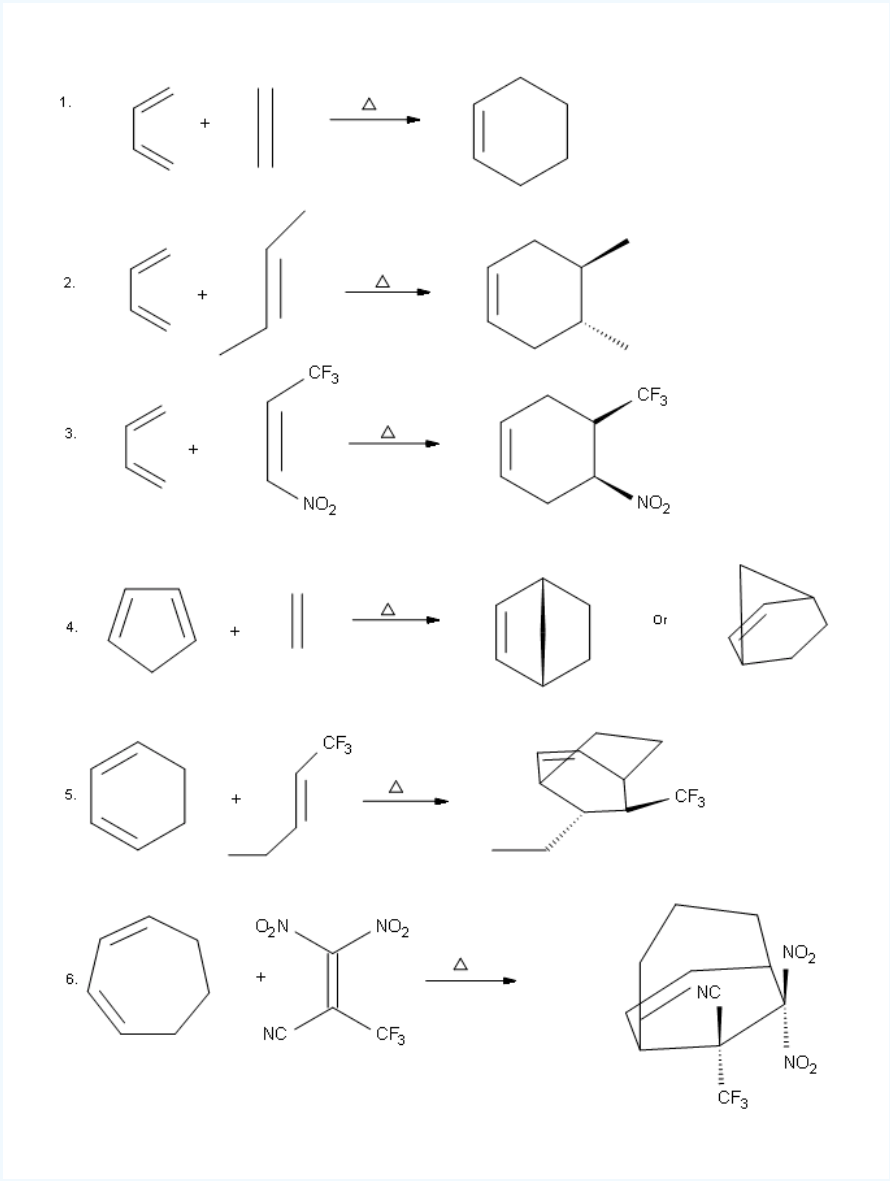


8) Predict the product of the following reaction.

https://chem.libretexts.org/@go/page/31553



Answer



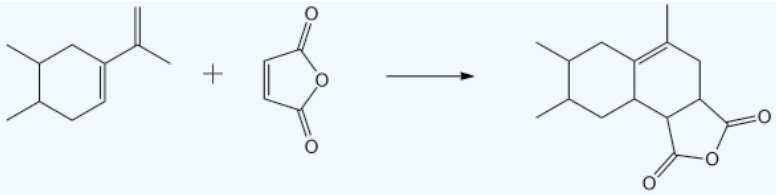
7)

A) s-trans, unable to rotate to become s-cis

B) s-cis

C) s-trans, can rotate to become s-cis.

8)



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14.6: DIENE POLYMERS- NATURAL AND SYNTHETIC RUBBERS

OBJECTIVES

After completing this section, you should be able to

1. show that the polymerization of a diene, such as 1,3-butadiene or isoprene (2-methyl-1,3-butadiene), can result in the formation of either a cis or trans polymer.
2. draw the structure of natural rubber.
3. explain, briefly, the process of vulcanization.

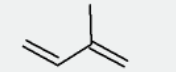
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

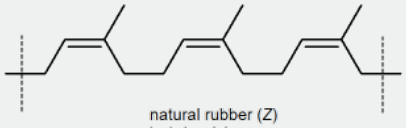
- cross-link
- vulcanization

STUDY NOTES

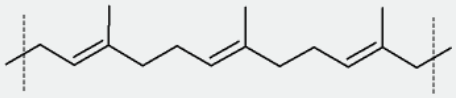
Natural rubber is formed from the isoprene monomer and has *Z* stereochemistry. The *E* polymer gutta-percha also occurs naturally, but is more brittle than rubber. Uses of this thermoplastic include dentistry, electrical insulators and the covering on golf balls.



isoprene
2-methyl-1,3-butadiene



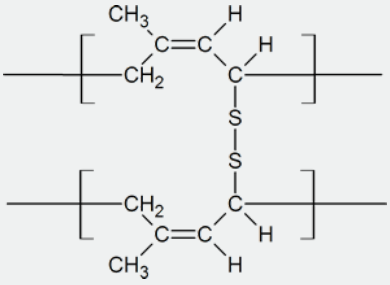
natural rubber (*Z*)
cis-1,4-polyisoprene



gutta-percha (*E*)
trans-1,4-polyisoprene

Before 1839, the uses of natural rubber were somewhat limited. It became sticky in summer, hardened and cracked in winter, and was susceptible to attack by a variety of solvents. Charles Goodyear became interested in rubber in 1831, and bought the Eagle India Rubber Company of Woburn, Massachusetts, in 1838. In January of 1839, Goodyear accidentally placed a sample of rubber that had been mixed with sulfur and lead(II) oxide on a hot stove; the result was a product similar to charred leather, which did not melt below 138°C. Goodyear was granted a U.S. patent for his process (called vulcanization) in June of 1844. The story of vulcanization is an example of how major scientific and technological advances are often brought about as a result of an accidental discovery.

Notice that in the vulcanization process, the sulfur bridges are attached to allylic carbon atoms which connect the long *Z* polymer chains of rubber.



Vulcanized rubber

The amount of sulfur used in the vulcanization process will depend on the rigidity required in the product. For example, about 5% sulfur is used when producing rubber for rubber bands; about 30% sulfur is used when making rubber for use in battery casings. There are several characteristics of dienes and rubbers that you should recognize. First, be aware of the similarity between the polymerization

of a diene and the 1,4-addition reactions of dienes. Second, recognize the similarity between a vulcanized rubber and a peptide containing cysteine cross-links. Third, be aware that as natural rubber contains double bonds, it will display some of the properties of simple alkenes.

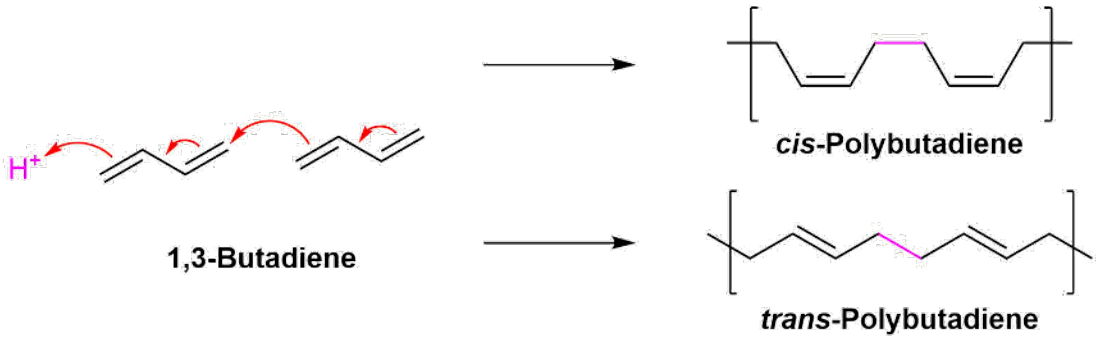
The 1,4 polymerization of 1,3-butadiene shown in the reading produces the *trans* form of polybutadiene. However, it should be noted that the *cis* form shown here can also be formed.



cis- polbutadiene

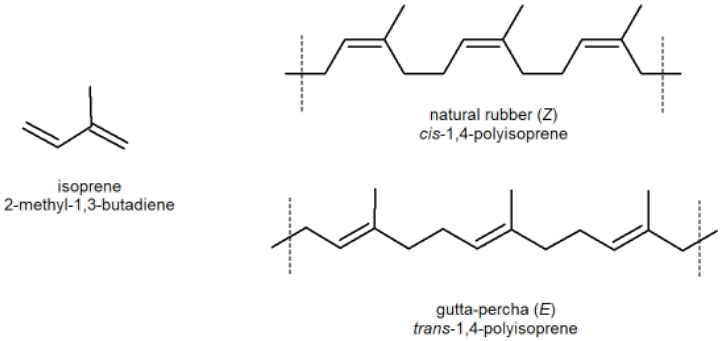
POLYMERIZATION OF 1,3-BUTADIENE

Conjugated dienes can be polymerized much like alkenes **(**Section 8-10**)** to form important compounds like rubber. Diene polymers are more structurally complex and have the possibility of forming different isomers. The polymerization of conjugated dienes are commonly initiated by ether a radical or an acid. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound. The polymerization takes place by a type of 1,4 addition to 1,3-butadiene which leads to the possibility of forming cis (*Z*) or trans (*E*) double bonds in the polymer product.

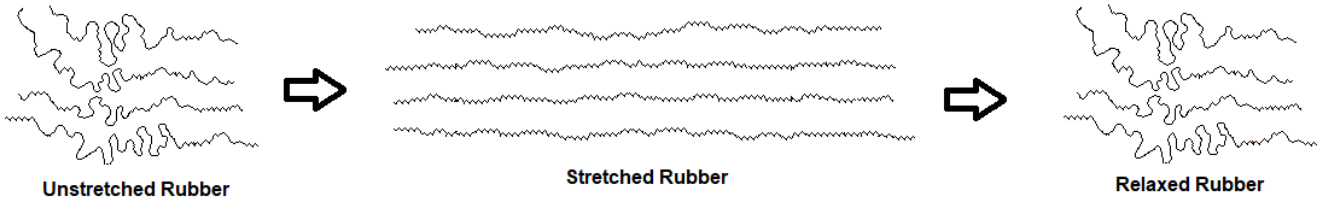


NATURAL RUBBER

Rubber is undoubtedly the best known and most widely used compound of this kind. Natural rubber is an addition polymer that is obtained as a milky white colloidal suspension known as latex with the major source being a tropical rubber tree (*Hevea brasiliensis*). Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure below) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

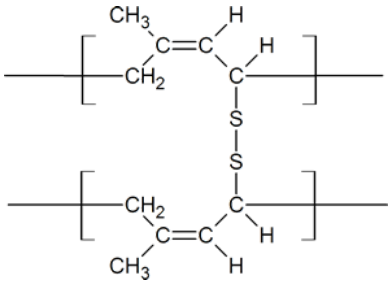


Due to rubber being an amorphous polymer, its coiled polymer chains can be straightened by stretching. The more highly-ordered chains in the stretched conformation are entropically unstable and return to their original coiled state when allowed to relax.

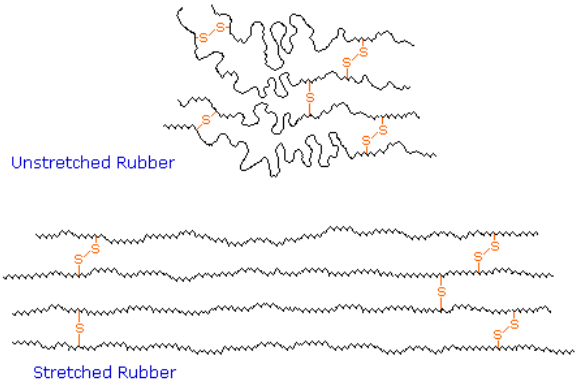


VULCANIZATION

Charles Goodyear accidentally discovered that by mixing sulfur and rubber, the properties of the rubber improved in being tougher, resistant to heat and cold, and increased in elasticity. This process was later called vulcanization after the Roman god of fire. Sulfur vulcanization is a chemical process for converting natural rubber or related polymers into more durable materials by heating them with sulfur or other equivalent curatives. Sulfur forms cross-links (bridges) between sections of polymer chains which results in increased rigidity and durability, as well as other changes in the mechanical and electronic properties of the material. A vast array of products are made with vulcanized rubber, including tires, shoe soles, hoses, and conveyor belts.

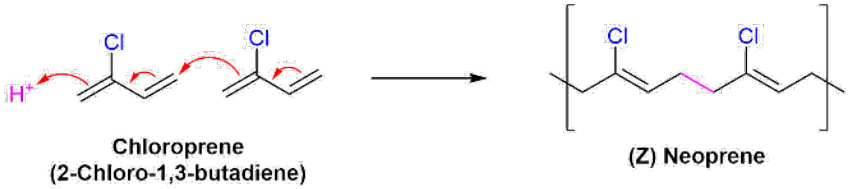


At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a section of amorphous rubber cross-linked with sulfur by the vulcanization process.



SYNTHETIC RUBBER

Neoprene (also **polychloroprene** or **pc-rubber**) is a family of synthetic rubbers that are produced by polymerization of 2-chloro-1,3-butadiene (chloroprene). Neoprene exhibits good chemical stability and maintains flexibility over a wide temperature range. Neoprene is sold either as solid rubber or in latex form and is used in a wide variety of applications, such as laptop sleeves, orthopaedic braces (wrist, knee, etc.), electrical insulation, liquid and sheet applied elastomeric membranes or flashings, and automotive fan belts.



EXERCISE 14.6.1

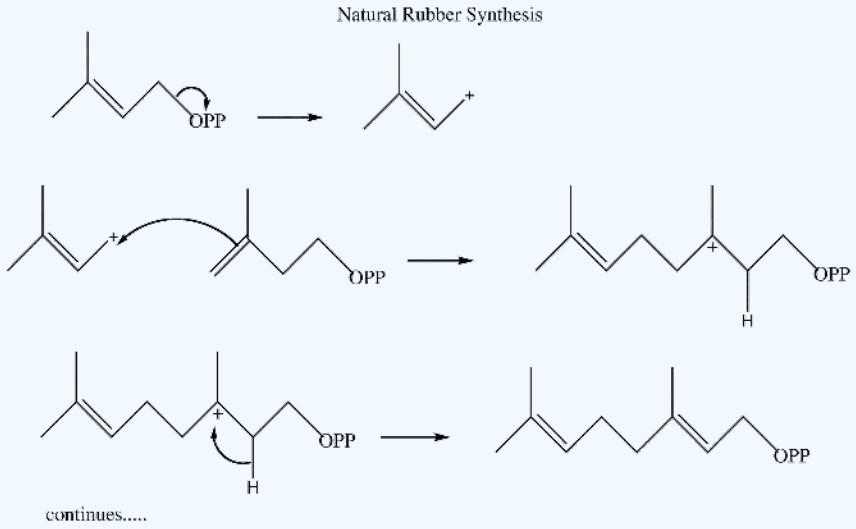
a. Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows

b. Draw a segment for the polymer that may be made from 2-*tert*-butyl-1,3-butadiene.

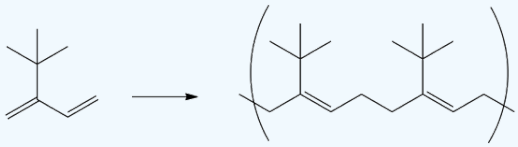
c. Propose the mechanism for the acid catalyzed polymerization of 2-methyl-1,3-butadiene.

Answer

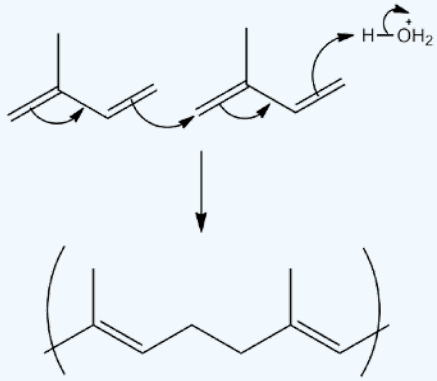
1)



2)



3)



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14.7: STRUCTURE DETERMINATION IN CONJUGATED SYSTEMS - ULTRAVIOLET SPECTROSCOPY

OBJECTIVES

After completing this section, you should be able to

1. identify the ultraviolet region of the electromagnetic spectrum which is of most use to organic chemists.
2. interpret the ultraviolet spectrum of 1,3-butadiene in terms of the molecular orbitals involved.
3. describe in general terms how the ultraviolet spectrum of a compound differs from its infrared and NMR spectra.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- ultraviolet (UV) spectroscopy
- Molar absorptivity

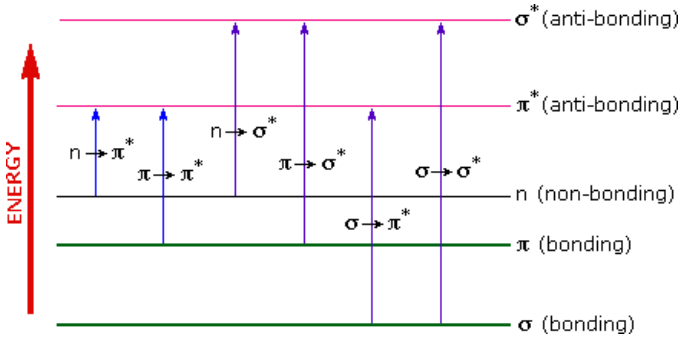
STUDY NOTES

Ultraviolet spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy). Thus, your study of this technique will be restricted to a brief overview. You should, however, note that for an organic chemist, the most useful ultraviolet region of the electromagnetic spectrum is that in which the radiation has a wavelength of between 200 and 400 nm.

UV-VISIBLE ABSORPTION SPECTRA

To understand why some compounds are colored and others are not, and to determine the relationship of conjugation to color, we must make accurate measurements of light absorption at different wavelengths in and near the visible part of the spectrum. Commercial optical spectrometers enable such experiments to be conducted with ease, and usually survey both the near ultraviolet and visible portions of the spectrum. Ultraviolet-visible absorption spectroscopy provides much less information about the structure of molecules than do the spectroscopic techniques studied earlier (infrared spectroscopy, mass spectroscopy, and NMR spectroscopy) and mainly provides information about conjugated pi systems. For an organic chemist the most useful ultraviolet region of the electromagnetic spectrum involves radiation with a wavelength between 200 and 400 nm. UV/Vis absorption spectra also involve radiation from the visible region of the electromagnetic spectrum with wavelengths between 400 and 800 nm.

A diagram highlighting the various kinds of electronic excitation that may occur in organic molecules is shown below. Of the six transitions outlined, only the two lowest energy ones, n to pi* and pi to pi* (colored blue) are achieved by the energies available in the 200 to 800 nm range of a UV/VIs spectrum. These energies are sufficient to promote or excite a molecular electron to a higher energy orbital in many conjugated compounds.



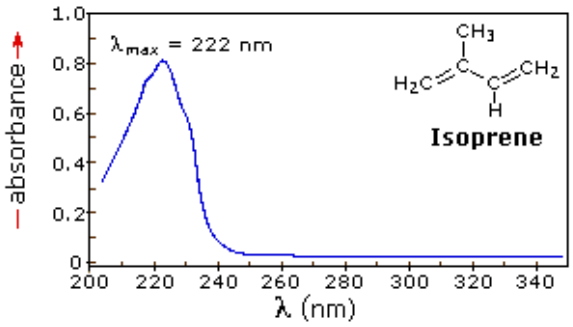
When sample molecules are exposed to light having an energy that matches a possible electronic transition within the molecule, some of the light energy will be absorbed as the electron is promoted to a higher energy orbital. A UV/Vis spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. A**bsorbance**, abbreviated 'A', is a unitless number which contains the same information as the 'percent transmittance' number used in IR spectroscopy. To calculate absorbance at a given

wavelength, the computer in the spectrophotometer simply takes the intensity of light at that wavelength *before* it passes through the sample (I_0), divides this value by the intensity of the same wavelength *after* it passes through the sample (I), then takes the $\log_{10}$ of that number:

$$A = \log\left(\frac{I_0}{I}\right)$$

The resulting spectrum is presented as a graph of absorbance (A) versus wavelength, as in the isoprene spectrum shown below. Since isoprene is colorless, it does not absorb in the visible part of the spectrum and this region is not displayed on the graph. Notice that the convention in UV-vis spectroscopy is to show the baseline at the bottom of the graph with the peaks pointing up. Wavelength values on the x-axis are generally measured in nanometers (nm) rather than in cm^{-1} as is the convention in IR spectroscopy.

Typically, there are two things that are noted and recorded from a UV-Vis spectrum. The first is λ_{max}, which is the wavelength at maximal light absorbance. As you can see, isoprene has λ_{max}, = 222 nm. The second valuable piece of data is the absorbance at the λ_{max}. In the isoprene spectrum the absorbance at the value λ_{max} of 222 nm is about 0.8.



MOLAR ABSORPTIVITY

Molar absorptivity (***epsilon***) is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular electron system in the molecule. Molar absorptivities may be very large for strongly absorbing chromophores (>100,000) and very small if absorption is weak (10 to 100). The magnitude of ***epsilon*** reflects both the size of the chromophore and the probability that light of a given wavelength will be absorbed when it strikes the chromophore. Molar absorptivity (ϵ) is defined via Beer's law as:

$$\epsilon = \frac{A}{c\,l}$$

where

- A is the sample absorbance
- c is the sample concentration in moles/liter
- l is the length of light path through the sample in cm

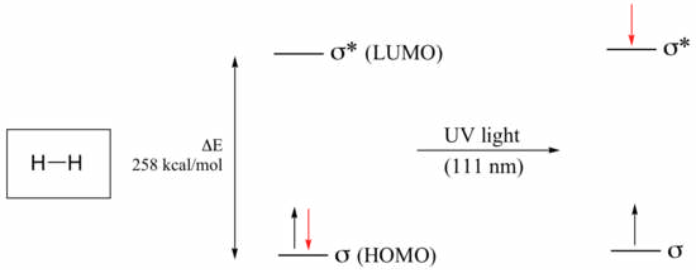
If the isoprene spectrum show above was obtained from a dilute hexane solution (c = 4 * 10^{-5} moles per liter) in a 1 cm sample cuvette, a simple calculation using the above formula indicates a molar absorptivity of 20,000 at the maximum absorption wavelength, symbolized as λ_{max}.

The only molecular moieties likely to absorb light in the 200 to 800 nm region are functional groups that contain pi-electrons and hetero atoms having non-bonding valence-shell electron pairs. Such light absorbing groups are referred to as **chromophores**. A list of some simple chromophores and their light absorption characteristics are provided below. The oxygen non-bonding electrons in alcohols and ethers do not give rise to absorption above 160 nm. Consequently, pure alcohol and ether solvents may be used for spectroscopic studies.

Chromophore	Example	Excitation	λmax, nm	ε @ λmax	Solvent
C=C	Ethene	π → π*	171	15,000	hexane
C≡C	1-Hexyne	π → π*	180	10,000	hexane
C=O	Ethanal	n → π* π → π*	290 180	15 10,000	hexane hexane
N=O	Nitromethane	n → π* π → π*	275 200	17 5,000	ethanol ethanol
C-X X=Br X=I	Methyl bromide Methyl Iodide	n → σ* n → σ*	205 255	200 360	hexane hexane

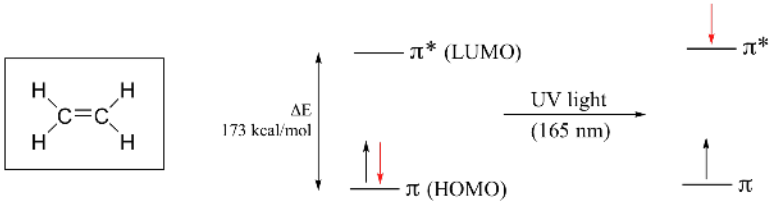
ELECTRONIC TRANSITIONS (CAUSE OF UV-VISIBLE ABSORPTION)

As previously noted, electronic transitions in organic molecules lead to UV and visible absorption. As a rule, energetically favored electron promotion will be from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO), and the resulting species is called an **excited state.** The molecular orbital picture for the hydrogen molecule (H_2) consists of one bonding σ MO, and a higher energy antibonding σ* MO. When the molecule is in the ground state, both electrons are paired in the lower-energy bonding orbital – this is the Highest Occupied Molecular Orbital (HOMO). The antibonding σ* orbital, in turn, is the Lowest Unoccupied Molecular Orbital (LUMO).

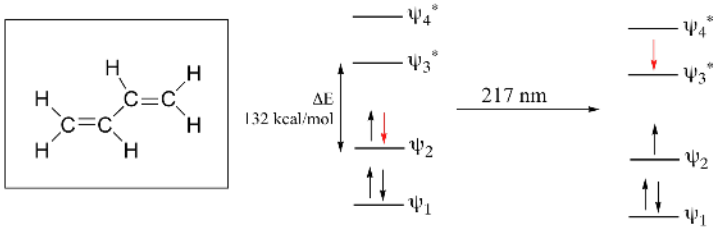


If the molecule is exposed to light of a wavelength with energy equal to ΔE, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. ΔE for this electronic transition is 258 kcal/mol, corresponding to light with a wavelength of 111 nm.

When a double-bonded molecule such as ethene (common name ethylene) absorbs light, it undergoes a **π - π* transition**. Because π- π* energy gaps are narrower than σ - σ* gaps, ethene absorbs light at 165 nm - a longer wavelength than molecular hydrogen.

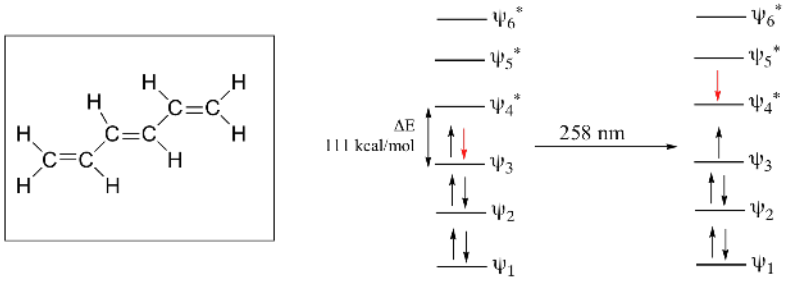


The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded. Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding.

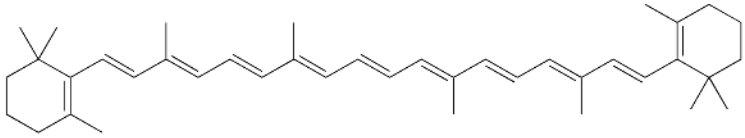


Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

As conjugated pi systems become larger, the energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm, corresponding to a **Δ**E of 111 kcal/mol.

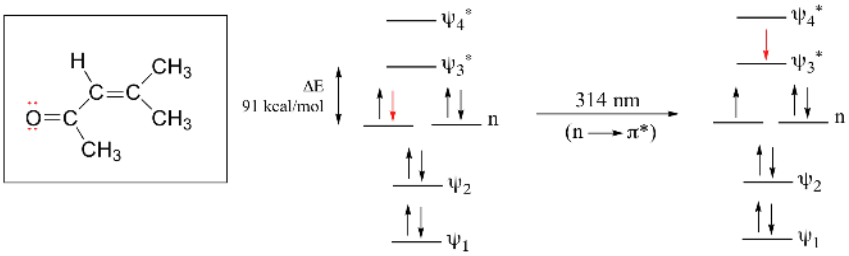


In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



β-carotene

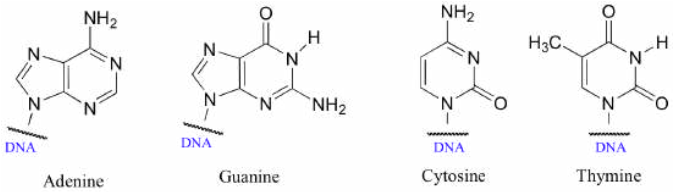
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an $n - \pi^*$ transition. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an $n - \pi^*$ transition is smaller that that of a $\pi - \pi^*$ transition – and thus the $n - \pi^*$ peak is at a longer wavelength. In general, $n - \pi^*$ transitions are weaker (less light absorbed) than those due to $\pi - \pi^*$ transitions.

USE OF UV/VIS SPECTROSCOPY IN BIOLOGICAL SYSTEMS

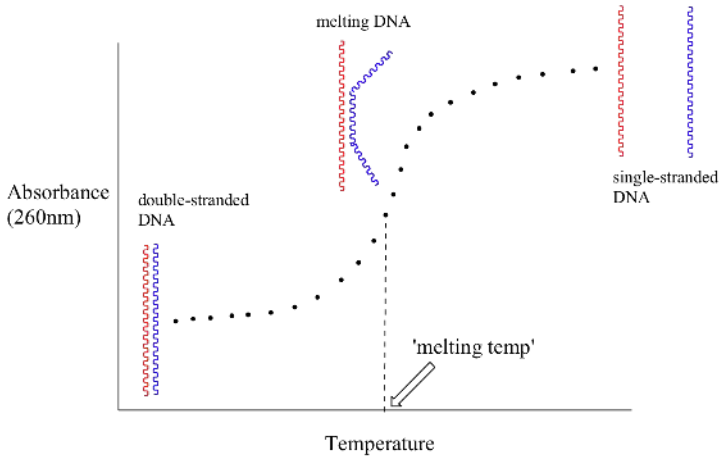
The bases of DNA and RNA are good chromophores:



Adenine Guanine Cytosine Thymine

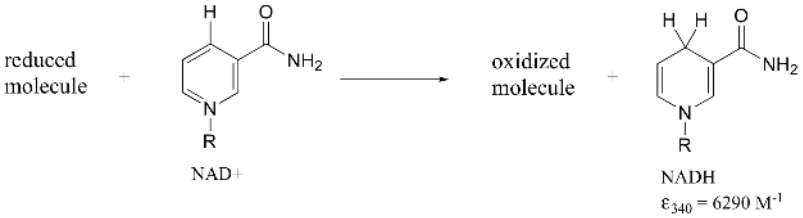
Biochemists and molecular biologists often determine the concentration of a DNA sample by assuming an average value of ε = 0.020 $ng^{-1} \times mL$ for double-stranded DNA at its λ_{max} of 260 nm (notice that concentration in this application is expressed in mass/volume rather than molarity: ng/mL is often a convenient unit for DNA concentration when doing molecular biology).

Because the extinction coefficient of double stranded DNA is slightly lower than that of single stranded DNA, we can use UV spectroscopy to monitor a process known as DNA melting. If a short stretch of double stranded DNA is gradually heated up, it will begin to 'melt', or break apart, as the temperature increases (recall that two strands of DNA are held together by a specific pattern of hydrogen bonds formed by 'base-pairing').

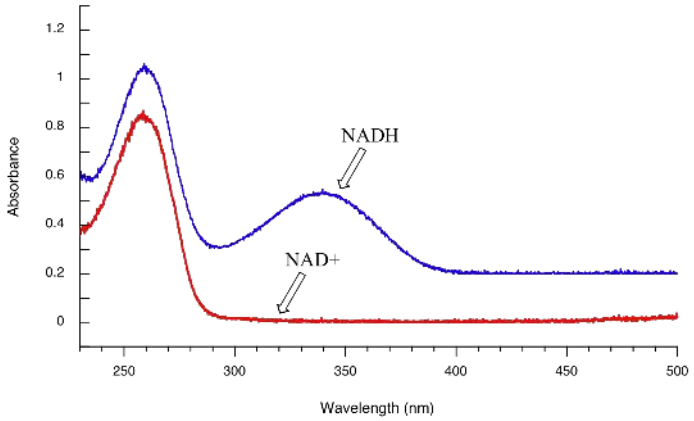


As melting proceeds, the absorbance value for the sample increases, eventually reaching a high plateau as all of the double-stranded DNA breaks apart, or ‘melts’. The mid-point of this process, called the ‘melting temperature’, provides a good indication of how tightly the two strands of DNA are able to bind to each other.

Later we will see how the Beer - Lambert Law and UV spectroscopy provides us with a convenient way to follow the progress of many different enzymatic redox (oxidation-reduction) reactions. In biochemistry, oxidation of an organic molecule often occurs concurrently with reduction of nicotinamide adenine dinucleotide (NAD^+, the compound whose spectrum we saw earlier in this section) to NADH:

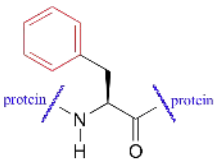


Both NAD^+ and NADH absorb at 260 nm. However NADH, unlike NAD^+, has a second absorbance band with λ_{max} = 340 nm and ε = 6290 $L_*mol^{-1}{}_*cm^{-1}$. The figure below shows the spectra of both compounds superimposed, with the NADH spectrum offset slightly on the y-axis:

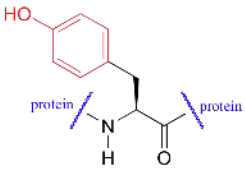


By monitoring the absorbance of a reaction mixture at 340 nm, we can 'watch' NADH being formed as the reaction proceeds, and calculate the rate of the reaction.

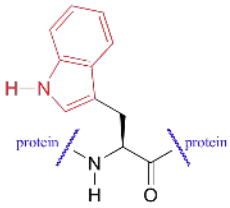
UV spectroscopy is also very useful in the study of proteins. Proteins absorb light in the UV range due to the presence of the aromatic amino acids tryptophan, phenylalanine, and tyrosine, all of which are chromophores.



phenylalanine



tyrosine

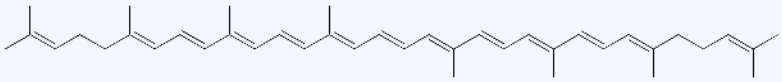


tryptophan

Biochemists frequently use UV spectroscopy to study conformational changes in proteins - how they change shape in response to different conditions. When a protein undergoes a conformational shift (partial unfolding, for example), the resulting change in the environment around an aromatic amino acid chromophore can cause its UV spectrum to be altered.

? EXERCISE 14.7.1

1. 50 microliters of an aqueous sample of double stranded DNA is dissolved in 950 microliters of water. This diluted solution has a maximal absorbance of 0.326 at 260 nm. What is the concentration of the original (more concentrated) DNA sample, expressed in micrograms per microliter?
2. What is the energy range for 300 nm to 500 nm in the ultraviolet spectrum? How does this compare to energy values from NMR and IR spectroscopy?
3. Identify all isolated and conjugated pi bonds in lycopene, the red-colored compound in tomatoes. How many pi electrons are contained in the conjugated pi system?


lycopene

Answer

1) Using ε = A/c, we plug in our values for ε and A and find that c = 3.27 x 10^{-5}M, or 32.7 mM.

2)

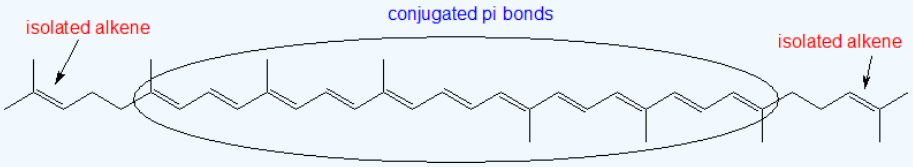
$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

The range of 3.972×10^{-19} to 6.62×10^{-19} joules. This energy range is greater in energy than the in NMR and IR.

3)



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14.8: INTERPRETING ULTRAVIOLET SPECTRA- THE EFFECT OF CONJUGATION

OBJECTIVE

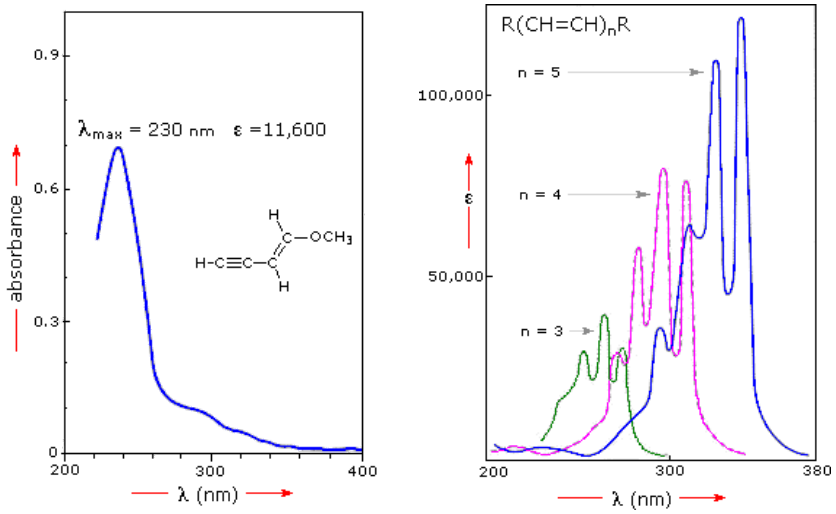
After completing this section, you should be able to use data from ultraviolet spectra to assist in the elucidation of unknown molecular structures.

STUDY NOTES

It is important that you recognize that the ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation in the molecule.

THE IMPORTANCE OF CONJUGATION

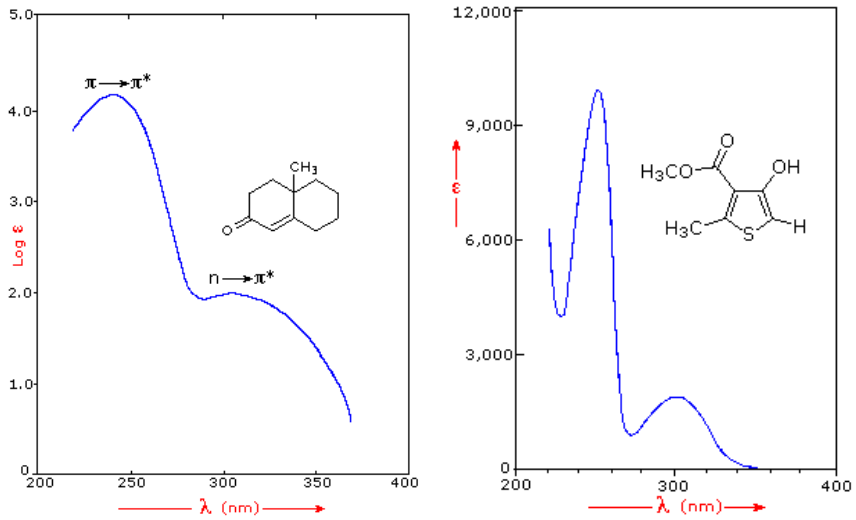
A comparison of the UV/Vis absorption spectrum of 1-butene, λ_{max} = 176 nm, with that of 1,3-butadiene, λ_{max} = 292 nm, clearly demonstrates that the effect of increasing conjugation is to shift toward longer wavelength (lower frequency, lower energy) absorptions. Further evidence of this effect is shown below. The spectrum on the left illustrates that conjugation of double and triple bonds also shifts the absorption maximum to longer wavelengths. From the polyene spectra displayed in the right it is clear that each additional double bond in the conjugated pi-electron system increases the absorption maximum about 30 nm. Also, the molar absorptivity (ε) roughly doubles with each new conjugated double bond. Spectroscopists use the terms defined in the table below when describing shifts in absorption. Thus, extending conjugation generally results in bathochromic and hyperchromic shifts in absorption.



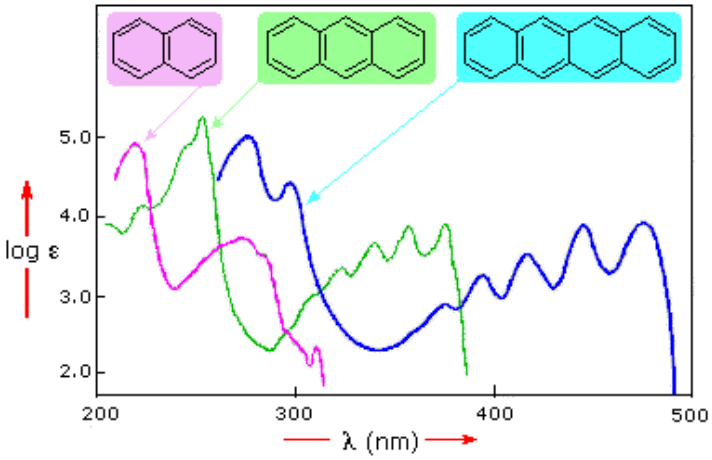
Terminology for Absorption Shifts

Nature of Shift	Descriptive Term
To Longer Wavelength	Bathochromic
To Shorter Wavelength	Hypsochromic
To Greater Absorbance	Hyperchromic
To Lower Absorbance	Hypochromic

Many other kinds of conjugated pi-electron systems act as chromophores and absorb light in the 200 to 800 nm region. These include unsaturated aldehydes and ketones and aromatic ring compounds. A few examples are displayed below. The spectrum of the unsaturated ketone (on the left) illustrates the advantage of a logarithmic display of molar absorptivity. The $\pi \rightarrow \pi^*$ absorption located at 242 nm is very strong, with an ε = 18,000. The weak $n \rightarrow \pi^*$ absorption near 300 nm has an ε = 100.

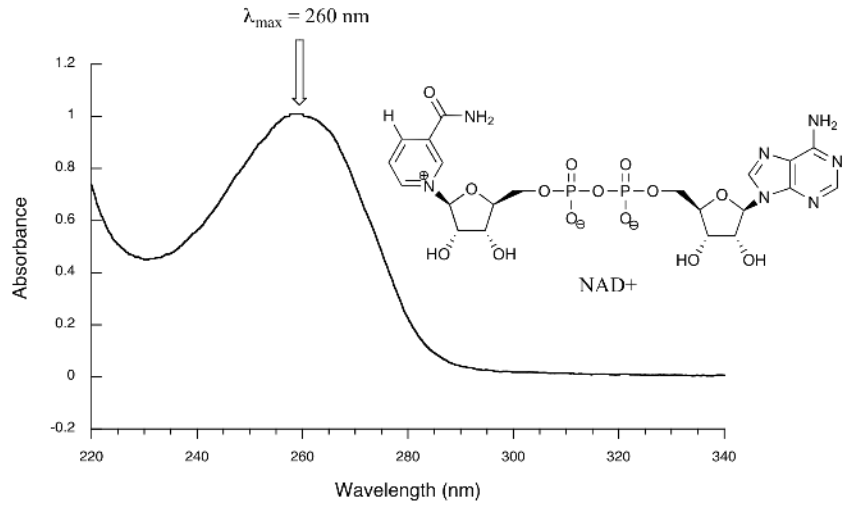


Benzene exhibits very strong light absorption near 180 nm (ε > 65,000) , weaker absorption at 200 nm (ε = 8,000) and a group of much weaker bands at 254 nm (ε = 240). Only the last group of absorptions are completely displayed because of the 200 nm cut-off characteristic of most spectrophotometers. The added conjugation in naphthalene, anthracene and tetracene causes bathochromic shifts of these absorption bands, as displayed in the chart below. All the absorptions do not shift by the same amount, so for anthracene (green shaded box) and tetracene (blue shaded box) the weak absorption is obscured by stronger bands that have experienced a greater red shift. As might be expected from their spectra, naphthalene and anthracene are colorless (with their absorptions in the UV range), but tetracene is orange (since its absorptions move into the visible range).

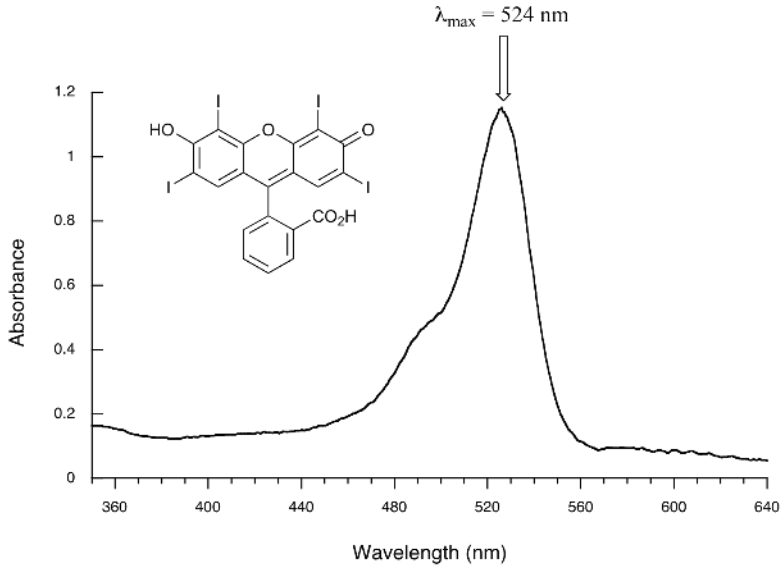


LOOKING AT UV-VIS SPECTRA

Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+. This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



Below is the absorbance spectrum of the common food coloring Red #3. The extended system of conjugated pi bonds causes the molecule to absorb light in the visible range. Because the λ_{max} of 524 nm falls within the green region of the spectrum, the compound appears red to our eyes (recalling the color wheel from Section 14.7).



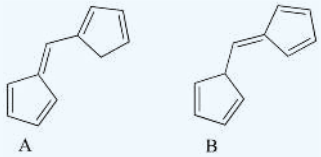
EXAMPLE 14.8.2

How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

EXAMPLE 14.8.3

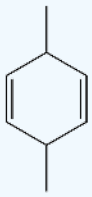
Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.

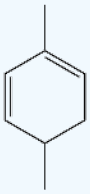


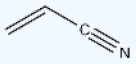
Solution

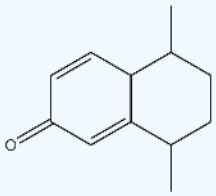
EXERCISE 14.8.1

Which of the following would show UV absorptions in the 200-300 nm range?

A) 

B) 

C) 

D) 

Answer

B and D would be in that range.

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14.9: CONJUGATION, COLOR, AND THE CHEMISTRY OF VISION

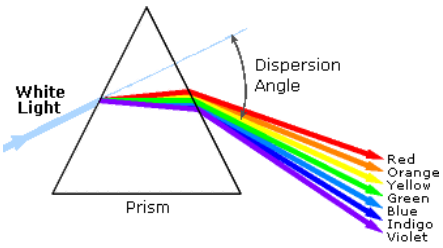
OBJECTIVES

After completing this section, you should be able to

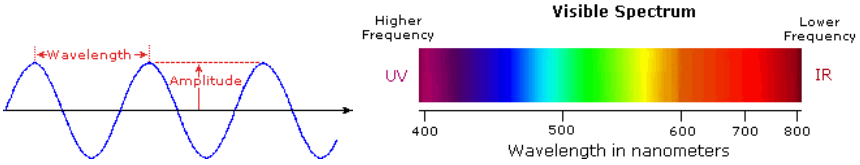
1. explain why some organic compounds have different colors based on compound structure and our perception of light.
2. state the relationship between frequency of light absorbed and the extent of conjugation in an extended pi electron system.

INTRODUCTION

An obvious difference between certain compounds is their color. Thus, quinone is yellow; chlorophyll is green; and aspirin is colorless. In this respect the human eye is functioning as a spectrometer analyzing the light reflected from the surface of a solid or passing through a liquid. Although we see sunlight (or white light) as uniform or homogeneous in color, it is actually composed of a broad range of radiation wavelengths in the ultraviolet (UV), visible and infrared (IR) portions of the spectrum. As shown on the image below, the component colors of the visible portion can be separated by passing sunlight through a prism, which acts to bend the light in differing degrees according to wavelength.

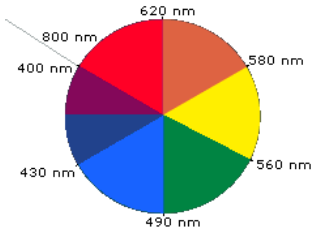


Visible wavelengths cover a range from approximately 400 to 800 nm. The longest visible wavelength is red and the shortest is violet. The wavelengths of what we perceive as particular colors in the visible portion of the spectrum are displayed and listed below.



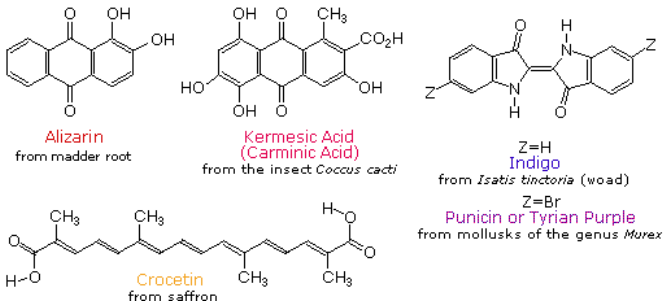
- **Violet:** 400 - 420 nm
- **Indigo:** 420 - 440 nm
- **Blue:** 440 - 490 nm
- **Green:** 490 - 570 nm
- **Yellow:** 570 - 585 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

When white light passes through or is reflected by a colored substance, a characteristic portion of the mixed wavelengths is absorbed. The remaining light will then assume the complementary color to the wavelength(s) absorbed. This relationship is demonstrated by the color wheel shown below. Here, complementary colors are diametrically opposite each other. Thus, absorption of violet (400-440 nm) light renders a substance yellow, and absorption of 490-560 nm (green) light makes it red. Green is unique in that it can be created by absorption close to 400 nm as well as absorption near 800 nm.

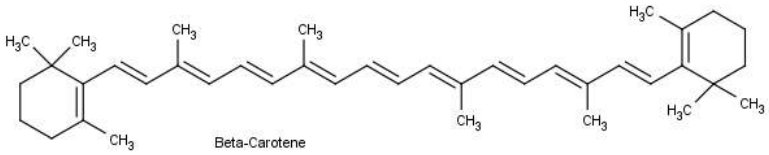


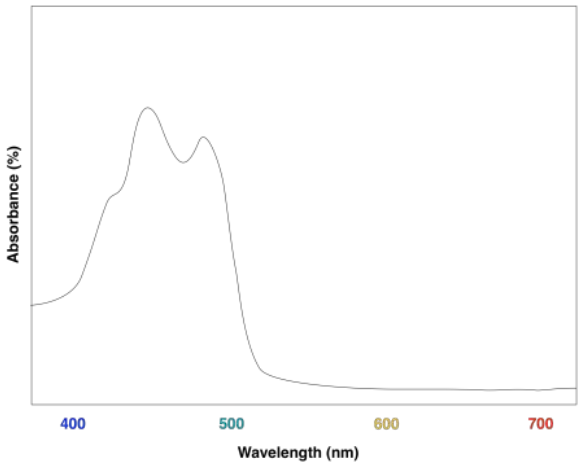
Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

Some Natural Organic Pigments

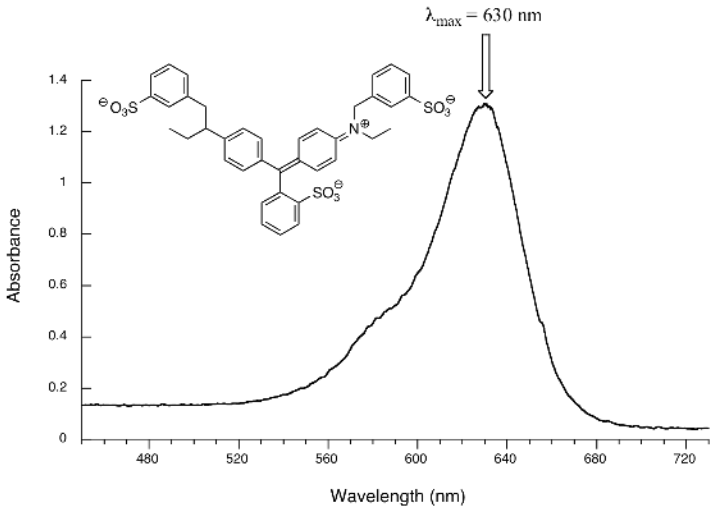


By understanding visible light, complementary colors, and adsorption the color of organic compounds can be understood. Beta-carotene, a compound found in carrots, is a deep orange color. Beta-carotene has 11 conjugated double bonds which places its λ_{max} at 455 nm which is within the blue region of the visible spectrum. The Beta-carotene compound absorbs blue from white light so it appears orange which is the the complementary color of blue.





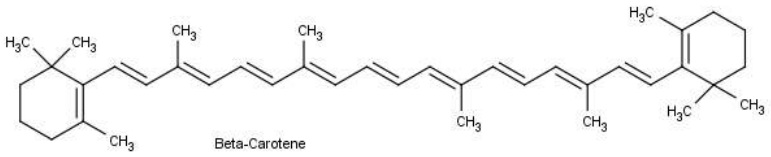
Another example is seen in the absorption spectrum of another food coloring, Blue #1:

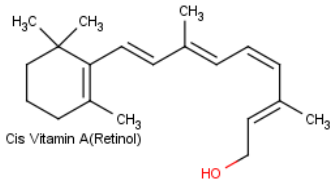


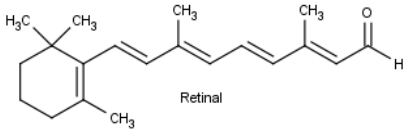
Blue #1 absorbs at a λ_{max} at 630 nm which is the color red in the visible spectrum. Blue is the complementary color of red.

MECHANISM OF VISION

Conjugation is also important in light sensitive compounds used for vision. Beta carotene, found in carrots and other natural products is cleaved into the liver and converted into Vitamin A, also known as retinol. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be oxidized to an aldehyde called retinal which is also important for vision.



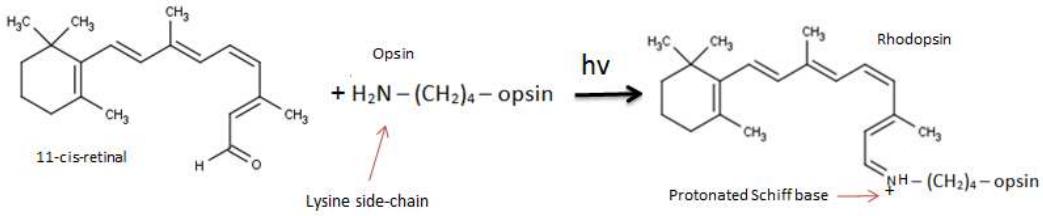




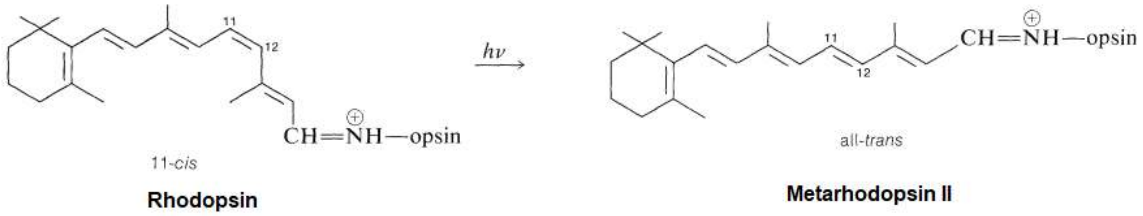
The eye is an extraordinarily sensitive instrument. Although its wavelength response is restricted to 400-800 nm, but its degree of sensitivity is such that a fully dark-adapted eye can clearly detect objects in light so dim as to correspond to a light input over the retina of only about 10,000 quanta per second - one light quantum per three minutes per receptor cell in the retina!

The retina is made up of two kinds of light-sensitive (photoreceptor) cells, known as rods and cones. The rods are the more sensitive and are responsible for vision in dim light. The cones are much fewer in number than the rods and provide detail and color vision in good light. The part of the retina that corresponds to the center of the visual field contains only cones. A red pigment called **rhodopsin** is the photosensitive substance in the rod cells of the retina. It absorbs most strongly in the blue-green region of the visible spectrum (λ_{max} = 500nm) and is essentially unaffected by the far-red end of the spectrum. Cone vision appears to involve a different pigment called **iodopsin**, which absorbs farther toward the red than does rhodopsin.

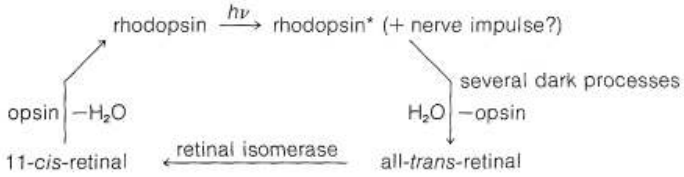
Rhodopsin, is made up of a protein (opsin) and retinal. Opsin does not absorb visible light, but when it is bonded with 11-cis-retinal to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum. Rhodopsin is formed by an an imine (Schiff base) functional group formed between the aldehyde group of the retinal and the side-chain amino function of a lysine unit of opsin.



Opsin itself is colorless, whereas 11-cis-retinal absorbs strongly at 370 nm. The combination of opsin with 11-cis-retinal produces a remarkable shift of λ_{max} to longer wavelengths (430 nm to 620 nm, depending on the species). Light striking the retina changes the color of rhodopsin from red to yellow. The primary photochemical event in this process was established by G. Wald (Nobel Laureate in Physiology and Medicine, 1967), who showed that light absorption led to a change of configuration about the C_{11}-C_{12} double bond of the retinal moiety fo rhodopsin from *cis* to *trans* to form a compound called metarhodopsin II. The new form of trans-retinal does not fit as well into the opsin protein, and so a series of geometry changes in the protein begins. As the protein changes its geometry, it initiates a cascade of biochemical reactions that result in changes in charge so that a large potential difference builds up across the neuron membranes. This potential difference is passed along to an adjoining nerve cell as an electrical impulse. The nerve cell carries this impulse to the brain, where the visual information is interpreted.

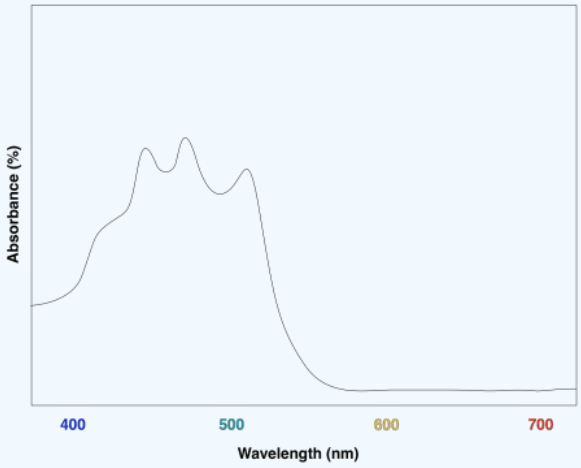


Metarhodopsin II can then be recycled back to rhodopsin by first cleaving to form all-*trans*-retinal and the isomerization back to 11-*cis*-retinal by the enzyme retinal isomerase. Finally, 11-*cis*-retinal is once again coupled with opsin to form rhodopsin.



EXERCISE 14.9.1

Lycopene is conjugated compound found in tomatoes. What colors correspond to the UV-Vis absorption maxima of lycopene? What color do we see when we look at lycopene?



Answer

The absorption maxima of lycopene are regions of blue and green in the visible spectrum. Lycopene would be expected to appears orange and red.

EXERCISE 14.9.2

Asprin has a λ_{max} of 220 nm. Briefly explain why Asprin appears white.

Answer

Asprin absorbs in the ultraviolet portion of the electromagnetic spectrum. Asprin cannot remove any colors from white light by absorption so the compound itself appears white. Many compounds with a relatively small amount of conjugation appear white because they only absorb in the ultraviolet and not the visible region.

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14.S: CONJUGATED COMPOUNDS AND ULTRAVIOLET SPECTROSCOPY (SUMMARY)

CONCEPTS & VOCABULARY

14.0 Introduction

- Dienes that consist of two double bonds separated by a single bond are conjugated.
- Dienes that have the double bonds separated by more than one single bond are isolated (non-conjugated)

14.1 Stability of Conjugated Dienes - Molecular Orbital Theory

- Conjugated dienes are more stable than non-conjugated dienes.
- Electrons in conjugated dienes are delocalized due to overlap of all 4 p-orbitals.
- Molecular orbitals show stability of dienes and allylic carbocations.

14.2 Electrophilic Additions to Conjugated Dienes - Allylic Carbocations

- Addition to conjugated dienes occur at multiple positions due to resonance of the allyl carbocation intermediate called 1,2 and 1,4 addition.

14.3 Kinetic vs. Thermodynamic Control of Reactions

- Lower transition states lead to kinetic products.
- More stable products lead to thermodynamic products.
- Kinetic reaction conditions favor 1,2 addition to conjugated dienes.
- Thermodynamic reaction conditions favor 1,4 addition to conjugated dienes.
- For some reactions, the kinetic and thermodynamic products are the same molecule.

14.4 The Diels-Alder Cycloaddition Reaction

- Cycloaddition reactions involve concerted bonding of two independent pi-electron systems for form a new ring.
- The Diels-Alder reaction is a widely used [4+2] cycloaddition that froms two new sigma bonds.

14.5 Characteristics of the Diels-Alder Reaction

- The Diels-Alder reaction is stereospecific with cis dienophiles yielding *cis* substitution and *trans* dienophiles generate trans substitution.
- The diene in a Diels-Alder reaction must be able to adopt an s-cis conformation.
- Diels-Alder reactions with cyclic dienes favor endo substituents.

14.6 Diene Polymers - Natural and Synthetic Rubbers

- Dienes can form polymers including natural examples such as rubber which is formed from isoprene monomers.

14.7 Ultraviolet Spectroscopy

- When UV and visible light is absorbed, electrons are excited from a bonding or non-bonding orbital to a nearby anti-bonding orbital.
- Colored organic molecules all include extensive conjugated pi electron systems.
- UV absorbance is higher energy than visible light, allowing for excitation of electrons without the low energy pi-bonding to pi anti-bonding transitions available in highly conjugated molecules.
- Chromophores are molecules or structural features that absorb light in the UV-Visible range.

14.8 Interpreting Ultraviolet Spectra: The Effect of Conjugation

- Conjugated pi systems lowers the energy gap for π -π* transitions causing the molecule to absorb light of a longer wavelength.
- Many molecules absorb in the UV spectrum. As the energy gap becomes smaller, these absorbances move into the visible spectrum, starting with violet light which makes the resulting molecules appear yellow.

14.9 Conjugation, Color, and the Chemistry of Vision

- Absorption of light causes chemical changes in the rods and cones in eyes leading to visual sensations.

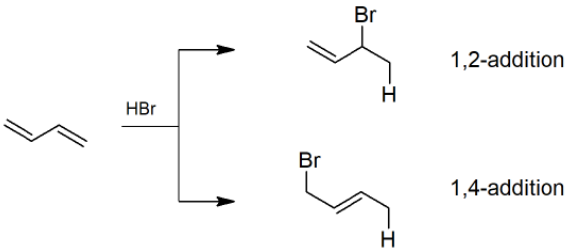
SKILLS TO MASTER

- Skill 14.1 Differentiate between conjugated and isolated dienes.
- Skill 14.2 Explain stability of conjugated dienes using Molecular Orbital Theory.
- Skill 14.3 Draw mechanisms for 1,2 and 1,4 addition to conjugated dienes.

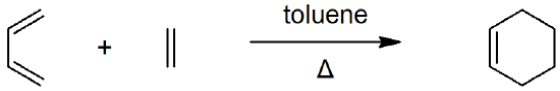
- Skill 14.4 Predict kinetic and thermodynamic products of addition reactions to conjugated dienes.
- Skill 14.5 Explain kinetic and thermodynamic control of reactions.
- Skill 14.6 Identify dienes and dienophiles for Diels-Alder Cycloaddition reactions.
- Skill 14.7 Determine products of Diels-Alder Cycloaddition, including stereochemistry and endo/exo.
- Skill 14.8 Draw mechanisms for Diels-Alder Cycloaddition.
- Skill 14.9 Apply reactions of conjugated dienes to polymerization and natural rubber formation.
- Skill 14.10 Explain the electronic transitions that occur with absorption of UV-Visible light.
- Skill 14.11 Explain the effects of conjugation on wavelength of light absorbed in π -π* transitions.

SUMMARY OF REACTIONS

Electrophilic Addition



Diels−Alder Cycloaddition



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CHAPTER OVERVIEW

15: BENZENE AND AROMATICITY

LEARNING OBJECTIVES

After you have completed Chapter 15, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. use the information presented in this chapter, along with material from earlier chapters, to solve problems, particularly road-map problems and those requiring an understanding of spectroscopy.
3. explain the concept of aromaticity and the stability of aromatic compounds.
4. define, and use in context, the key terms introduced.

In Chapter 3, we identified an aromatic compound as being a compound which contains a benzene ring (or phenyl group). It is now time to define aromaticity in a more sophisticated manner. In this chapter, we discuss the stability of benzene and other aromatic compounds, explaining it in terms of resonance and molecular orbital theory. You will study the nomenclature of aromatic compounds and the Hückel ($4n + 2$) rule for predicting aromaticity. The chapter concludes with a brief summary of the spectroscopic properties of arenes.

15.0: Introduction
15.1: Naming Aromatic Compounds
15.2: Structure and Stability of Benzene
15.3: Aromaticity and the Hückel 4n + 2 Rule
15.4: Aromatic Ions
15.5: Aromatic Heterocycles - Pyridine and Pyrrole
15.6: Polycyclic Aromatic Compounds
15.7: Spectroscopy of Aromatic Compounds
15.S: Benzene and Aromaticity (Summary)

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15.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. explain what is meant by the term “aromatic compound.”
2. identify the aromatic portions present in naturally occurring compounds, given the necessary structures.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- aromatic

STUDY NOTES

At this point in the course, we shall use the term *aromatic* to describe those compounds which contain a benzene ring. A broader definition of aromaticity will be given in Section 15.3.

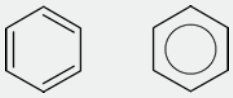
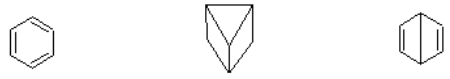


Figure 15.0.1: Two common ways of representing a benzene ring

THE 100 YEAR MYSTERY OF BENZENE

It took humans over 100 years to determine and confirm the structure of benzene. Why did it take so long? Why was there such a curiosity? The 1:1 ratio of carbon to hydrogen in the empirical formula and low chemical reactivity of benzene were a paradox to chemists in the early 1800's.In 1825, Michael Faraday isolated an oily residue of gas lamps. Faraday called this liquid "bicarburet of hydrogen" and measured the boiling point to be 80°C. Additionally, Faraday determined the empirical formula to be CH. About nine years later, Eilhard Mitscherlich synthesized the same compound from benzoic acid and lime (CaO).

During the mid to late 1800's, several possible structures (shown below) were proposed for benzene.



It was not until the 1930's that Kekule's structure was confirmed by X-ray and electron diffraction. During the end of Kekule's career he revealed that the structure came to him in a vision after enjoying a glass or two of wine by the fire in his favorite chair. His inspiration for the structure of benzene was derived from an ouroboros in the flames.



Benzene, C_6H_6, is the simplest member of a large family of hydrocarbons, called aromatic hydrocarbons. These compounds contain ring structures and exhibit bonding that must be described using the resonance hybrid concept of valence bond theory or the delocalization concept of molecular orbital theory. (To review these concepts, refer to the earlier chapters on chemical bonding). The resonance structures for benzene, C_6H_6, are:

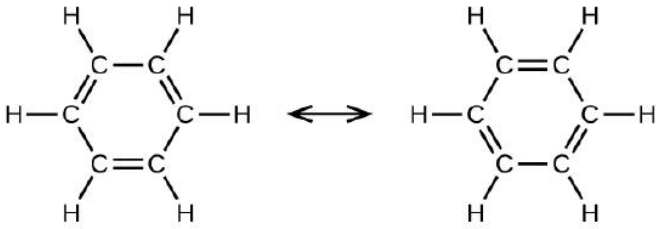


Figure **15.0.1**.

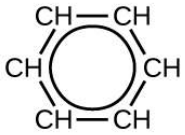
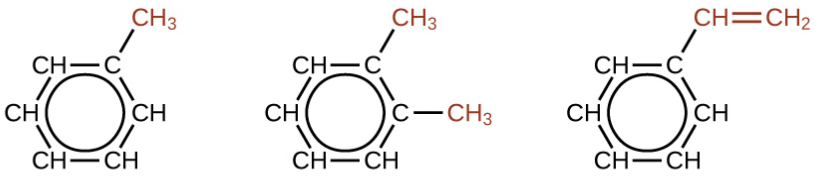


Figure **15.0.1**: This condensed formula shows the unique bonding structure of benzene.

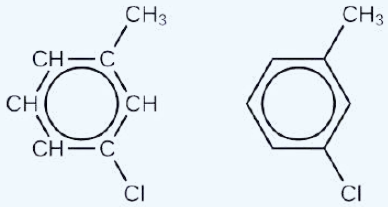
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. The following are typical examples of substituted benzene derivatives:



Toluene and xylene are important solvents and raw materials in the chemical industry. Styrene is used to produce the polymer polystyrene.

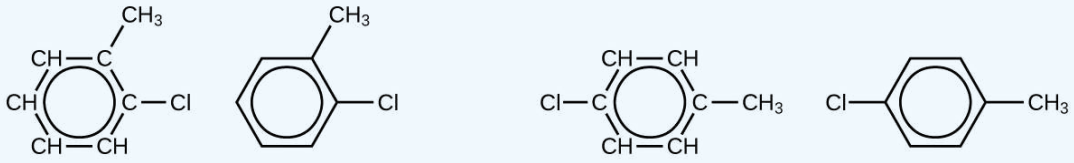
STRUCTURE OF AROMATIC HYDROCARBONS

One possible isomer created by a substitution reaction that replaces a hydrogen atom attached to the aromatic ring of toluene with a chlorine atom is shown here. Draw two other possible isomers in which the chlorine atom replaces a different hydrogen atom attached to the aromatic ring:



Solution

Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:

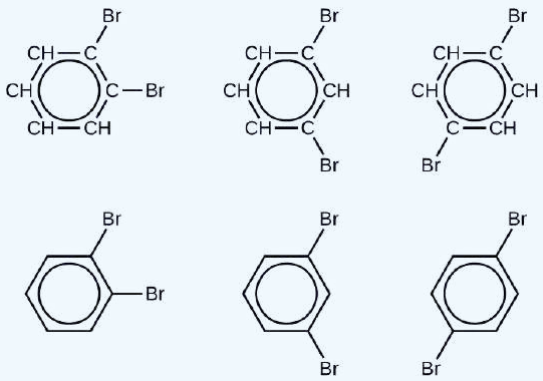


EXERCISE 15.0.1

Draw three isomers of a six-membered aromatic ring compound substituted with two bromines.

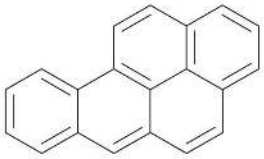
Answer

https://chem.libretexts.org/@go/page/31561



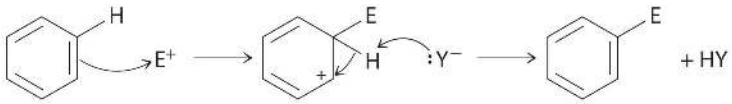
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive substituents can result in a net dipole moment that increases intermolecular attractive forces and raises the melting and boiling points. For example, 1,4-dichlorobenzene, a compound used as an alternative to naphthalene in the production of mothballs, has a melting point of 52.7°C, which is considerably greater than the melting point of benzene (5.5°C).

Certain aromatic hydrocarbons, such as benzene and benz[a]pyrene, are potent liver toxins and carcinogens. In 1775, a British physician, Percival Pott, described the high incidence of cancer of the scrotum among small boys used as chimney sweeps and attributed it to their exposure to soot. His conclusions were correct: benz[a]pyrene, a component of chimney soot, charcoal-grilled meats, and cigarette smoke, was the first chemical carcinogen to be identified.



Benz[a]pyrene

Although arenes are usually drawn with three C=C bonds, benzene is about 150 kJ/mol more stable than would be expected if it contained three double bonds. This increased stability is due to the delocalization of the π electron density over all the atoms of the ring. Compared with alkenes, arenes are poor nucleophiles. Consequently, they do not undergo addition reactions like alkenes; instead, they undergo a variety of electrophilic aromatic substitution reactions that involve the replacement of –H on the arene by a group –E, such as $–NO_2$, $–SO_3H$, a halogen, or an alkyl group, in a two-step process. The first step involves addition of the electrophile (E) to the π system of benzene, forming a carbocation. In the second step, a proton is lost from the adjacent carbon on the ring:



The carbocation formed in the first step is stabilized by resonance.

> *Arenes undergo substitution reactions rather than elimination because of increased stability arising from delocalization of their π electron density.*

Many substituted arenes have potent biological activity. Some examples include common drugs and antibiotics such as aspirin and ibuprofen, illicit drugs such as amphetamines and peyote, the amino acid phenylalanine, and hormones such as adrenaline.

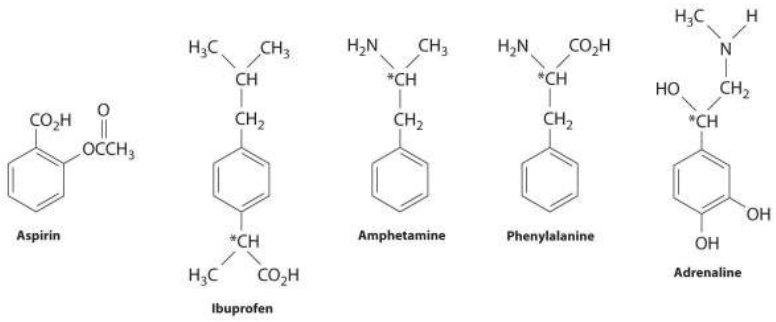


Figure **15.0.2**: Biologically Active Substituted Arenes

Aspirin (antifever activity), ibuprofen (antifever and anti-inflammatory activity), and amphetamine (stimulant) have pharmacological effects. Phenylalanine is an amino acid. Adrenaline is a hormone that elicits the "fight or flight" response to stress. Chiral centers are indicated with an asterisk.

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15.1: NAMING AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. draw the structure of each of the common aromatic compounds in Figure 16 (Common benzene derived compounds with various substituents), given their IUPAC-accepted trivial names.
2. write the IUPAC-accepted trivial name for each of the compounds in Figure 16, given the appropriate Kekulé, condensed or shorthand structure.
3. identify the ortho, meta and para positions in a monosubstituted benzene ring.
4. use the ortho/meta/para system to name simple disubstituted aromatic compounds.
5. draw the structure of a simple disubstituted aromatic compound, given its name according to the ortho/meta/para system.
6. provide the IUPAC name of a given aromatic compound containing any number of the following substituents: alkyl, alkenyl or alkynyl groups; halogens; nitro groups; carboxyl groups; amino groups; hydroxyl groups.
7. draw the structure of an aromatic compound containing any number of the substituents listed in Objective 6, above, given the IUPAC name.
8. provide the IUPAC name of a given aromatic compound in which the phenyl group is regarded as a substituent.
9. draw the Kekulé, condensed or shorthand structure of an aromatic compound in which the phenyl group is regarded as a substituent, given its IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- arene
- benzyl group
- phenyl group

STUDY NOTES

You should already know the names and structures of several of the hydrocarbons shown in Figure 15.1. A compound containing a benzene ring which has one or more alkyl substituents is called an arene.

A phenyl group consists of a benzene ring with one of its hydrogens removed.

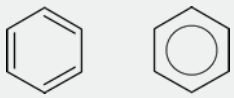


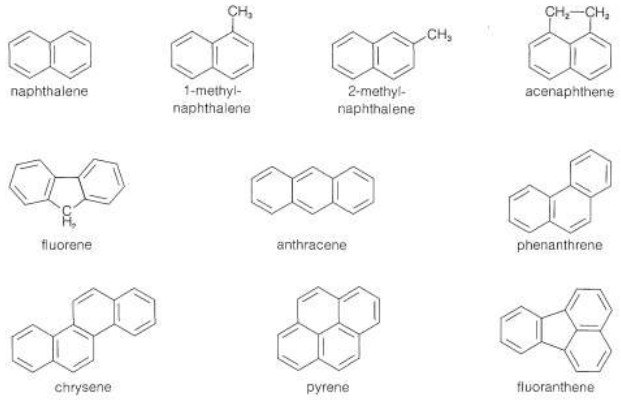
Figure **15.1.1**: Two ways of representing a phenyl group

You should memorize the structures and formulas shown in Figure 16. You will meet these compounds frequently throughout the remainder of this course.

Note that the ortho/meta/para system cannot be used when more than two substituents are present in the benzene ring. The “numbering system” can be used instead of the ortho/meta/para system in most cases when only two substituents are present.

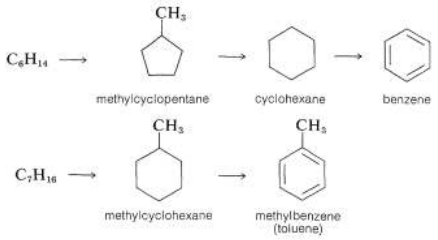
SOURCES OF AROMATIC COMPOUNDS

Initially aromatic compounds were isolated from coal tar. Coal tar, which is a distillate obtained when heating coal at 1000 ºC in the absence of air, is a source of an amazing number of aromatic compounds. Many simple aromatic compounds, some of which includes nitrogen, oxygen, and sulfur, as well as hydrocarbons are obtained.



Some of the Aromatic Compounds Obtained from Coal Tar

Prior to World War II, coal tar was the only important source of aromatic hydrocarbons, but during the war the demand for benzene and toluene, a precursor to the explosive TNT, rose so sharply that other sources had to be found. Today, most of the benzene and almost all of the toluene produced in the United States are derived from petroleum. Although petroleum does contain some aromatic compound, it primarily made up of alkanes of various chain lengths. Aromatic compounds are synthesized from petroleum the by a process referred to in the petroleum industry as catalytic re-forming or hydroforming. This involves heating a C6-C10 alkane fraction of petroleum with hydrogen in the presence of a catalyst to modify the molecular structure of its components. Some amazing transformations take place, and the C6-C7 alkanes can be converted to cycloalkanes, which, in turn, are converted to arenes. Benzene, and methylbenzene (toluene) are produced primarily in this way.



NOMENCLATURE OF MONO-SUBSTITUTED BENZENES

Unlike aliphatic organics, nomenclature of benzene-derived compounds can be confusing because a single aromatic compound can have multiple possible names (such as common and systematic names) be associated with its structure. Common names are often used in the nomenclature of aromatic compounds. IUPAC still allows for some of the more widely used common name to be used. A partial list of these common name is shown in Figure **15.1.2** and there are numerous others. These common names take the place of the benzene base name. Methylbenzene is commonly known with the base name toluene, hydroxyphenol is known as phenol etc. It is very important to be able to identify these structures as they will be utilized in the nomenclature of more complex compounds.

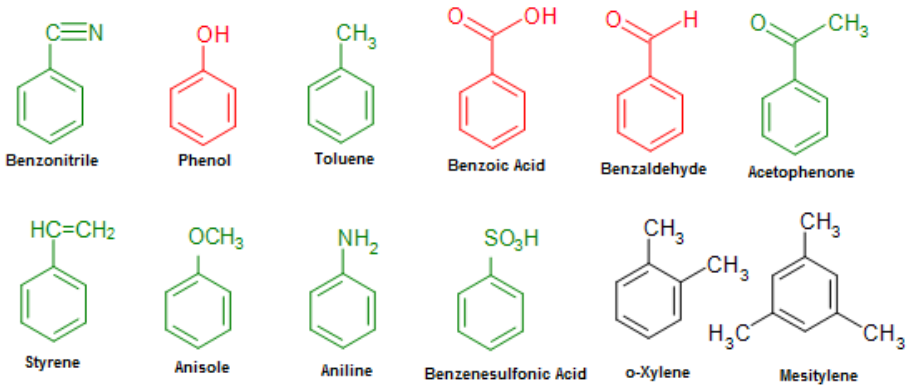
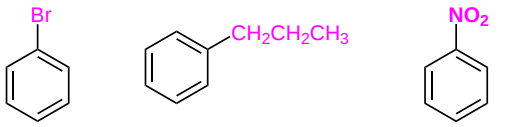


Figure **15.1.2**: Common Names for Mono-Substituted Benzenes

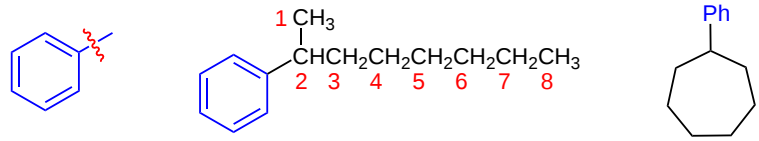
Mono-substituted benzene rings, with a substituent not on the list above, are named with benzene being the parent name. These compounds are named as such: *Name of the substituent + Benzene.*



Bromobenzene **Propyl**benzene **Nitro**benzene

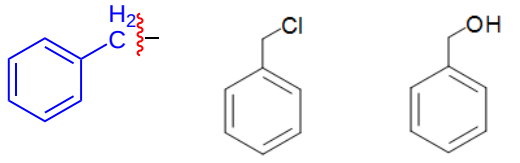
THE USE OF PHENYL AND BENZYL IN NOMENCLATURE

If the alkyl group attached to the benzene contains seven or more carbons the compounds is named as a phenyl substituted alkane. The name phenyl (C_6H_5-)is often abbreviated (Ph) and comes from the Greek word **pheno** which means "I bear light". This name commemorates the fact that benzene was first isolated by Michael Faraday in 1825 from the residue left in London street lamps which burned coal gas. If the alkyl substituent is smaller than the benzene ring (six or fewer carbons), the compound is named as an alkyl-substituted benzene following the rules listed above.



Phenyl group **2-Phenyl**octane **Phenyl**cycloheptane

The benzyl group (abbv. Bn), similar to the phenyl group and can be written as $C_6H_5CH_2$-R, $PhCH_2$-R, or Bn-R. Nomenclature of benzyl group based compounds are very similar to the phenyl group compounds. For example, a chlorine attached to a benzyl group would simply be called benzyl chloride, whereas an OH group attached to a benzyl group would simply be called benzyl alcohol.

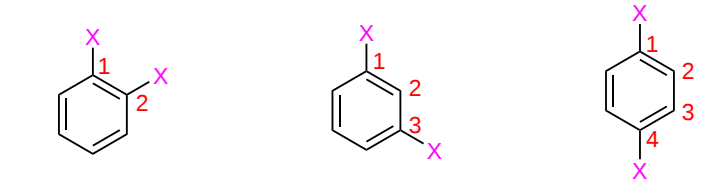


Benzyl group **Benzyl Chloride** **Benzyl Alcohol**

NOMENCLATURE OF DISUBSTITUTED BENZENES

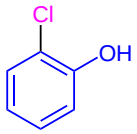
With disubstituted benzenes there are three distinct positional isomers which can occur and must be identified in the compounds name. Although numbering can be used to indicate the position of the two subsituents it is much more common for the compounds to be named using prefixes. These prefixes are italicized and are often abbreviated with a single letter. They are defined as the following:

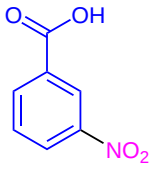
- ***ortho*- *(o-):*** 1,2- (next to each other in a benzene ring)
- ***meta*- *(m):*** 1,3- (separated by one carbon in a benzene ring)
- ***para*- *(p):*** 1,4- (across from each other in a benzene ring)

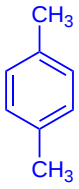


***ortho*-Disubstituted (1,2)** ***meta*-Disubstituted (1,3)** **para-Disubstituted (1,4)**

Figure **15.1.2**. If any do appear then the compound is not named as a benzene but with a different parent name. These compounds are named as such: *Position prefix-Name of the substituent + Name of parent chain.*

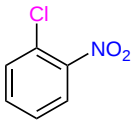


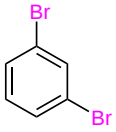


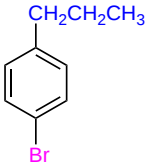


ortho-Chlorophenol **meta-Nitrobenzoic acid** **para-Xylene**

Figure **15.1.2** the compound is named as such: *Position prefix-Names of the substituents in alphabetical order + benzene.* Remember if two of the same substituent appears then the prefix *di-* is used before the substituent's name.



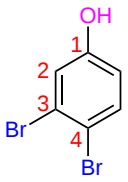


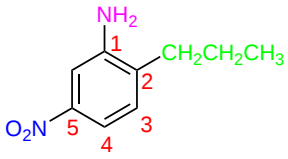


ortho-Chloronitrobenzene **meta-Dibromobenzene** **para-Bromopropylbenzene**

NOMENCLATURE OF BENZENES WITH THREE OR MORE SUBSTITUENTS

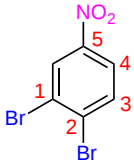
When three or more substituents are present the ortho, meta, para positional prefixes become inadequate and a numbering system for the ring must be applied. Here again it is important to check if any of the substituents are listed in **Figure 15.1.2.** If a substituent from **Figure 15.1.2** is present it is given the parent name in the nomenclature. Also, this substituent is given position one in the numbering system. The other substituents are numbered such that they get the lowest possible sum. In the compound's name the subsituents are given their position number and listed alphabetically. Remember that di-, tri, tetra- prefixes are still used to indicate multiple of the same substituent being present but are ignored for alphabetical listing.



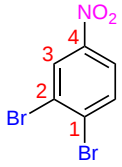


3,4-Dibromophenol **5-Nitro-2-propylaniline**

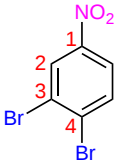
Figure **15.1.2**, the benzene ring is name in the same fashion as cycloalkanes. The lowest possible number is given to the substituents present. This is best done by arbitrarily giving a substituent position one and then numbering the rest of the substituents. Then this process is repeated with the other substituents. Which ever iteration provides the lowest overall sum of numbers will be used in the compound's name. The substituents are assigned a location number, listed alphabetically and the suffix *-benzene* is added.



1,2-Dibromo-5-nitrobenzene



1,2-Dibromo-4-nitrobenzene



3,4-Dibromo-1-nitrobenzene

This numbering provides the lowest numbers to the substituents

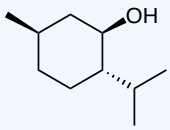
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EXERCISES

EXERCISE 15.1.1



(True/False) The compound above contains a benzene ring and thus is aromatic.

Answer

False, this compound does not contain a benzene ring in its structure.

EXERCISE 15.1.2

Benzene unusual stability is caused by how many conjugated pi bonds in its cyclic ring? ____

Answer

3

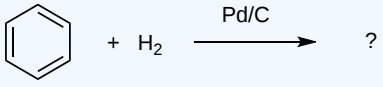
EXERCISE 15.1.3

Menthol, a topical analgesic used in many ointments for the relief of pain, releases a peppermint aroma upon exposure to the air. Based on this conclusion, can you imply that a benzene ring is present in its chemical structure? Why or why not?

Answer

No, a substance that is fragrant does not imply a benzene ring is in its structure. See camphor example (figure 1)

EXERCISE 15.1.4



Answer

No reaction, benzene requires a special catalyst to be hydrogenated due to its unusual stability given by its three conjugated pi bonds.

EXERCISE 15.1.5

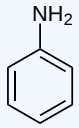
At normal conditions, benzene has ___ resonance structures.

Answer

2

EXERCISE 15.1.6

Which of the following name(s) is/are correct for the following compound?



a. nitrohydride benzene
b. phenylamine
c. phenylamide
d. aniline
e. nitrogenhydrogen benzene
f. All of the above is correct

Answer

b, d

EXERCISE 15.1.7

Convert 1,4-dimethylbenzene into its common name.

Answer

p-Xylene

EXERCISE 15.1.8

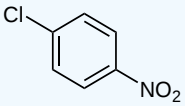
TNT's common name is: _____

Answer

2,4,6-trinitrotoluene

EXERCISE 15.1.9

Name the following compound using OMP nomenclature:



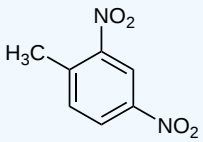
Answer

p-chloronitrobenzene

EXERCISE 15.1.10

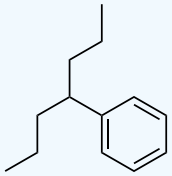
Draw the structure of 2,4-dinitrotoluene.

Answer



EXERCISE 15.1.11

Name the following compound:

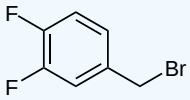


Answer

4-phenylheptane

EXAMPLE 15.1.12

Which of the following is the correct name for the following compound?



a. 3,4-difluorobenzyl bromide
b. 1,2-difluorobenzyl bromide
c. 4,5-difluorobenzyl bromide
d. 1,2-difluoroethyl bromide
e. 5,6-difluoroethyl bromide
f. 4,5-difluoroethyl bromide

Solution

a

EXERCISE 15.1.13

(True/False) Benzyl chloride can be abbreviated Bz-Cl.

Answer

False, the correct abbreviation for the benzyl group is Bn, not Bz. The correct abbreviation for Benzyl chloride is Bn-Cl.

EXERCISE 15.1.14

Benzoic Acid has what R group attached to its phenyl functional group?

Answer

COOH

EXERCISE 15.1.15

(True/False) A single aromatic compound can have multiple names indicating its structure.

Answer

True. TNT, for example, has the common name 2,4,6-trinitrotoluene and its systematic name is 2-methyl-1,3,5-trinitrobenzene.

EXERCISE 15.1.16

List the corresponding positions for the OMP system (o-, m-, p-).

Answer

Ortho - 1,2 ; Meta - 1,3 ; Para - 1,4

EXERCISE 15.1.17

A scientist has conducted an experiment on an unknown compound. He was able to determine that the unknown compound contains a cyclic ring in its structure as well as an alcohol (-OH) group attached to the ring. What is the unknown compound?

a. Cyclohexanol
b. Cyclicheptanol
c. Phenol
d. Methanol
e. Bleach
f. Cannot determine from the above information

Answer

The correct answer is f). We cannot determine what structure this is since the question does not tell us what kind of cyclic ring the -OH group is attached on. Just as cyclohexane can be cyclic, benzene and cycloheptane can also be cyclic.

EXERCISE 15.1.18

Which of the following statements is **false** for the compound, phenol?

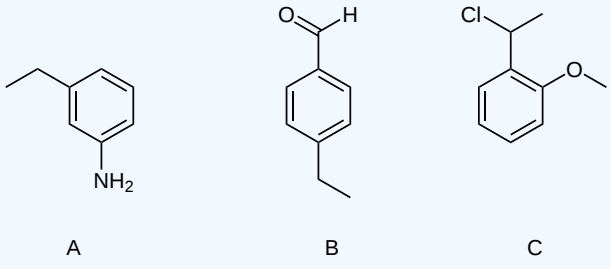
a. Phenol is a benzene derived compound.
b. Phenol can be made by attaching an -OH group to a phenyl group.
c. Phenol is highly toxic to the body even in small doses.
d. Phenol can be used as a catalyst in the hydrogenation of benzene into cyclohexane.
e. Phenol is used as an antiseptic in minute doses.
f. Phenol is amongst one of the three common names retained in the IUPAC nomenclature.

Answer

d

EXERCISE 15.1.19

State wither the following is para, meta, or ortho substituted.



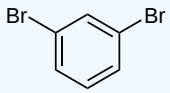
A B C

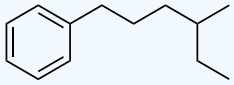
Answer

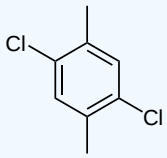
A – meta; B – para; C – ortho

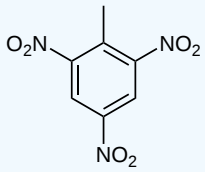
EXERCISE 15.1.20

Name the following compounds.

A) 

B) 

C) 

D) 

Answer

a. 1,3-Dibromobenzene

b. 1-phenyl-4-methylhexane

c. 1,4-Dichloro-2,5-dimethylbenzene

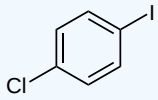
d. 2-methyl-1,3,5-trinitrobenzene. (Also known as trinitrotoluene, or TNT)

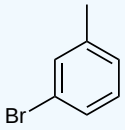
EXERCISE 15.1.21

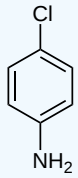
Draw the following structures

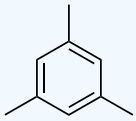
a. p-chloroiodobenzene
b. m-bromotoluene
c. p-chloroaniline
d. 1,3,5-trimethylbenzene

Answer

A) 

C) 

B) 

D) 

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15.2: STRUCTURE AND STABILITY OF BENZENE

OBJECTIVES

After completing this section, you should be able to

1. compare the reactivity of a typical alkene with that of benzene.
2. Use the heat of hydrogenation data to show that benzene is more stable than might be expected for “cyclohexatriene.”
3. state the length of the carbon-carbon bonds in benzene, and compare this length with those of bonds found in other hydrocarbons.
4. describe the geometry of the benzene molecule.
5. describe the structure of benzene in terms of resonance.
6. describe the structure of benzene in terms of molecular orbital theory.
7. draw a molecular orbital diagram for benzene.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- degenerate

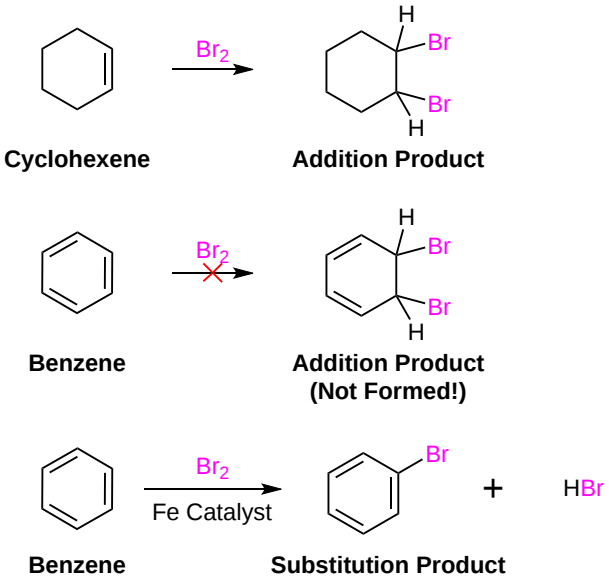
STUDY NOTES

You may wish to review Sections 1.5 and 14.1 before you begin to study this section.

Note that the figure showing the molecular orbitals of benzene has two bonding (π_2 and π_3) and two anti-bonding (π^* and π_5^*) orbital pairs at the same energy levels. Orbitals with the same energy are described as degenerate orbitals.

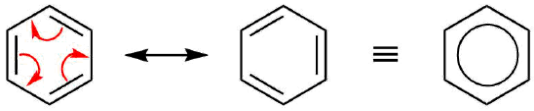
STRUCTURE OF BENZENE

When benzene (C_6H_6) was first discovered its low hydrogen to carbon ratio (1:1) led chemists to believe it contained double or triple bonds. Since double and triple bonds rapidly add bromine (Br_2), this reaction was applied to benzene. Surprisingly, benzene was entirely unreactive toward bromine. In addition, if benzene is forced to react with bromine through the addition of a catalyst, it undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. These experiments suggested that the six-carbon benzene core is unusually stable to chemical modification.

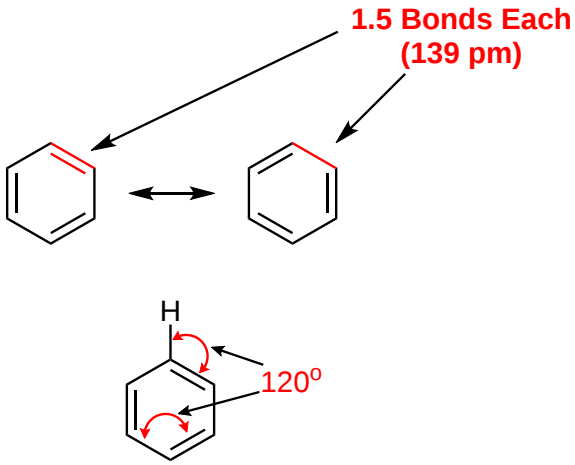


The conceptual contradiction presented by a high degree of unsaturation (low H:C ratio) and high chemical stability for benzene and related compounds remained an unsolved puzzle for many years. Eventually, the presently accepted structure of benzene as a hexagonal, planar ring of carbons with alternating single and double bonds was adopted, and the exceptional chemical stability of this system was attributed to

special resonance stabilization of the conjugated cyclic triene. No single structure provides an accurate representation of benzene as it is a combination of two structurally and energetically equivalent resonance forms representing the continuous cyclic conjugation of the double bonds. In the past, the benzene resonance hybrid was represented by a hexagon with a circle in the center to represent the benzene's pi-electron delocalization. This method has largely been abandoned because it does not show the pi electrons contained in benzene. Currently, the structure of benzene is usually represented by drawing one resonance form with the understanding that it does not completely represent the true structure of benzene.

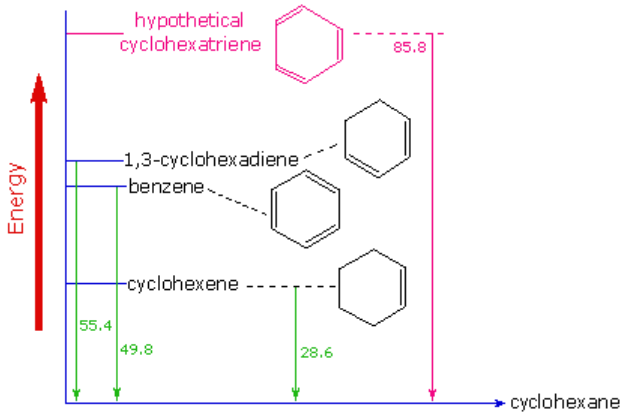


The six-membered ring in benzene is a perfect hexagon with all carbon-carbon bonds having an identical length of 139 pm[1]. The 139 pm bond length is roughly in between those of a C=C double bond (134 pm) and a C-C single (154 pm) which agrees with the benzene ring being a resonance hybrid made up of 1.5 C-C bonds. Each carbon in the benzene ring is sp^2 hybridized which makes all the C-C-C and H-C-C bond angles in benzene 120° and makes the overall molecule planar.



THE HIGH STABILITY OF BENZENE

In previous polyalkene, examples the electron delocalization described by resonance enhanced the stability of the molecule. However, benzene's stability goes beyond this. Evidence for the enhanced thermodynamic stability of benzene was obtained from measurements of the heat released when double bonds in a six-carbon ring are hydrogenated (hydrogen is added catalytically) to give cyclohexane as a common product. In the following diagram cyclohexane represents a low-energy reference point. Addition of hydrogen to cyclohexene produces cyclohexane and releases heat amounting to 28.6 kcal per mole. If we take this value to represent the energy cost of introducing one double bond into a six-carbon ring, we would expect a cyclohexadiene to release 57.2 kcal per mole on complete hydrogenation, and 1,3,5-cyclohexatriene to release 85.8 kcal per mole.



These **heats of hydrogenation** would reflect the relative thermodynamic stability of the compounds. In practice, 1,3-cyclohexadiene is slightly more stable than expected, by about 2 kcal, presumably due to conjugation of the double bonds. **Benzene, however, is an**

extraordinary 36 kcal/mole more stable than expected. This sort of stability enhancement is called **aromaticity** and molecules with aromaticity are called aromatic compounds. Benzene is the most common aromatic compound but there are many others. Aromatic stabilization explains benzene's lack of reactivity compared to typical alkenes.

ATOMIC ORBITALS OF BENZENE

Also, each of benzene's six carbon atoms are sp^2 hybridized and have an unhybrized p orbital perpendicular to plane of the ring. Because each of the six carbon atoms and their corresponding p orbitals are equivalent, it is impossible for them to only overlap with one adjacent p orbital to create three defined double bonds. Instead each p orbital overlaps equally with both adjacent orbitals creating a cyclic overlap involving all six p orbitals. This allows the p orbitals to be delocalized in molecular orbitals that extend all the way around the ring allowing for more overlap than would be obtained from the linear 1,3,5-hexatriene equivalent.

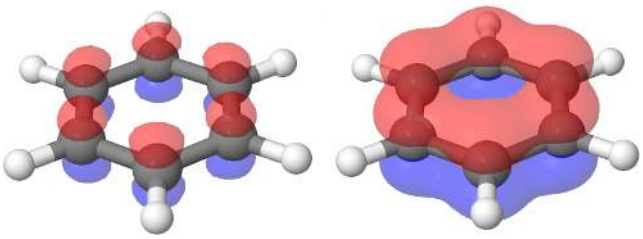


Figure **15.2.1**: Each carbon in the benzene ring is sp2 hybrized with a p orbital perpendicular to the ring plane (Left) Being planar and cyclic allows benzene's p orbitals to undergo cyclic overlap (Right)

For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn't overlap properly and benzene is known to be a flat molecule. An electrostatic potential map of benzene, shown below, shows that the pi electrons are evenly distributed around the ring and that every carbon equivalent.

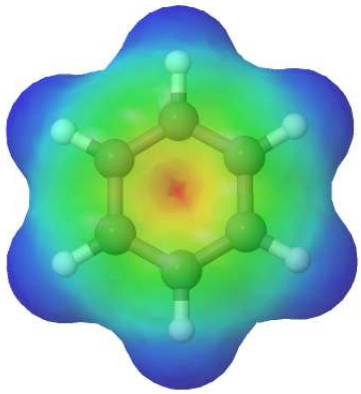
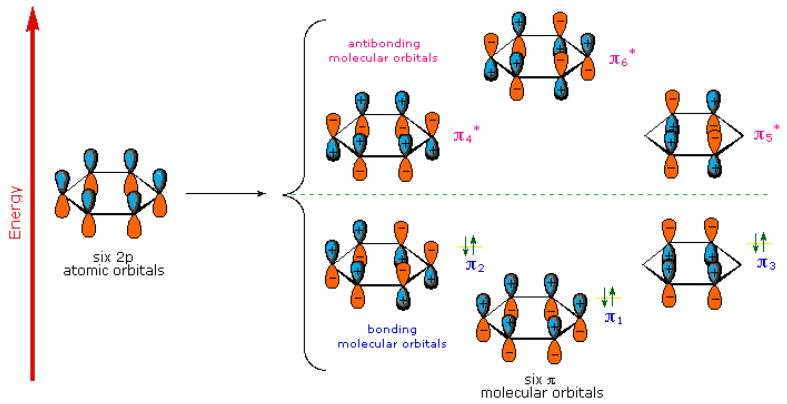


Figure **15.2.2**: An electrostatic potential map of benzene

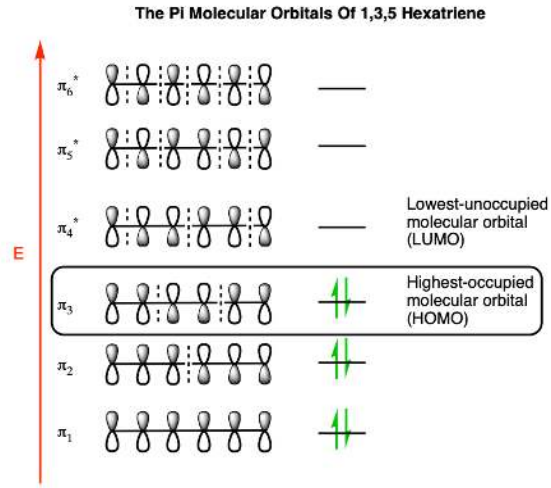
THE MOLECULAR ORBITALS OF BENZENE

A molecular orbital description of benzene provides a more satisfying and more general treatment of "aromaticity". We know that benzene has a planar hexagonal structure in which all the carbon atoms are sp^2 hybridized, and all the carbon-carbon bonds are equal in length. As shown below, the remaining cyclic array of six p-orbitals (one on each carbon) overlap to generate six molecular orbitals, three bonding and three antibonding. The plus and minus signs shown in the diagram do not represent electrostatic charge, but refer to phase signs in the equations that describe these orbitals (in the diagram the phases are also color coded). When the phases correspond, the orbitals overlap to generate a common region of like phase, with those orbitals having the greatest overlap (e.g. π_1) being lowest in energy. The remaining carbon valence electrons then occupy these molecular orbitals in pairs, resulting in a fully occupied (6 electrons) set of bonding molecular orbitals. It is this completely filled set of bonding orbitals, or **closed shell**, that gives the benzene ring its thermodynamic and chemical stability, just as a filled valence shell octet confers stability on the inert gases.



To better see source of the stabilizing aromaticity effect created by the cyclic p orbitals of benzene, the molecular orbitals of 1,3,5-hexatriene must be investigated. The molecule 1,3,5-hexatriene contains six p orbitals which all overlap but in a linear fashion. As with benzene, this overlap creates 3 stabilized bonding molecular which are completely filled with six p electron. As expected, the conjugation creates a marked increase of stability in 1,3,5-hexatriene but not as much as in benzene.





The main difference in stability can be seen when comparing the lowest energy molecular orbital of 1,3,5-hexatriene and benzene: pi_1. In pi_1 molecular orbital of 1,3,5-hexatriene there are 5 stabilizing bonding interactions where there are 6 stabilizing bonding interactions in the pi_1 of benzene. The sixth bonding interaction is made possible by benzene's p orbitals being in a ring. Because benzene's pi_1 molecular orbital has more stabilizing bonding interactions it is lower in energy than the pi_1 molecular orbital of 1,3,5-hexatriene. This gives benzene the additional aromatic stability not seen in the acyclic 1,3,5-hexatriene.

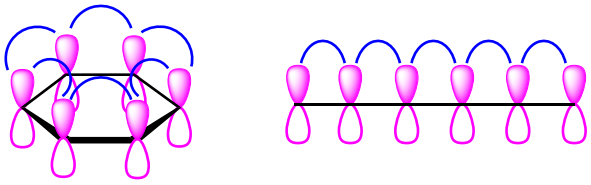
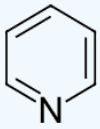


Figure **15.2.3**: The pi_1 molecular orbital of benzene (Left) has 6 stabilizing bonding interaction where 1,3,5-hexatriene's (Right) only has 5.

EXERCISES

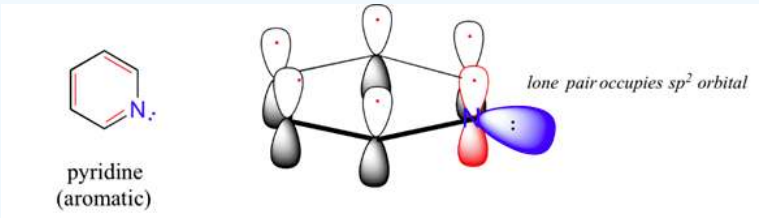
EXERCISE 15.2.1

The molecule, pyridine, is planar with bond angles of 120º. Pyridine has many other characteristics similar to benzene. Draw a diagram showing the p orbitals in pyridine and use it to explain its similarity to benzene.



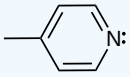
Answer

The nitrogen and each carbon in the pyridine ring is sp^2 hybridized. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair electrons. The unhybridized p orbital contains a single electron, which is part of the 6 pi-electron system delocalized around the ring. Pyridine is most likely aromatic which gives it its planar shape and 120º bond angles.

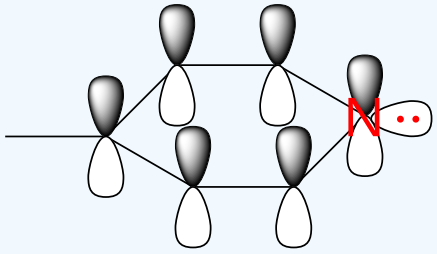


EXERCISE 15.2.2

The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer



REFERENCES

https://royalsocietypublishing.org/d...rspa.1964.0092 "A crystallographic study of solid benzene by neutron diffraction" G.E. Bacon, N. A. Curry, and S.A. Wilson, 1964

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15.3: AROMATICITY AND THE HÜCKEL 4N + 2 RULE

OBJECTIVES

After completing this section, you should be able to

1. define aromaticity in terms of the Hückel $4n + 2$ rule.
2. use the Hückel $4n + 2$ rule to determine whether or not a given polyunsaturated cyclic hydrocarbon should exhibit aromatic properties.
3. describe the difference in properties between an aromatic hydrocarbon, such as benzene, and a non-aromatic polyunsaturated cyclic hydrocarbon, such as cyclobutadiene or cyclooctatetraene.
4. draw molecular orbital diagrams for aromatic species, such as benzene, the cyclopentadienyl anion and pyridine, and compare these diagrams with those obtained for non-aromatic species, such as cyclobutadiene and the cyclopentadienyl cation.

STUDY NOTES

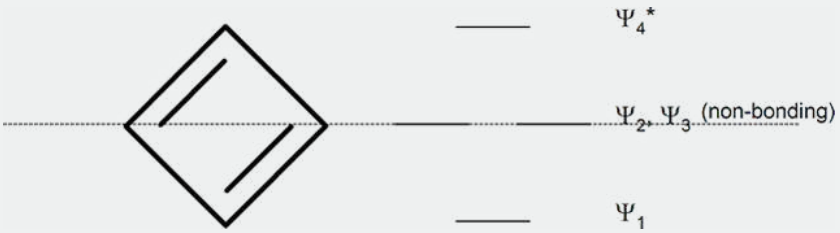
The following mnemonic device will help you establish the approximate energy levels for the molecular orbitals of various organic ring systems.

Whatever the size of the ring, place one point of the ring down to the bottom. The corners of the ring, where the carbons are located, will roughly approximate the location and pattern of the molecular orbital energy levels. Cut the ring exactly in half. The energy levels in the top half will be anti-bonding (Ψ^*) orbitals and those in the bottom will be bonding (Ψ) orbitals. If the carbons fall directly in the centre of the ring (e.g., four-membered rings) the energy levels there are non-bonding.

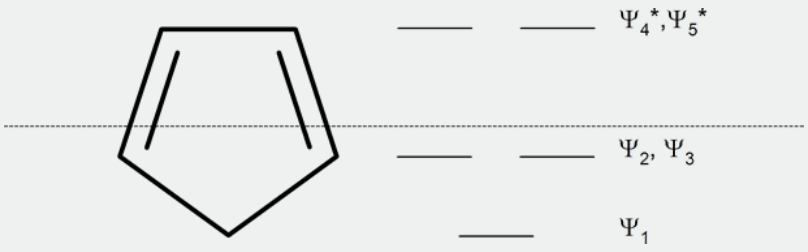
cyclopropenyl ring (three-membered ring)



cyclobutadienyl ring (four-membered ring)



cyclopentadienyl ring (five-membered ring)



In 1931, German chemist and physicist Erich Hückel proposed a theory to help determine if a planar ring molecule would have aromatic properties. His rule states that if a cyclic, planar molecule has $4n + 2$ π electrons, it is considered aromatic. This rule would come to be known as **Hückel's Rule**.

FOUR CRITERIA FOR AROMATICITY

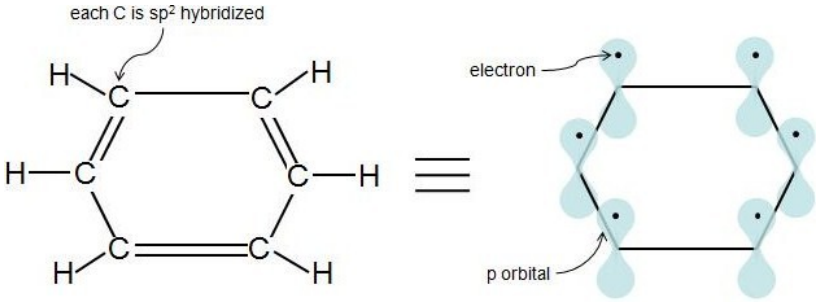
When deciding if a compound is aromatic, go through the following checklist. If the compound does not meet all the following criteria, it is likely not aromatic.

1. The molecule is cyclic (a ring of atoms)

1. The molecule is cyclic (a ring of atoms)
2. The molecule is planar (all atoms in the molecule lie in the same plane)
3. The molecule is fully conjugated (p orbitals at every atom in the ring)
4. The molecule has 4n+2 π electrons (n=0 or any positive integer)

COUNTING Π ELECTRONS?

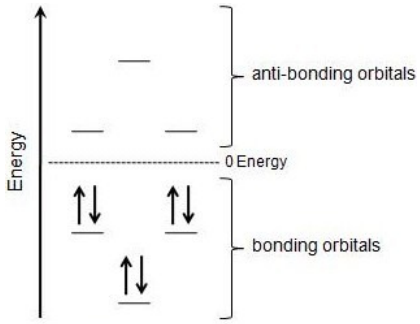
Perhaps the toughest part of Hückel's Rule is figuring out which electrons in the compound are actually π electrons. Once this is figured out, the rule is quite straightforward. Pi electrons lie in the p orbitals and sp^2 hybridized atoms have 1 of these p orbitals each. When looking at a C=C double bond we know that there is one sigma bond and one pi bond. The pi bond is formed by the overlap of 1 p orbital from each carbon in the double bond. Each p orbital contains one electron so when the two p orbitals overlap the two electrons become a pi bond and are thus called pi electrons. Because aromaticity deals directly with double bonds and conjugation it is simpler to just count the number pi electrons in a compound. Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.



benzene has 6 π electrons

WHY 4N+2 Π ELECTRONS?

According to Hückel's Molecular Orbital Theory, a compound is particularly stable if all of its bonding molecular orbitals are filled with paired electrons. This is true of aromatic compounds, meaning they are quite stable. With aromatic compounds, 2 electrons fill the lowest energy molecular orbital, and 4 electrons fill each subsequent energy level (the number of subsequent energy levels is denoted by n), leaving all bonding orbitals filled and no anti-bonding orbitals occupied. This gives a total of 4n+2 π electrons. You can see how this works with the molecular orbital diagram for the aromatic compound, benzene, below. Benzene has 6 π electrons. Its first 2 π electrons fill the lowest energy orbital, and it has 4 π electrons remaining. These 4 fill in the orbitals of the succeeding energy level. Notice how all of its bonding orbitals are filled, but none of the anti-bonding orbitals have any electrons.



molecular orbital diagram for benzene

To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to 4n+2 and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

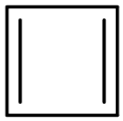
$$4n + 2 = 6 \quad (15.3.1)$$
$$4n = 4 \quad (15.3.2)$$
$$n = 1 \quad (15.3.3)$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

With Hückel's theory we can assume that if a molecule meets the other criteria for aromaticity and also has 2, 6, 10, 14, 18 ect. pi electrons it will most likely be aromatic.

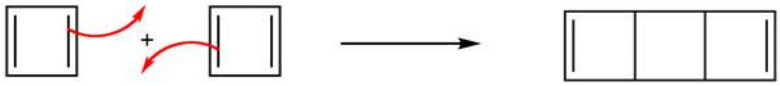
ANTIAROMATICITY

More than 100 years ago, chemists recognized the possible existence of other conjugated cyclic polyalkenes, which at least superficially would be expected to have properties like benzene. The most interesting of these are cyclobutadiene, whose shape and alignment of p orbitals suggested it should have substantial electron-delocalization energies.



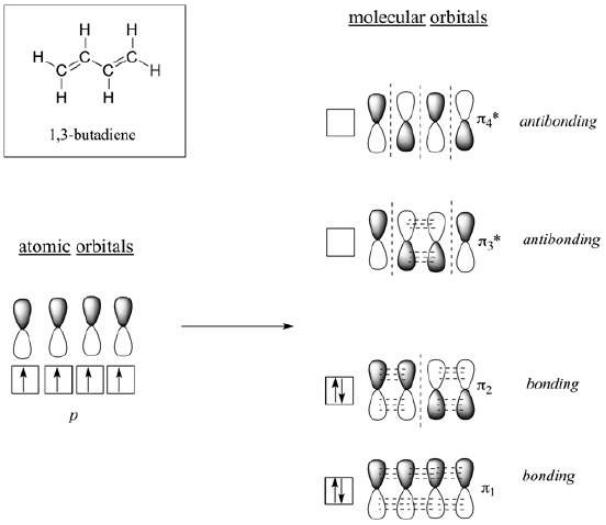
Cyclobutadiene

However, cyclobutadiene was found to be an extremely unstable molecules. In fact, cyclobutadiene is even more reactive than most alkenes. The synthesis of cyclobutadiene eluded chemists for almost 100 years. As more work was done, it became increasingly clear that the molecule, when formed in reactions, was immediately converted to something else. Finally, cyclobutadiene was captured in an essentially rigid matrix of argon at 8K. On warming to even 35K , it dimerizes through a Diels Alder reaction to yield a tricyclicdiene.



Due to the square ring, cyclobutadiene was expected to have some degree of destabilization associated with ring strain. However, estimations of the strain energies, though substantial, did not account for cyclobutadiene's high degree of instability. Also, why was it not being stabilized through cyclic conjugation in the same way as benzene. The answer can be seen in the molecular orbitals.

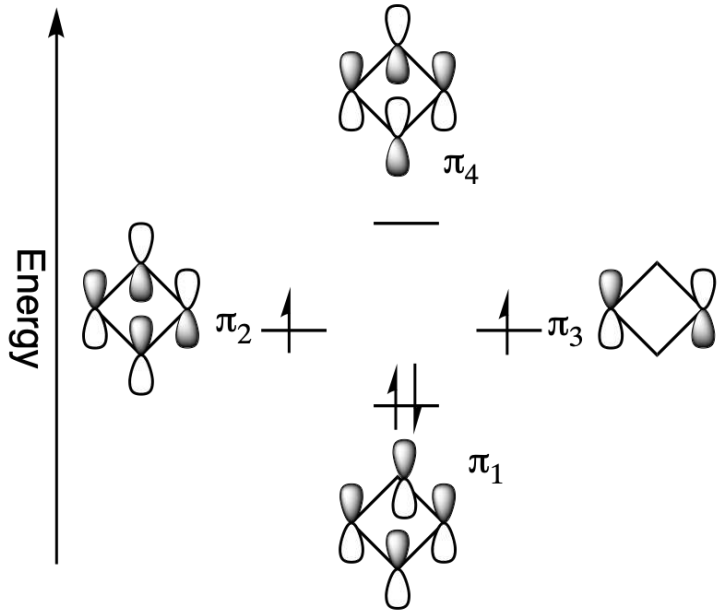
We considering the molecular orbitals diagram of the analogous 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.



However, when placed into a ring the molecular orbitals undergo a significant change. The four p orbitals of cyclobutadiene combine to form the following 4 molecular orbitals:

- a bonding molecular orbital which is lower in energy than the atomic orbitals
- two degenerate non-bonding molecular orbitals which are of equivalent energy to the atomic orbitals
- one antibonding molecular orbital which is higher in energy

The non-bonding orbitals represent that there is no direct interaction between adjacent atoms. When adding cyclobutadiene's 4 pi electrons to the molecular orbital diagram, the bonding orbital is filled and both non-bonding orbitals are singly occupied. If cyclobutadiene's double bonds were delocalized, all the pi electrons would be in low energy bonding orbitals. However, only two of the pi electrons are in bonding orbitals; the other two are non-bonding. In addition, the molecular orbital diagram shows that two of the electrons are unpaired, a situation called a triplet state, which usually makes organic molecules very reactive. For cyclobutadiene cyclic conjugation has made the molecule less stable. This unexpected instability in 4n π-electron cyclic conjugated compounds is termed **antiaromaticity** and the compounds are called antiaromatic.



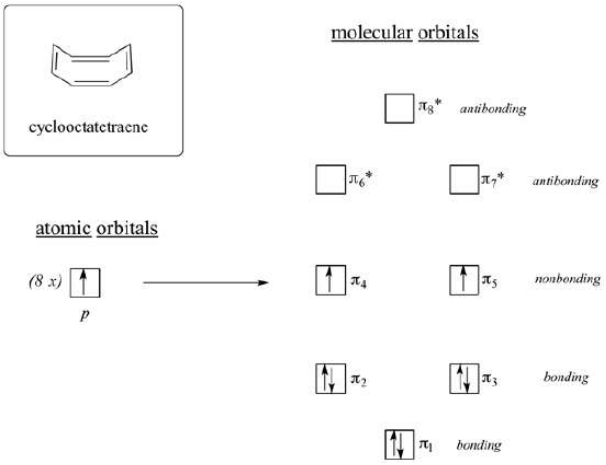
Antiaromaticity gives cyclobutadiene some interesting structural features. Cyclobutadiene's single and double bonds have different bond lengths, 158 pm and 135 pm respectively which give it a rectangular shape. If the double bonds were conjugated, there would only be one average bond length, like benzene, and shape would be square. In fact, cyclobutadiene's double bonds are not conjugated but locked into position.

Just like 4n + 2 rule with aromaticity, compounds which are flat, cyclic, have a p orbital at every member of the ring, and 4n pi electrons should be antiaromatic. Another potentially antiaromatic molecule is 1,3,5,7-cyclooctatetraene.

Cyclooctatetraene was first synthesized in 1911 by a German chemist, R. Willstatter (Nobel Prize 1915), who reported an extraordinary thirteen-step synthesis of cyclooctatetraene from a rare alkaloid called pseudopelletierine isolated from the bark of pomegranate trees. However, during the Second World War, the German chemist W. Reppe found that cyclooctatetraene can be made in reasonable yields by the tetramerization of ethyne under the influence of a nickel cyanide catalyst:



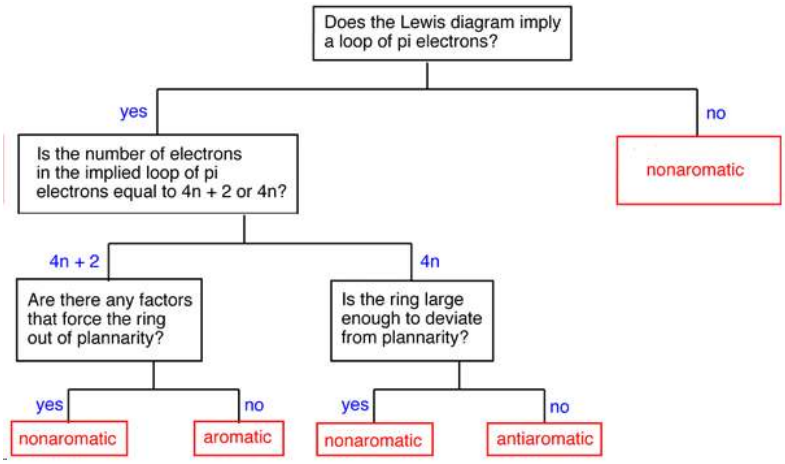
If cyclooctatetraene was flat it would have all the requirements to be antiaromatic. It is cyclic, has a p orbital in every member of the ring, and has 8 pi electrons. When looking at the molecular orbital diagram of cyclooctatetraene we see it shares certain characteristics in common with cyclobutadiene. Two of the molecular orbitals are degenerate non-bonding orbitals. When the molecular orbitals are fill with cyclooctatetraene's 8 pi electrons the last two electrons are unpaired in the two nonbonding orbitals creating a triplet state. Based off the molecular orbital diagram cyclooctatetraene should be antiaromatic.



However, cyclooctatetraene is easily prepared and relatively stable. Also, it undergoes addition reactions typical of alkenes. In reality, cyclooctatetraene is not flat but has a tub-like shape. By assuming this shape, the p orbtials between double bond are out of alignment for overlap. Because the double bonds are not conjugated, cyclooctatetraene escapes the destabilizing effects of antiaromaticity. This makes its its pi bonds react like 'normal' alkenes. Because cyclooctatetraene is not flat nor conjugated it is properly defined as non-aromatic. In general, if an antiaromatic compound has the ability to form a non-planar shape it will do so to avoid destabilization by becoming non-aromatic.

DETERMINING IF A COMPOUND IS AROMATIC, ANTIAROMATIC, OR NONAROMATIC

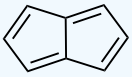
To make this determination it is important to first as if the compound has the possibility of cyclic conjugation. This requires that the compound be cyclic and have a p orbital at every atom in the ring. If the compound does not have both of these criteria it cannot be aromatic or antiaromatic and must therefore be nonaromatic. Next the number of pi electrons in the ring is determined to see if it follows the count of aromaticity (4n + 2) or antiaromaticity (4n). Before making the final determination, it is vital to know the actual geometry of the molecule. Despite the number of pi electrons, a compound cannot be aromatic or antiaromatic if its geometry is not planar to allow for p orbital overlap.



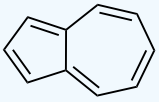
EXAMPLE 15.3.1



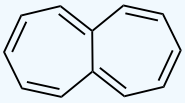
Cyclopentadiene (planar)
4 p Electrons
Nonaromatic



Pentalene (planar)
8 p Electrons
Antiaromatic



Azulene (planar)
10 p Electrons
Aromatic



Heptalene (planar)
12 p Electrons
Antiaromatic

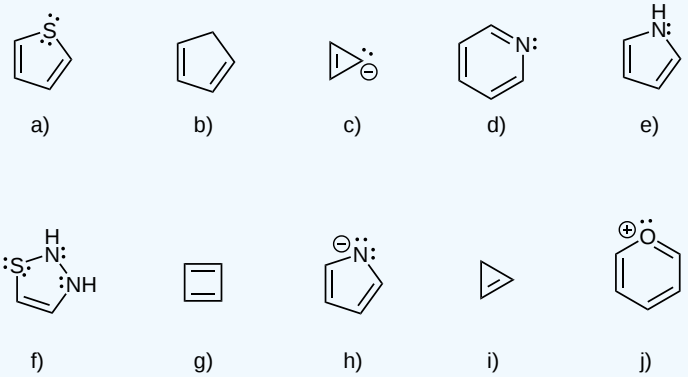
A COMMON MISCONCEPTION

A very common misconception is that hybridization can be used to predict the geometry, or that hybridization somehow involves an energy cost associated with 'promoting' electrons into the hybrid orbitals. **This is entirely wrong.** Hybridization is always determined by geometry. You can only assign hybridization states to an atom if you already know its geometry, based on some experimental or theoretical evidence. The geometry of the oxygen in furan is trigonal planar and therefore the hybridization must be sp^2.

The *specific* rule is that if you have an sp^2 conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel 4n+2 aromaticity. For furan with *two* lone pairs on the oxygen atom, if we count electrons from the carbon atoms, we have 4 (one per carbon). So adding two electrons from one of the lone pairs will give 6 = 4(1)+2, so Hückel rule is applicable and furan is aromatic.

EXERCISE 15.3.1

Using the criteria for aromaticity, determine if the following molecules are aromatic:



a) b) c) d) e)

f) g) h) i) j)

Answer

a) Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1

b) Not aromatic - not fully conjugated, top C is sp^3 hybridized

c) Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2

d) Aromatic - N is using its 1 p orbital for the electrons in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

e) Aromatic - there are 6 π electrons, n=1

f) Not aromatic - all atoms are sp^2 hybridized, but only 1 of S's lone pairs counts as π electrons, so there 8 π electrons, n=1.5

g) Not aromatic - there are 4 π electrons, n=1/2

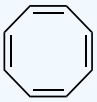
h) Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1

i) Not aromatic - not fully conjugated, top C is sp^3 hybridized

j) Aromatic - O is using its 1 p orbital for the elections in the double bond, so its lone pair of electrons are not π electrons, there are 6 π electrons, n=1

EXERCISE 15.3.2

To be aromatic, a molecule must be planar conjugated, and obey the 4n+2 rule. The following is the following molecule aromatic?



Answer

No, it is not. It does not obey the 4n+2 rule. Also it is not planar.

REFERENCES

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman & Company, 2007.
2. Berson, Jerome. Chemical Creativity: Ideas from the Work of Woodward, Hückel, Meerwein, and Others. New York: Wiley-VCH, 1999.
3. Badger, G.M. Aromatic Character and Aromaticity. London, England: Cambridge University Press, 1969.
4. Lewis, David and David Peters. Facts and Theories of Aromaticity. London, England: Macmillan Press, 1975.

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15.4: AROMATIC IONS

OBJECTIVES

After completing this section, you should be able to

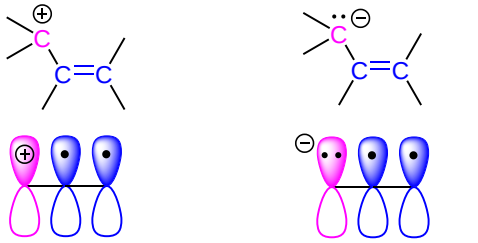
1. use the Hückel 4*n* + 2 rule to explain the stability of the cyclopentadienyl anion, the cycloheptatrienyl cation and similar species.
2. use the Hückel 4*n* + 2 rule to determine whether or not a given unsaturated cyclic hydrocarbon anion or cation is aromatic.
3. draw the resonance contributors for the cyclopentadienyl anion, cation and radical, and similar species.

AROMATIC IONS

As previously, noted a ring must be fully conjugated to have the potential to be aromatic. This means that every atom in the ring must have a *p* orbital which can overlap with adjacent *p* orbitals. Until now the atoms providing the *p* orbitals have been neutral sp^2 hybridized carbons, however it is also possible for sp^2 hybridized carbons to have a charge. There are several examples of cationic and anionic compounds with unexpected stabilities that suggest that they are aromatic. It is important to understand how charged carbons in these compounds will affect the determination of aromaticity.

There are two main situations which need to be considered: The conjugation of a carbocation and the conjugation of a carbanion. A carbocation carbon is surrounded by three electron groups giving it sp^2 hybridization. The remaining unhybridized *p* orbital holds the carbocation's positive charge and is vacant of pi electrons. Although a carbocation is capable of extending conjugation it does not add to the compound's pi electron count.

A carbanion carbon is surrounded by four electron groups and would normally be sp^3 hybridized. However, to obtain the stabilizing effects of conjugation, carbanion carbons can becomes sp^2 hybridized putting the set of lone pair electrons into the unhybridized *p* orbital. Because the carbanion's *p* orbital contains two electrons in the form of a set of lone pair electrons, it increases a compound's pi electron count by 2.

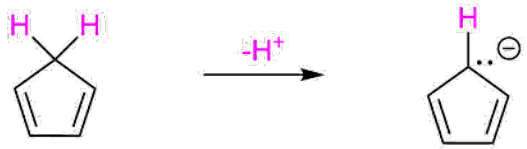


2 p Electrons Total
The carbocation adds
0 p Electrons

4 p Electrons Total
The carbanion adds
2 p Electrons

CYCLOPENTADIENE ION

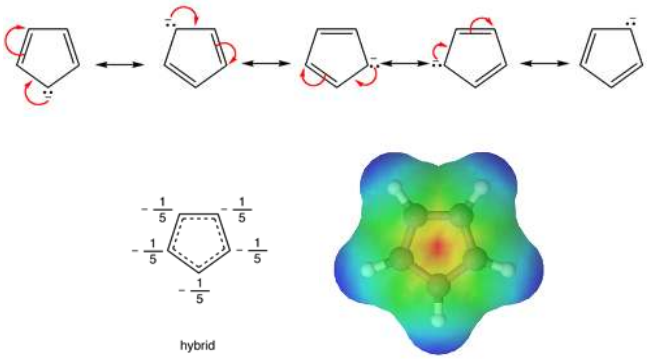
One of the most well know examples of an aromatic ion is the 1,3-cyclopentadiene ion. 1,3-Cyclopentadiene is nonaromatic due to the presence of an intervening sp^3 hybridized -CH_2- carbon atom which prevents pi electrons from delocalizing about the entire ring. Also, it only has 4 pi electrons which does not follow Hückel's 4n + 2 rule. However, if a proton is removed form the CH_2 group to form the cyclopentadienyl anion, the carbon atom becomes sp^2 hybridized and the two electrons of the resulting lone pair occupy the newly produced *p* orbital. This increases the number of pi electrons in the cyclopentadienyl anion to 6 which follows the 4n +2 rule. Moreover, this new *p* orbital overlaps with the *p* orbitals already present allowing for cyclic delocalization of pi electrons about the entire ring.



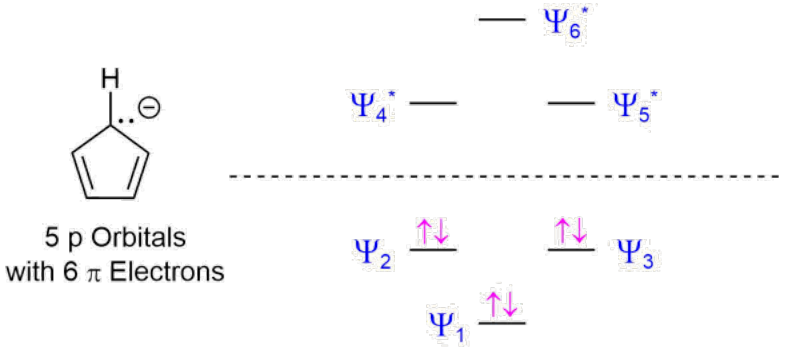
1,3-Cyclopentadiene
Nonaromatic
4 π electrons

Cyclopentadienyl Anion
Aromatic
6 π electrons

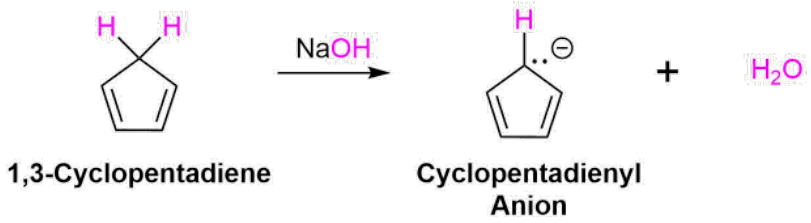
The lone pair electrons and the negative charge are conjugated about the entire ring making each carbon in the cyclopentadienyl anion equivalent with 1/5 the negative charge. The resonance hybrid can be shown by drawing a series of five resonance form. Also, the electrostatic potential map of the cyclopentadienyl anion show the negative charge, seen in red/yellow is distributed over the entire ring. The fact that the red/yellow color is held in the center of the ring indicates that the extra electrons of the ion are involved in the aromatic p-electron system.



The reason why the 4n +2 rule still works for a 5 p orbital ring system can be seen by looking the molecular orbital diagram of the cyclopentadienyl anion. As discussed in **Section 15.3**, the molecular orbital diagram of a 5 p orbital system is made up of 3 bonding MO's and 2 antibonding MO's. The 6 pi electrons gained by forming an anion is enough to completely fill the bonding MO's in the diagram giving the cyclopentadienyl anion aromaticity.



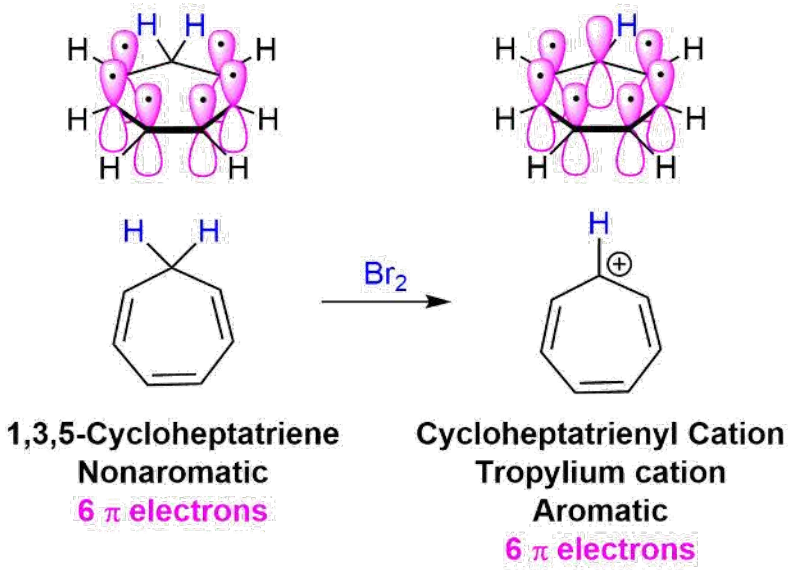
One of the effects of the aromaticity of the cyclopentadienyl anion is that the acidity of 1,3-cyclopentadiene is unusually strong. As previously discussed, stabilizing the conjugate base increases the acidity of the corresponding acid. In this case, the conjugate base of 1,3-cyclopentadiene, the cyclopentadienyl anion, is stabilized through aromaticity. This makes 1,3-cyclopentadiene one of the most acidic hydrocarbons known with a pK_a of 16. This is almost 10^{30} times more acidic than cyclopentane. Because of its acidity, cyclopentadiene can be deprotonated by moderately strong bases such as NaOH.



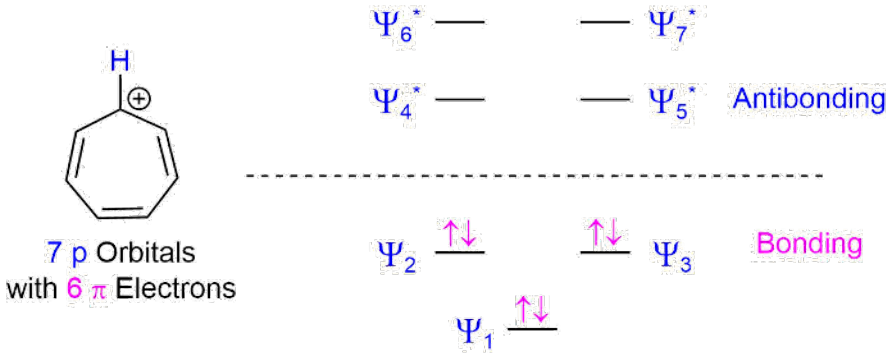
TROPYLIUM ION

The molecule 1,3,5-cycloheptatriene has six pi electrons but is nonaromatic due the presence of an sp^3 hybridized -CH_2- group which prevents cyclic delocalization. When 1,3,5-cycloheptatriene is reacted with a reagent that can remove a hydride ion ($H:^-$), the 1,3,5-cycloheptatrienyl cation, which is commonly known as the tropylium cation, is formed with unexpected ease. Despite the presence of an electron deficient carbocation, the tropylium cation, is unusually stable and can be isolated as a salt.

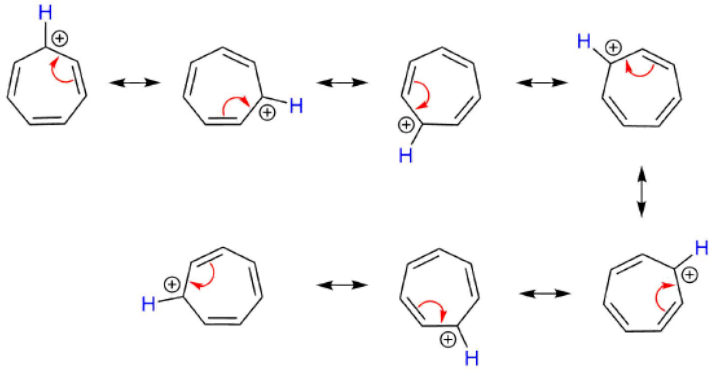
Removal of a hydride from the -CH_2- group in 1,3,5-cycloheptatriene creates an sp^2 hybridized carbocation with a vacant *p* orbital. The new *p* orbital allows for cyclic conjugation to occur among the seven *p* orbitals in the tropylium cation. The vacant *p* orbital does not change the pi electron count so the tropylium cation has 6 pi electrons which obeys the 4n + 2 rule for aromaticity.

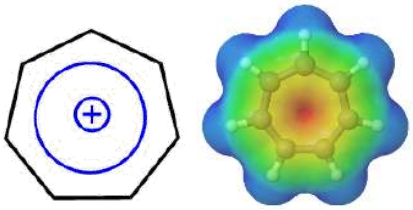


The molecular orbital diagram for the 7 *p* orbitals in the tropylium cation has three bonding MO's and 4 antibonding MO's. The tropylium cation's 6 pi electrons completely fill the bonding molecular orbitals which is consistent with the tropylium cation being aromatic and therefore unusually stable.



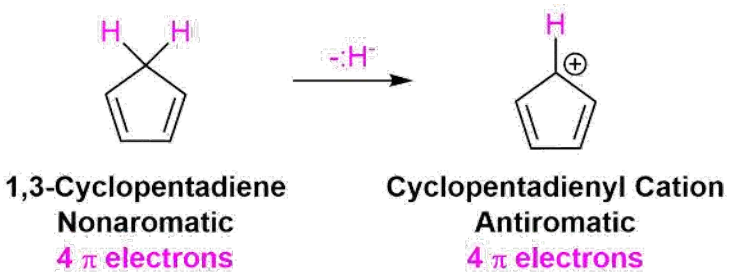
As predicted with aromaticity, the positive charge is completely conjugated about the entire ring giving each carbon +1/7 charge. The true resonance hybrid can be depicted by drawing a series of seven resonance form. Also, the electrostatic potential map of the tropylium cation shows the positive charge is evenly distributed over the entire ring. The equivalency of the carbons in the seven membered ring is experimentally supported by an ^{1}H NMR spectrum of the tropylium cation which contains one peak showing that all seven protons are equivalent.



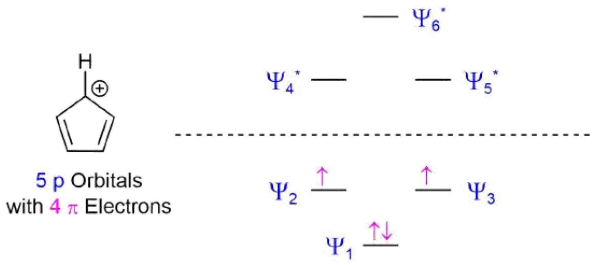


ANTIAROMATIC IONS

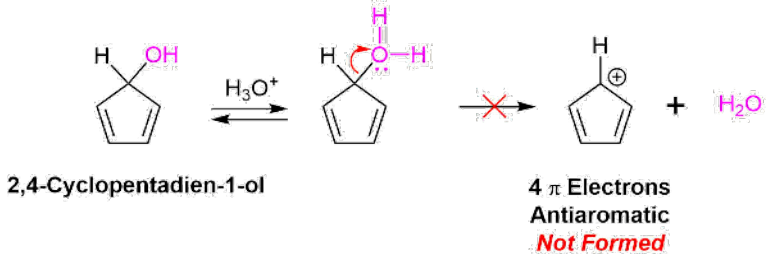
In a similar fashion, cyclically conjugated ions with 4n pi electrons can be predicted to be antiaromatic and therefore highly unstable. An excellent example is the cyclopentadienyl cation. Above, the cyclopentadienyl anion was shown to be aromatic, however, the formation of a carbocation produces a different result. Although the vacant *p* orbital provided by the carbocation allows for cyclic conjugation to occur the compound only has 4 pi electrons.



After placing these 4 pi electrons into the molecular orbital for a cyclic 5 *p* orbital species the bonding molecular orbitals remain unfilled. Two of the pi electrons are unpaired in degenerate molecular orbitals creating the highly unstable triplet state. As predicted by Hückel's Rule, the cyclopentadienyl cation has 4n pi electrons and should be anitaromatic and very unstable.



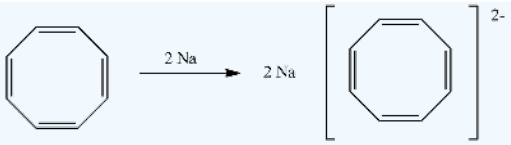
Although there is some discussion as to whether the cyclopentadienyl cation is truly antiaromatic, there is experimental evidence which shows it is usually unstable. In particular, the compound 2,4-cyclopentadien-1-ol is usually resistant to S_N1 reactions with acid halides. The carbocation intermediate created during the mechanism of this reaction would be expected to easily form due to the resonance stabilization provided by the two double bonds. Because the carbocation intermediate is antiaromatic it does not form so the reaction does not occur.



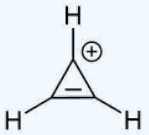
? EXERCISE 15.4.1

1) Are all bonds equivalent cyclopentadienyl anion? How many lines (signals) would you expect to see in a H^1 and C^{13} NMR spectrum?

2) The following reaction occurs readily. Propose a reason why this occurs?



3) Is the cyclopropenium ion aromatic? Use the 4n + 2 rule and the MO diagram for a 3 p orbital ring system to explain your answer.



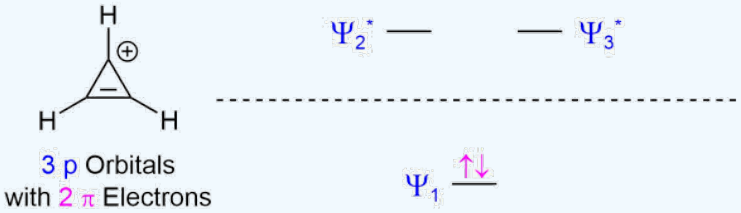
Cyclopropenium Ion

Answer

1) Due to the cyclopentadienyl anion being fully conjugated a protons and carbons are equivalent. Both the ^{1}H and ^{13}C NMR spectrum would only have one signal.

2) The addition of two electrons gives the ring system 10 pi electrons which follows the 4n+2 rule making the dianion aromatic. When looking at the MO diagram for an 8 p orbital ring system, 10 pi electrons completely fills the three bonding MO's and the two nonbonding MO's allowing for aromaticity.

3) The cyclopropenium ion has 2 pi electrons which follows the 4n + 2 rule when n = 0. When considering the molecular orbital diagram for a 3 p orbital ring system the is one bonding MO and two antibonding MO's. The two pi electrons completely fill the bonding MO allowing for aromaticity.



EXERCISES

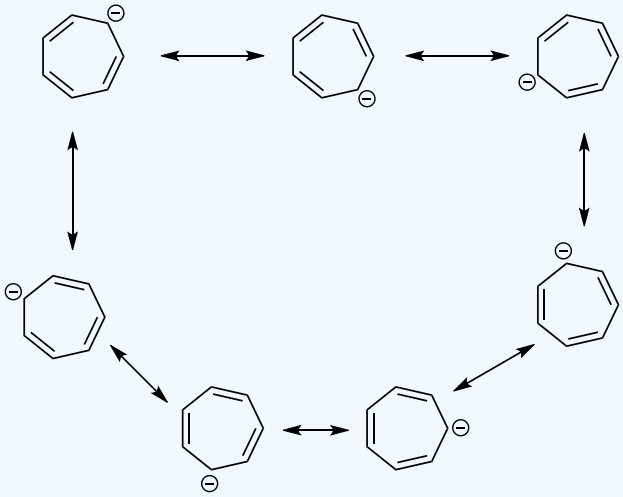
? EXERCISE 15.4.2

Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^{1} NMR? C^{13} NMR?

Answer

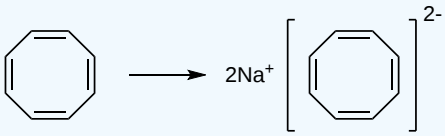
All protons and carbons are the same, so therefore each spectrum will only have one signal each in the proton NMR and carbon NMR.

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EXERCISE 15.4.3

The following reaction occurs readily. Propose a reason why this occurs?



Answer

The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

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15.5: AROMATIC HETEROCYCLES - PYRIDINE AND PYRROLE

OBJECTIVES

After completing this section, you should be able to

1. draw the structure of the common aromatic heterocycles pyridine and pyrrole.
2. use the Hückel $4n + 2$ rule to explain the aromaticity of each of pyridine and pyrrole.
3. draw a diagram to show the orbitals involved in forming the conjugated six-pi-electron systems present in aromatic heterocycles such as pyridine, pyrrole, etc.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

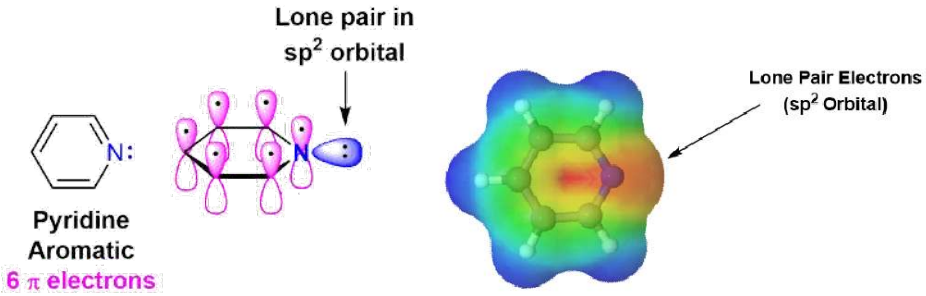
- carbocycles
- heterocycles

AROMATIC HETEROCYCLES

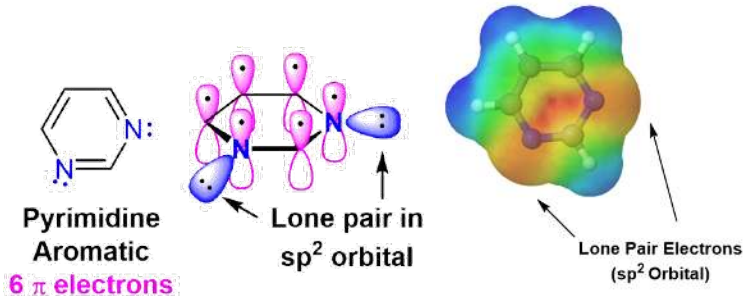
Many cyclic compounds have an element other than carbon present in the ring. Cyclic compounds that include one or more elements other than carbon are called a heterocycle. The most common heterocyclic compounds contain carbon along with nitrogen, oxygen, or sulfur. Because some heterocyclic compounds are aromatic, it is important to discuss how the inclusion of non-carbon atoms affects the determination of aromaticity. The reactivity and general physical properties of aromatic nitrogen heterocycles will be discussed in greater detail in Section 24.9.

PYRIDINE & PYRIMIDINE

Pyridine is an example of a six-membered aromatic heterocycle and has an electronic structure similar to benzene. In the bonding picture of pyridine the five carbons and single nitrogen are all sp^2 hybridized. All six of these atoms have a p orbital perpendicular to the plane of the ring and each contains one pi electron which allows the ring to be fully conjugated. This makes the pi electron count for pyridine 6 pi electrons. In much the same fashion as benzene, the 6 pi electrons follow the 4n + 2 rule and completely fill the bonding molecular orbitals which fulfills the electronic requirement for aromaticity. The lone pair electrons on pyridine's nitrogen are contained in a sp^2 orbital that lies in the same plane as the ring and does not overlap with the p orbitals of the ring. The lone pair electrons are not part of the aromatic system and do not affect the p electron count. Pyridine's electrostatic potential map shows that the lone pair electrons, shown in a yellow/red color, are locked onto the nitrogen and not distributed around the ring.

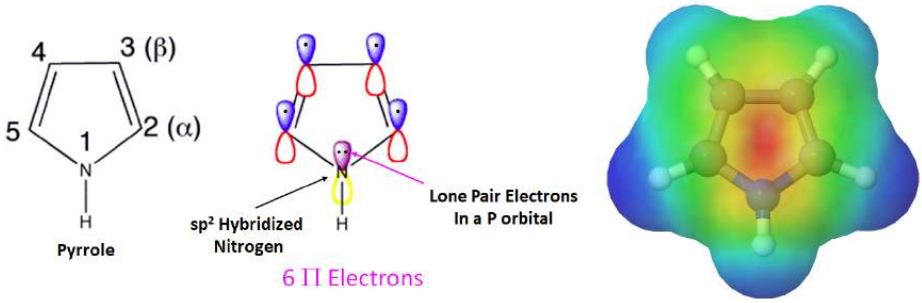


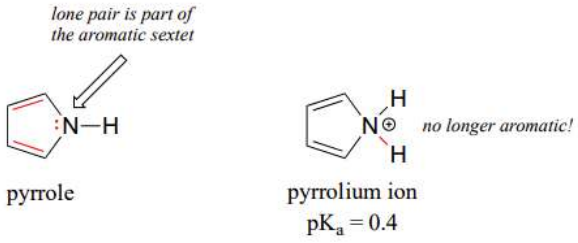
Pyrimidine is an another six-membered aromatic heterocycle that is analogous to pyridine. Pyrimidine has four carbons atoms and two nitrogen atoms that are sp^2 hybridized. Each of these atoms contributes a p orbital and a pi election allowing pyrimidine to be fully conjugated and aromatic. Both of the nitrogens in pyrimidine have lone pair electrons contained in a sp^2 orbitals and are not involved in the aromatic system. An electrostatic potential map of pyrimidine shows that neither set of lone pair electrons is distributed around the ring.



PYRROLE

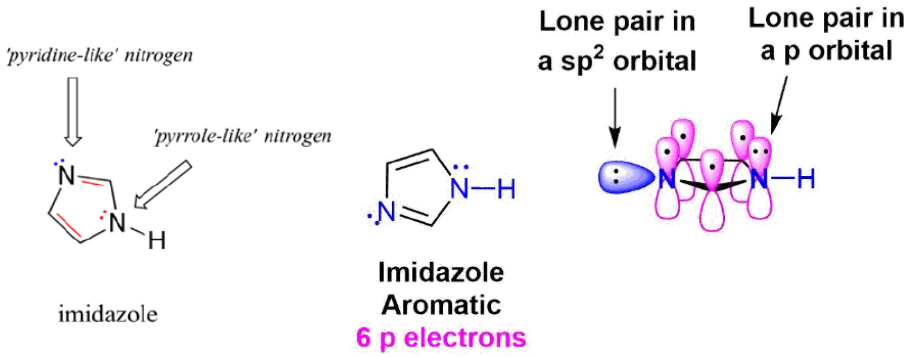
Pyrrole is a five-membered heterocyclic ring which has 5 p orbitals and six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one p orbital and pi electron. The nitrogen in pyrrole contributes two pi electrons by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. The electrostatic potential map of pyrrole show the nitrogen's lone pair electrons are distributed in the ring. Because the nitrogen lone pair *is* part of the aromatic sextet the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the molecule loses aromaticity). Pyrrole is a very weak base: the conjugate acid, the pyrrolium ion, is a strong acid with a pK_a of 0.4.

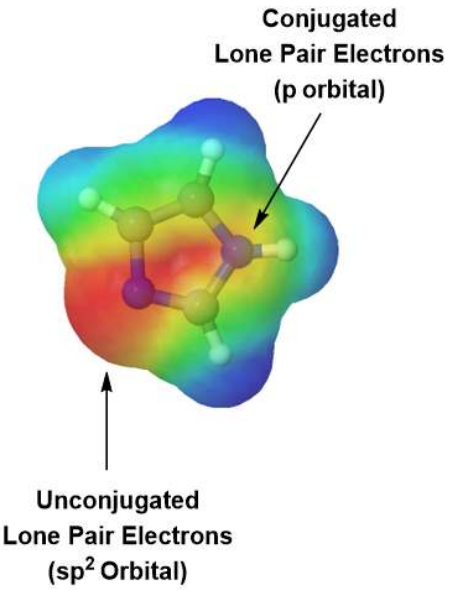




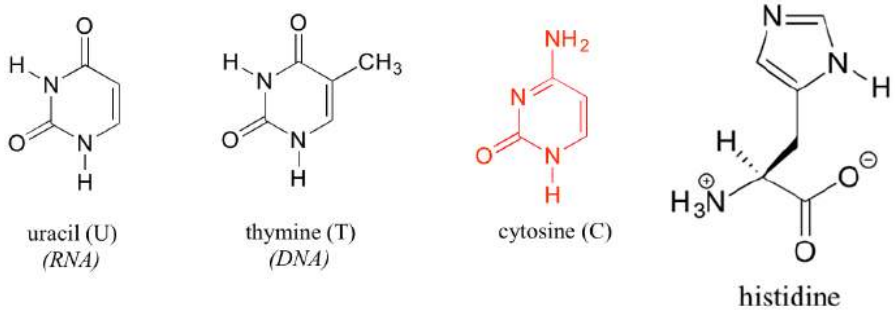
IMIDAZOLE

Imidazole is another five-membered heterocyclic ring which has 6 pi electrons and is aromatic. Both of the nitrogen atoms are sp^2 hybridized. One nitrogen is pyridine-like because it is part of a double bond and adds one pi electron to the aromatic pi ring. The other nitrogen is not part of a double bond making it pyrrole-like allowing it to contribute 2 pi electrons from it lone pair electrons. When looking at the electrostatic potential map of imidazole, the lone pair electrons on the pyrrole-like nitrogen are distributed around the ring while the lone pair electrons on the pyridine-like nitrogen are non-conjugated and locked into place.





Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the amino acids found in proteins.



? WORKED EXAMPLE 15.5.1

Determine if furan is aromatic. Draw an orbital diagram to support your answer.

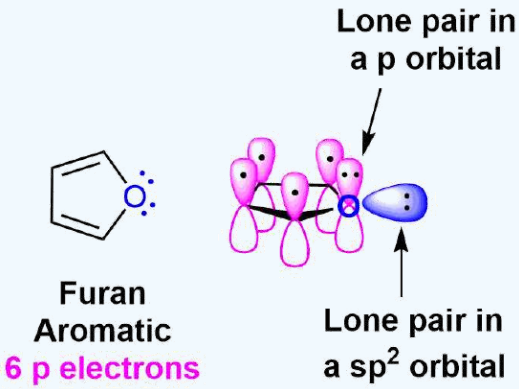


Furan

Answer

For a molecule to be aromatic it must: Be cyclic, be planar, be fully conjugated, and have 4n+2 π electrons.

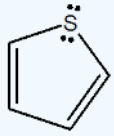
Furan is obviously cyclic and can be assumed to be planar due to the constrains of having a five membered ring with two double bonds. To be fully conjugated each atom in the ring must have a p orbital. Although the oxygen has 4 electron groups and appears to be sp^3 hybridized, it will become sp^2 hybridized to gain the stability of conjugation. Becoming sp^2 hybridized allows the oxygen atom to put a set of lone pair electrons into a p orbital allowing it to be part of the cyclic conjugation. These two pi electrons along with the 4 pi electrons provided by the two double bonds gives furan 6 pi electrons total. This follows the 4n + 2 rule making furan aromatic.



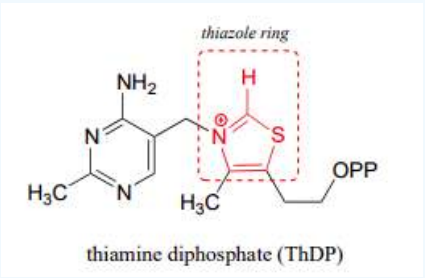
EXERCISES

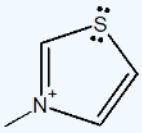
? EXERCISE 15.5.1

1) Draw the orbitals of thiophene to show that it is aromatic.



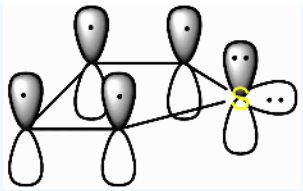
2) The thiazolium ring is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate (ThDP). Describe how thiazolium ring is aromatic.



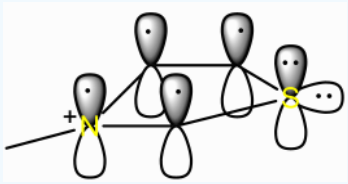


Answer

1) This drawing shows thiophene has 6 electrons in the pi-orbital.



2) Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.



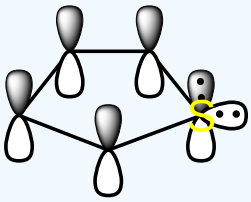
EXERCISE 15.5.2

Draw the orbitals of thiophene to show that is aromatic.



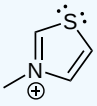
Answer

This drawing shows it has 6 electrons in the pi-orbital.



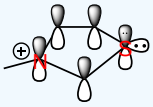
EXERCISE 15.5.3

The following ring is called a thiazolium ring. Describe how it is aromatic.



Answer

Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.



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15.6: POLYCYCLIC AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to draw the resonance contributors for polycyclic aromatic compounds, such as naphthalene, anthracene, etc.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- polycyclic aromatic compounds

STUDY NOTES

As their name indicates, *polycyclic aromatic hydrocarbons* are aromatic hydrocarbons which contain more than one benzenoid (i.e., benzene-like) ring. This section deals only with those compounds in which the benzenoid rings are fused together; in other words, compounds in which at least one carbon-carbon bond is common to two aromatic rings. Another type of polycyclic aromatic hydrocarbon contains two or more benzenoid rings joined by a carbon-carbon single bond. The simplest compound of this type is biphenyl, the compound from which PCBs (polychlorinated biphenyls) are derived.

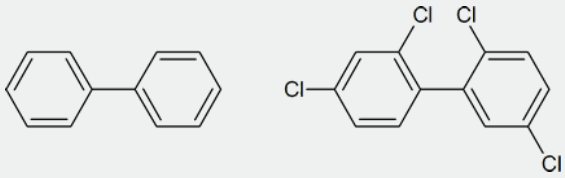


Figure 15.3: Structures of biphenyl and a typical PCB

POLYCYCLIC AROMATIC COMPOUNDS

Hückel's 4n +2 rule for aromaticity does not only apply to mono-cyclic compounds. Benzene rings may be joined together (fused) to give larger polycyclic aromatic compounds. A few examples are drawn below, together with the approved numbering scheme for substituted derivatives. The peripheral carbon atoms (numbered in all but the last three examples) are all bonded to hydrogen atoms. Unlike benzene, all the C-C bond lengths in these fused ring aromatics are not the same, and there is some localization of the pi-electrons. The six benzene rings in coronene are fused in a planar ring; whereas the six rings in hexahelicene are not joined in a larger ring, but assume a helical turn, due to the crowding together of the terminal ring atoms (in the structure below, note that the top right and center right rings are not attached to one another). This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

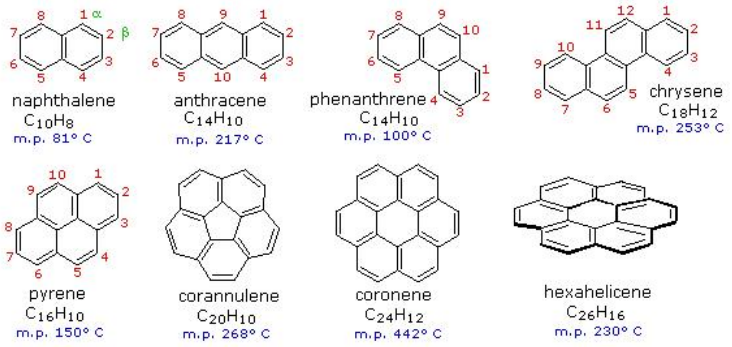
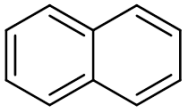
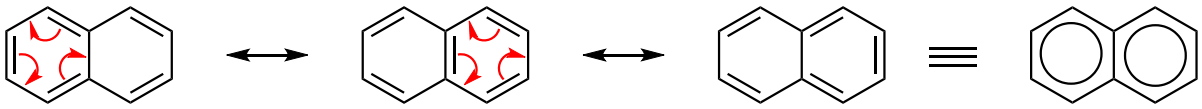


***Figure 2**: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).*

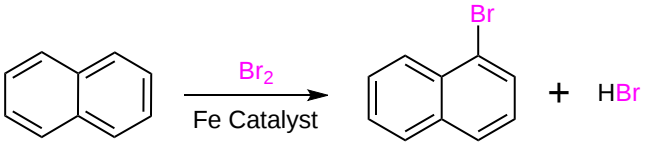
Probably the most well know polycyclic aromatic compound which only contains carbon is naphthalene ($C_{10}H_8$). Naphthalene shares many of the same characteristic as benzene. Naphthalene is cyclic and known to be flat. Each carbon in naphthalene is sp^2 hybridized so it is completely conjugated. The true structure of naphthalene is a combination of three resonance hybrids.



Naphthalene

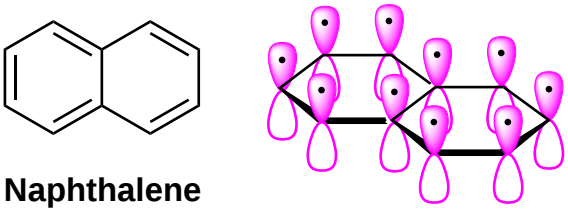


Heat of hydrogenation experiments with naphthalene shows an unusual "aromatic" stabilization energy. Also, naphthalene prefers to react with electrophiles to give substitution products rather than the typical double bond addition products.

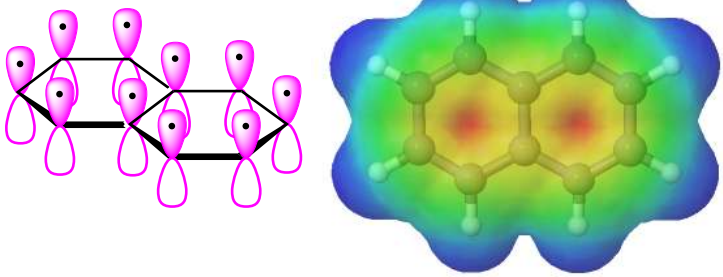


Naphthalene **1-Bromonaphthalene Substitution Product**

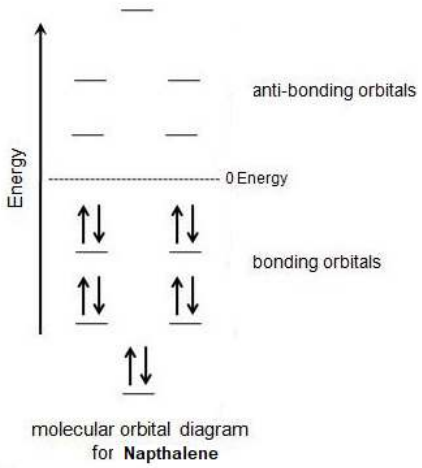
Every carbon in naphthalene is sp^2 hybridized so there is conjugated p orbital overlap over the entire ring system. The electrostatic potential map shows that pi electrons in naphthalene are evenly distributed making each carbon equivalent.



Naphthalene
Aromatic
10 p electrons



Lastly, naphthalene has 10 pi electrons which fulfills Hückel's rule. The importance of the 4n + 2 rule can be seen when considering the molecular orbital diagram of naphthalene. Naphthalene has 10 p orbitals which is 4 more than benzene. In the molecular orbital diagram of naphthalene, the 4 additional p orbitals become 2 bonding orbitals and two anti-bonding orbitals. The two additional bonding orbitals require 4 additional pi electrons to be filled so naphthalene needs 10 pi electrons in total to fill all of the bonding molecular orbitals.



molecular orbital diagram for **Napthalene**

POLYCYCLIC AROMATIC HETEROCYCLES

There is a wide variety of polycyclic aromatic heterocycles, many of which contain nitrogen, oxygen, or sulfur. Some of the biologically important structures, are the nitrogen containing polycyclic aromatic heterocycles indole, quinoline, isoquinoline, and purine which are all polycyclic aromatic heterocycles commonly found in nature. Notice that these compound all have 10 pi electrons.

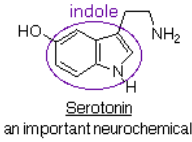

Indole


Quinoline

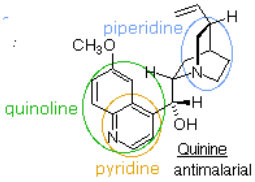

Isoquinoline


Purine

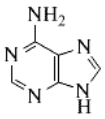
Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.

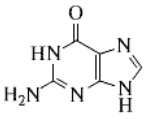


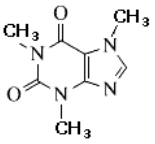
Serotonin
an important neurochemical



Quinine
antimalarial


adenine

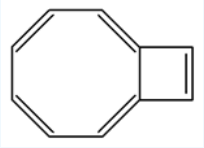

guanine


caffeine

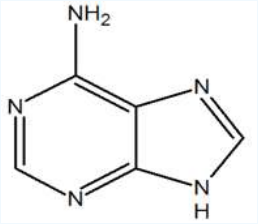
EXERCISES

? EXERCISE 15.6.1

1) The following molecule is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



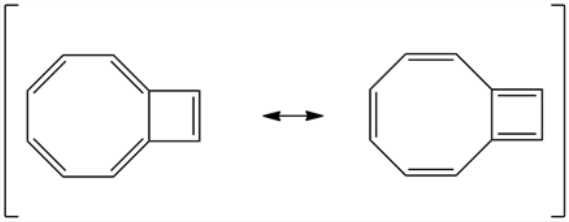
2) The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?



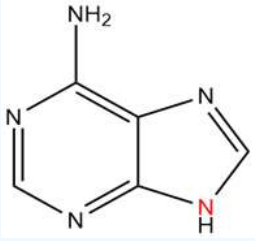
Answer

1) It has 10 pi electrons which follows the 4n+2 rule making it aromatic.

https://chem.libretexts.org/@go/page/31567

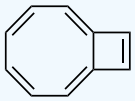


2) There is only one nitrogen of the core that contributes a set of lone pair electrons as 2 pi electrons (in red). All of the other nitrogens are sp2 hybrized and contribute 1 pi electron each. In total, the core is aromatic with 10 electrons in the pi-system.



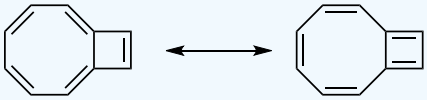
? EXERCISE 15.6.2

This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



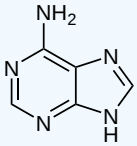
Answer

Yes, it is aromatic. 4n+2 pi-electrons.



? EXERCISE 15.6.3

The following molecule is adenine. It has a purine core. Of the nitrogen in the core, how many electrons are donated into the pi system?



Answer

There is only one nitrogen of the core that contributes to the pi-system (in red). With this one lone pair the core is aromatic with 10 electrons in the pi-system.



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15.7: SPECTROSCOPY OF AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. determine whether an unknown compound contains an aromatic ring by inspection of its infrared spectrum, given a table of characteristic infrared absorptions.
2. state the approximate chemical shift of aryl protons in a proton NMR spectrum.
3. explain why signals resulting from the presence of aryl protons are found downfield from those caused by vinylic protons in a proton NMR spectrum.
4. propose possible structures for an unknown aromatic compound, given its proton NMR spectrum, other spectroscopic data (such as a ^{13}C NMR or infrared spectrum), or both.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- ring current

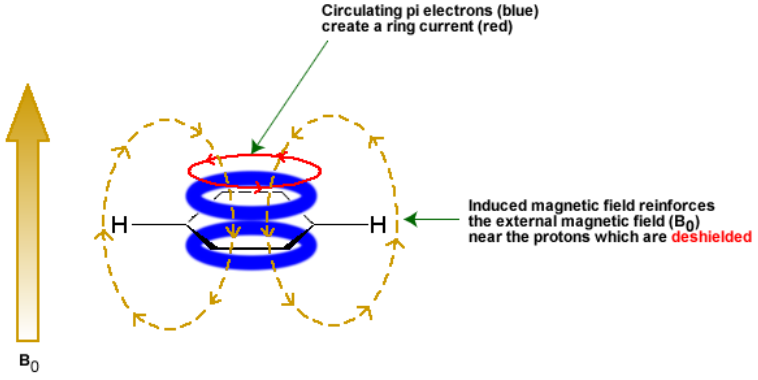
STUDY NOTES

It is not necessary that you memorize detailed spectroscopic data. In the laboratory, on assignments and when writing examinations, you will be provided with a table of characteristic infrared absorptions to assist you in interpreting infrared spectra.

The important points to note about the proton NMR of aromatic compounds are the approximate chemical shifts of such protons and the complex splitting pattern that is sometimes observed. You are advised not to spend too long trying to understand why the signal for an aryl proton is found downfield from the signal for a vinylic proton. In general, we want you to be able to interpret NMR spectra, and leave the underlying theory for subsequent chemistry courses.

THE CHEMICAL SHIFTS OF AROMATIC PROTONS

Some protons resonate much further downfield than can be accounted for simply by the deshielding effect of nearby electronegative atoms. Vinylic protons (those directly bonded to an alkene carbon) and aromatic (benzylic) protons are dramatic examples.



We'll consider the aromatic proton first. Recall that in benzene and many other aromatic structures, a sextet of p electrons is delocalized around the ring. When the molecule is exposed to B_0, these p electrons begin to circulate in a **ring current**, generating their own induced magnetic field that opposes B_0. In this case, however, the induced field of the p electrons does not shield the benzylic protons from B_0 as you might expect– rather, it causes the protons to experience a *stronger* magnetic field in the direction of B_0 – in other words, it *adds* to B_0 rather than subtracting from it.

To understand how this happens, we need to understand the concept of **diamagnetic anisotropy** (anisotropy means `non-uniformity`). So far, we have been picturing magnetic fields as being oriented in a uniform direction. This is only true over a small area. If we step back and take a wider view, however, we see that the lines of force in a magnetic field are actually anisotropic. They start in the 'north' direction, then loop around like a snake biting its own tail.

If we are outside the ring in the figure above, we feel a magnetic field pointing in a northerly direction. If we are inside the ring, however, we feel a field pointing to the south.

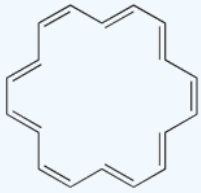
In the induced field generated by the aromatic ring current, the benzylic protons are outside the ring – this means that the induced current in this region of space is oriented in the *same* direction as B_0.

In total, the benzylic protons are subjected to three magnetic fields: the applied field (B_0) and the induced field from the electrons pointing in one direction, and the induced field of the non-aromatic electrons pointing in the opposite (shielding) direction. The end result is that benzylic protons, due to the anisotropy of the induced field generated by the ring current, appear to be highly de-shielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

The presence of anisotropy effects is often used to indicate aromaticity in a molecule. An example is the nonaromatic 8 pi electron cyclooctatetraene. In order to avoid anti-aromatic destabilization, the molecule takes a non-planar conformation which prevents conjugation and ring currents. Consequently, the molecule's protons absorbed at 5.8 ppm which is within the alkene region of ^{1}H NMR.

? EXERCISE 15.7.1

The ^{1}H-NMR spectrum of [18] annulene has two peaks, at 8.9 ppm and -1.8 ppm (upfield of TMS!) with an integration ratio of 2:1. Explain the unusual chemical shift of the latter peak.



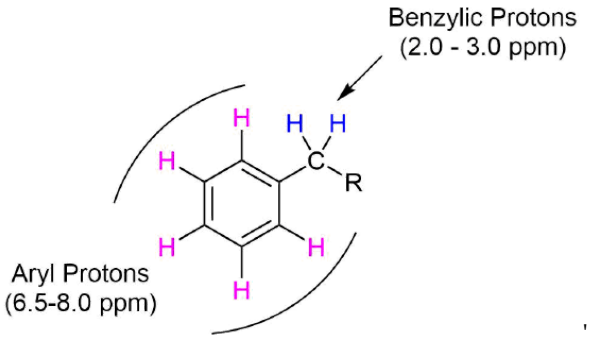
[18] annulene

Answer

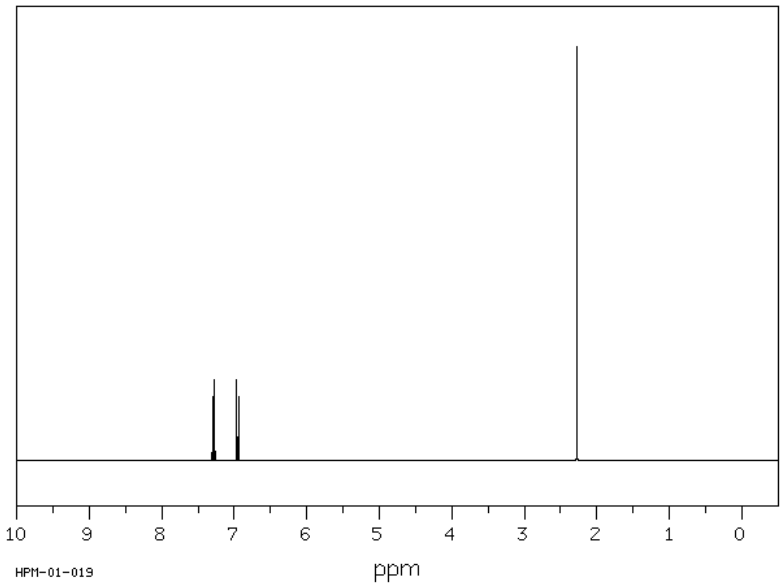
The molecule contains two groups of equivalent protons: the twelve pointing to the outside of the ring, and the six pointing into the center of the ring. The molecule is aromatic, as evidenced by the chemical shift of the 'outside' protons' (and the fact that there are 18 p electrons - a Hückel number). The inside protons are *shielded* by the induced field of the aromatic ring current, because *inside the ring this field points in the opposite direction of B_0*. This is the source of the unusually low (negative relative to TMS) chemical shift for these protons.

CHARACTERISTIC ^{1}H NMR ABSORPTIONS OF AROMATIC COMPOUNDS

Protons directly attached to an aromatic ring, commonly called aryl protons, show up about 6.5-8.0 PPM. This range is typically called the aromatic region of an ^{1}H NMR spectrum. Protons on carbons directly bonded to an aromatic ring, called benzylic protons, show up about 2.0-3.0 PPM.



For the ^{1}H NMR spectrum of p-bromotoluene, the absorption for the benzylic protons appears as a strong singlet at 2.28 ppm. Due to the molecule's symmetry, the aryl protons appear as two doublets at 6.96 & 7.29 ppm.



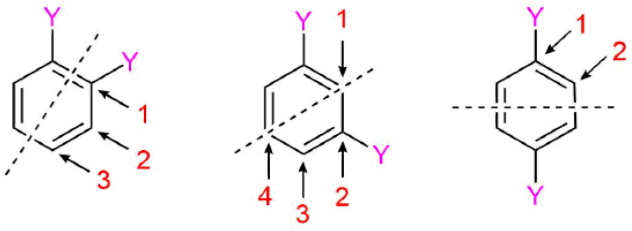
CHARACTERISTIC ^{13}C NMR ABSORPTIONS OF AROMATIC COMPOUNDS

Carbons in an aromatic ring absorb in the range of 120-150 ppm in a ^{13}C NMR spectrum. This is virtually the same range as nonaromatic alkenes (110-150 ppm) so peaks in this region are not definitive proof of a molecule's aromaticity.

Due to the decoupling in ^{13}C NMR, the number of absorptions due to aromatic carbons can easily be observed. This can be used to determine the relative positions (*ortho*, *meta*, or *para*) for di-substituted benzenes. Peak assignments can be simplified by noting that ^{13}C peaks tend to be larger if two carbons contribute to the absorption.

SYMMETRICAL DI-SUBSTITUTED BENZENES

Benzenes substituted with two identical groups have a relatively high amount of symmetry. In all three configurations, there is a plane of symmetry which reduces the number of distinct aryl carbon absorptions to less than six. The *ortho* configuration has a plane of symmetry which mirrors each carbon in the benzene ring causing only three ^{13}C aryl absorptions to occur. The *meta* configuration's plane of symmetry mirrors two carbons of the benzene ring allowing for four aryl absorptions to occur. The *para* configuration actually has two planes of symmetry (one vertical and one horizontal on the structure below) through the benzene ring, which only allows two distinct aryl absorptions to occur.



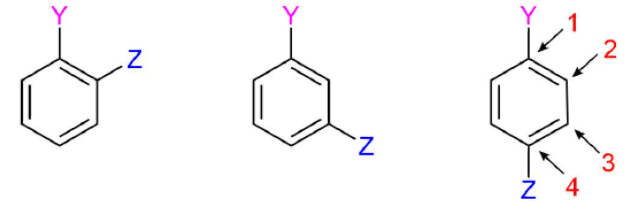
Ortho
Three ^{13}C
Arene Peaks

Meta
Four ^{13}C
Arene Peaks

Para
Two ^{13}C
Arene Peaks

ASYMMETRICAL DI-SUBSTITUTED BENZENES

The lack of a plane of symmetry in asymmetrical di-substituted benzenes makes each carbon in the *ortho* and *meta* configuration unique. Consequently, their ^{13}C NMR spectra show six arene absorptions. However, the *para* configuration has a plane of symmetry drawn through the two substituents which mirrors two carbons of the benzene ring causing only 4 arene absorptions to appear.

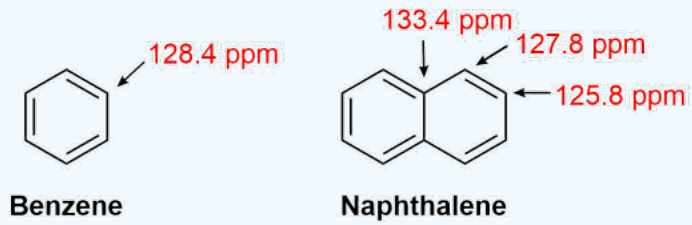


Ortho
No Symmetry
Six ^{13}C
Arene Peaks

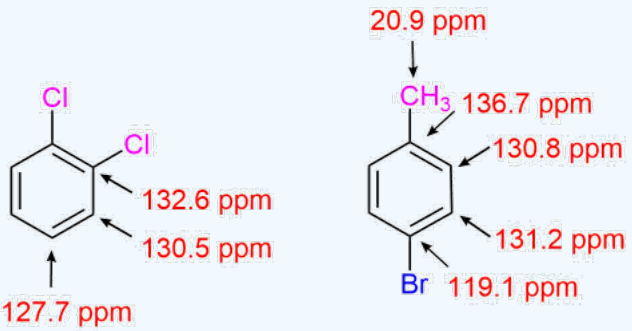
Meta
No Symmetry
Six ^{13}C
Arene Peaks

Para
Four ^{13}C
Arene Peaks

✔ EXAMPLE 15.7.1



Benzene **Naphthalene**



***o*-Dichlorobenzne** ***p*-Bromotoluene**

CHARATERISTIC IR ABSORPTION OF BENZENE DERIVATIVES

Arenes have absorption bands in the 650-900 cm^{-1} region due to bending of the C–H bond out of the plane of the ring. The exact placement of these absorptions can indicate the pattern of substitution on a benzene ring. However, this is beyond the scope of introductory organic chemistry. Arenes also possess a characteristic absorption at about 3030-3100 cm^{-1} as a result of the aromatic C–H stretch. It is somewhat higher than the alkyl C–H stretch (2850–2960 cm^{-1}), but falls in the same region as olefinic compounds. Two bands (1500 and 1660 cm^{-1}) caused by C=C in plane vibrations are the most useful for characterization as they are intense and are likely observed.

In aromatic compounds, each band in the spectrum can be assigned:

- C–H stretch from 3100-3000 cm^{-1}
- overtones, weak, from 2000-1665 cm^{-1}
- C–C stretch (in-ring) from 1600-1585 cm^{-1}
- C–C stretch (in-ring) from 1500-1400 cm^{-1}
- C–H "oop" from 900-675 cm^{-1}

Note that this is at slightly higher frequency than is the –C–H stretch in alkanes. This is a very useful tool for interpreting IR spectra. Only alkenes and aromatics show a C–H stretch slightly higher than 3000 cm^{-1}.

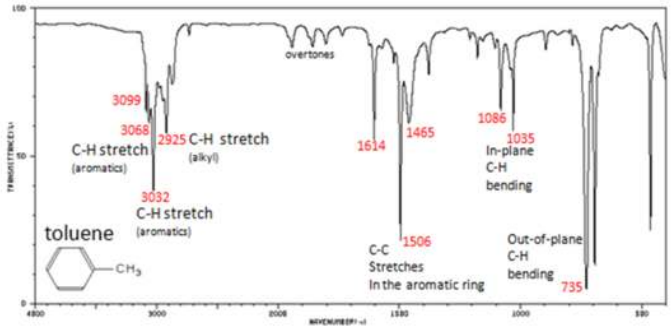
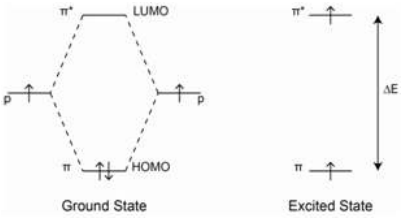


Figure 6. Infrared Spectrum of Toluene

ULTRAVIOLET SPECTROSCOPY

The presence of conjugated π bonds makes aromatic rings detectable in a UV/Vis spectrum. Benzene primarily absorbs through a be a π-π* transition over the range from 160-208 nm with a λ_{max} value of about 178 nm.



Benzene shows a less intense absorption in 230-276 nm range. These absorptions are due to vibrational fine structure often displayed by rigid molecules such as benzene and other aromatic compounds.

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15.S: BENZENE AND AROMATICITY (SUMMARY)

CONCEPTS & VOCABULARY

15.0 Introduction

- Aromatic compounds contain ring structures with a special type of resonance delocalization.
- Aromatic compounds can be drawn with alternating single and double bonds, each atom in the ring must have a p-orbital available.

15.1 Naming Aromatic Compounds

- Disubstituted benzene derivatives are often named using ortho (1,2), meta (1,3) and para (1,4).
- There are common benzene derivative names that are used by IUPAC such as toluene, phenol, benzoic acid and benzaldehyde.
- A benzene group that is named as a substituent is called phenyl.
- A benzene with a CH_2 as a substituent group is called benzyl.

15.2 Structure and Stability of Benzene

- Benzene does not undergo the same reactions that alkenes do, due to its aromatic stability.
- Aromatic molecules must have all ring atoms in the same plane to allow delocalization of the pi electrons.
- Heats of hydrogenation can be used to show the special stability of benzene compared to what would be expected for a theoretical cyclohexatriene molecule.

15.3 Aromaticity and the Hückel 4n + 2 Rule

- The four criteria for aromaticity are that the molecule must:
  - be cyclic
  - be planar
  - be fully conjugated
  - have 4n+2 π Electrons
- Ionic molecules and heterocyclic molecules can also be aromatic if they meet the four criteria.

15.4 Aromatic Ions

- Carbanions and carbocations that meet the rules for aromaticity are also aromatic.

15.5 Aromatic Heterocycles: Pyridine and Pyrrole

- Heterocycles that meet the rules for aromaticty are also aromatic.
- If a lone pair of electrons on a ring atom can result in 4n+2 π Electrons, they will be in a p-orbital. If not, they will remain in hybrid orbitals.

15.6 Polycyclic Aromatic Compounds

- Benzene rings can be fused together to give larger aromatic compounds with mutliple rings called polycyclic aromatic compounds (or polycyclic aromatic hydrocarbons).

15.7 Spectroscopy of Aromatic Compounds

- Aromatic compounds can be identified by common infrared absorptions in the 3000-3100 cm^{-1} and 1500-1600 cm^{-1}.
- In ^1H NMR, aromatic hydrogens appear in the 6.5-8 ppm region.

SKILLS TO MASTER

- Skill 15.1 Using IUPAC rules to name substituted benzene molecules.
- Skill 15.2 Use heats of hydrogenation to explain aromatic stabilization.
- Skill 15.3 Draw molecular orbital diagram for benzene (all 6 MO's).
- Skill 15.4 Use the criteria for aromaticity to determine if a molecule is aromatic or not.
- Skill 15.5 Determine whether lone pairs of electrons for ions and heterocycles will be in p orbitals or hybrid orbitals.
- Skill 15.6 Identify aromatic absorbances in infrared spectroscopy.
- Skill 15.7 Identify aromatic resonances in ^1H NMR spectroscopy.

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CHAPTER OVERVIEW

16: CHEMISTRY OF BENZENE - ELECTROPHILIC AROMATIC SUBSTITUTION

LEARNING OBJECTIVES

When you have completed Chapter 16, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. solve road-map problems that require an understanding of the chemistry discussed in this chapter and those that preceded it.
3. design multistep syntheses using the reactions discussed in this and the preceding chapters. In particular you should be prepared to show how an aromatic compound containing two or more substituents could be synthesized, taking care to introduce the substituents into the ring in the correct order.
4. define, and use in context, the key terms introduced.

In the preceding chapter, you studied the concept of aromaticity and spent considerable time on the theoretical aspects of the chemistry of aromatic compounds. In this chapter, you will begin to study the chemical reactions of aromatic compounds, focusing in particular on electrophilic aromatic substitution, and to a lesser extent on nucleophilic aromatic substitution. We will discuss, in detail, the mechanism of electrophilic substitution, paying particular attention to the factors that determine both the rate and position of substitution in those aromatic compounds which already have one or more substituents present in the aromatic ring. When we discuss nucleophilic aromatic substitution, you will see that it can be achieved by two different mechanisms, one of which involves the formation of an unusual looking intermediate, benzyne.

You will also see how alkyl and acyl groups can be introduced on to an aromatic ring; how, once introduced, alkyl groups can be converted to carboxyl groups; and how bromine can be introduced to the alkyl side chain of alkylbenzene. The latter reaction is particularly useful because the benzylic bromide so produced undergoes the reactions of a typical alkyl bromide, thus providing us with a synthetic route to a large variety of compounds.

16.0: Introduction
16.1: Electrophilic Aromatic Substitution Reactions - Bromination
16.2: Other Aromatic Substitutions
16.3: Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction
16.4: Substituent Effects in Substituted Aromatic Rings
16.5: An Explanation of Substituent Effects
16.6: Trisubstituted Benzenes - Additivity of Effects
16.7: Nucleophilic Aromatic Substitution
16.8: Benzyne
16.9: Oxidation of Aromatic Compounds
16.10: Reduction of Aromatic Compounds
16.11: Synthesis of Polysubstituted Benzenes
16.S: Chemistry of Benzene - Electrophilic Aromatic Substitution (Summary)

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16.0: INTRODUCTION

OBJECTIVE

After completing this section, you should be able to identify electrophilic substitution as the single most important reaction of aromatic compounds.

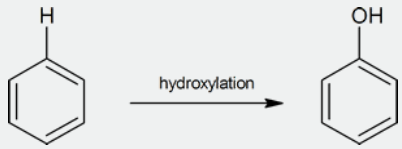
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acylation
- alkylation
- electrophilic substitution
- halogenation
- hydroxylation
- nitration
- sulfonation

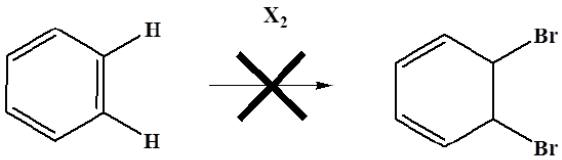
STUDY NOTES

In this chapter, you will study all of the reactions shown in the Reaction Type table. In addition to these five reaction types, we also add a sixth common electrophilic substitution known as hydroxylation.



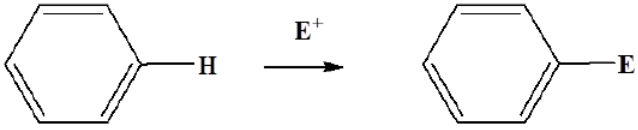
It is important that you recognize the similarities between these reactions to minimize the amount you must memorize.

The six pi electrons obey Huckel's rule so benzene is especially stable. This means that the aromatic ring want to be retained during reactions. Because of this benzene does not undergo addition like other unsaturated hydrocarbons.



Non-Aromatic

Benzene can undergo electrophilic aromatic substitution because aromaticity is maintained.



Product is Aromatic

OTHER EXAMPLES OF ELECTOPHILIC AROMATIC SUBSTITUTION

Many other substitution reactions of benzene have been observed, the five most useful are listed below (chlorination and bromination are the most common halogenation reactions). Since the reagents and conditions employed in these reactions are electrophilic, these reactions are commonly referred to as **Electrophilic Aromatic Substitution**. The catalysts and co-reagents serve to generate the strong electrophilic

species needed to effect the initial step of the substitution. The specific electrophile believed to function in each type of reaction is listed in the right hand column.

Reaction Type	Typical Equation				Electrophile $E^{(+)}$
Halogenation:	C_6H_6	+ Cl_2 & heat $FeCl_3$ catalyst	⟶	C_6H_5Cl + HCl Chlorobenzene	$Cl^{(+)}$ or $Br^{(+)}$
Nitration:	C_6H_6	+ HNO_3 & heat H_2SO_4 catalyst	⟶	$C_6H_5NO_2$ + H_2O Nitrobenzene	$NO_2^{(+)}$
Sulfonation:	C_6H_6	+ H_2SO_4 + SO_3 & heat	⟶	$C_6H_5SO_3H$ + H_2O Benzenesulfonic acid	$SO_3H^{(+)}$
Alkylation: Friedel-Crafts	C_6H_6	+ R-Cl & heat $AlCl_3$ catalyst	⟶	C_6H_5-R + HCl An Arene	$R^{(+)}$
Acylation: Friedel-Crafts	C_6H_6	+ RCOCl & heat $AlCl_3$ catalyst	⟶	C_6H_5COR + HCl An Aryl Ketone	$RCO^{(+)}$

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16.1: ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS - BROMINATION

OBJECTIVES

After completing this section, you should be able to

1. write the detailed mechanism for the reaction of bromine with benzene in the presence of a suitable catalyst.
2. draw the resonance contributors for the carbocation which is formed during the reaction of bromine with benzene.
3. compare the reaction which takes place between bromine and benzene and the reaction which takes place between bromine and an alkene.
4. draw an energy diagram for the reaction of bromine with benzene.
5. identify the reagents required to bring about aromatic bromination.
6. write an equation to represent aromatic bromination.

STUDY NOTES

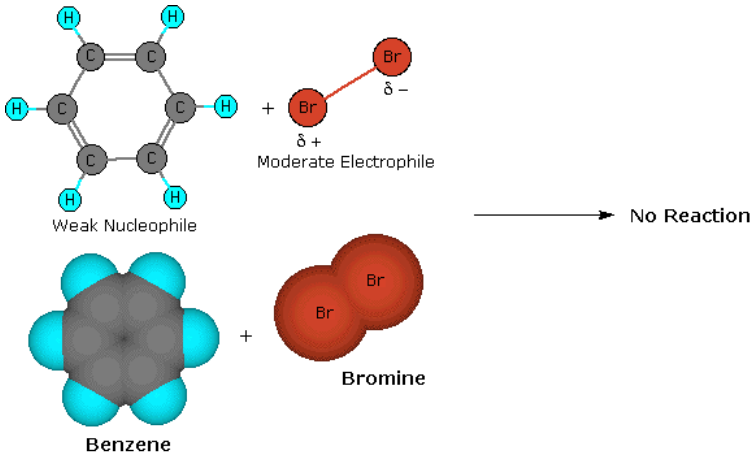
The Mechanism for Electrophilic Substitution Reactions of Benzene is the key to understanding electrophilic aromatic substitution. You will see similar equations written for nitration, sulphonation, acylation, etc., with the major difference being the identity of the electrophile in each case.

Note that the carbocation intermediate formed has a number of resonance forms. Also, you may wish to review Section 8.2 to meet Objective 3.

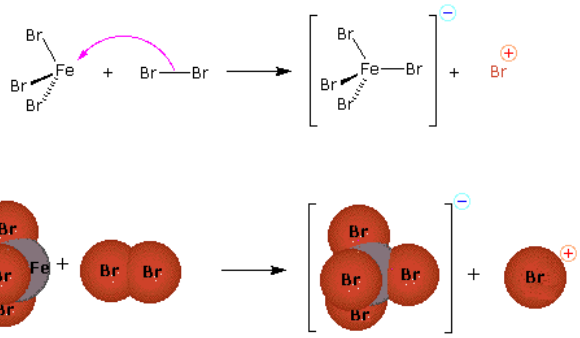
Halogenation is an example of electrophillic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substition of hydrogens. However, halogens are not electrophillic enough to break the aromaticity of benzenes, which require a catalyst to activate.

A MECHANISM FOR ELECTROPHILIC SUBSTITUTION REACTIONS OF BENZENE

A two-step mechanism has been proposed for these electrophilic substitution reactions. In the first, slow or rate-determining, step the electrophile forms a sigma-bond to the benzene ring, generating a positively charged **arenium intermediate**. In the second, fast step, a proton is removed from this intermediate, yielding a substituted benzene ring. The following four-part illustration shows this mechanism for the bromination reaction. Also, an animated diagram may be viewed.

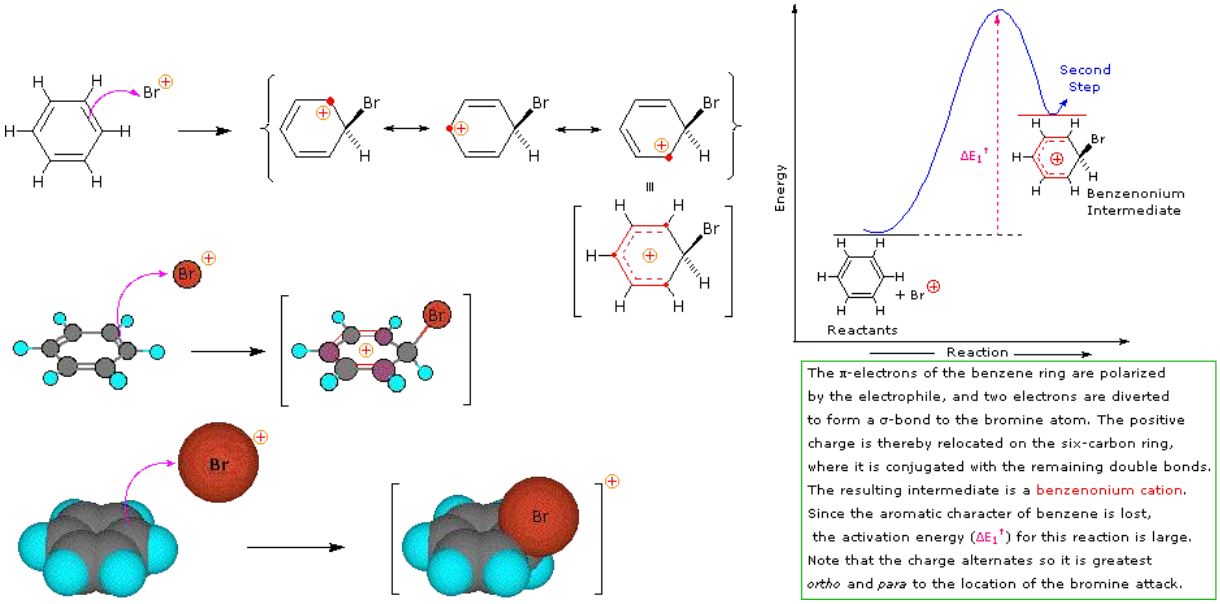


The bromine molecule is polarized so that one end is electrophilic and the other nucleophilic. Although the electrophilic end reacts easily with simple alkenes and dienes, it fails to react with the more stable and weaker nucleophilic π-electron system of benzene.



Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

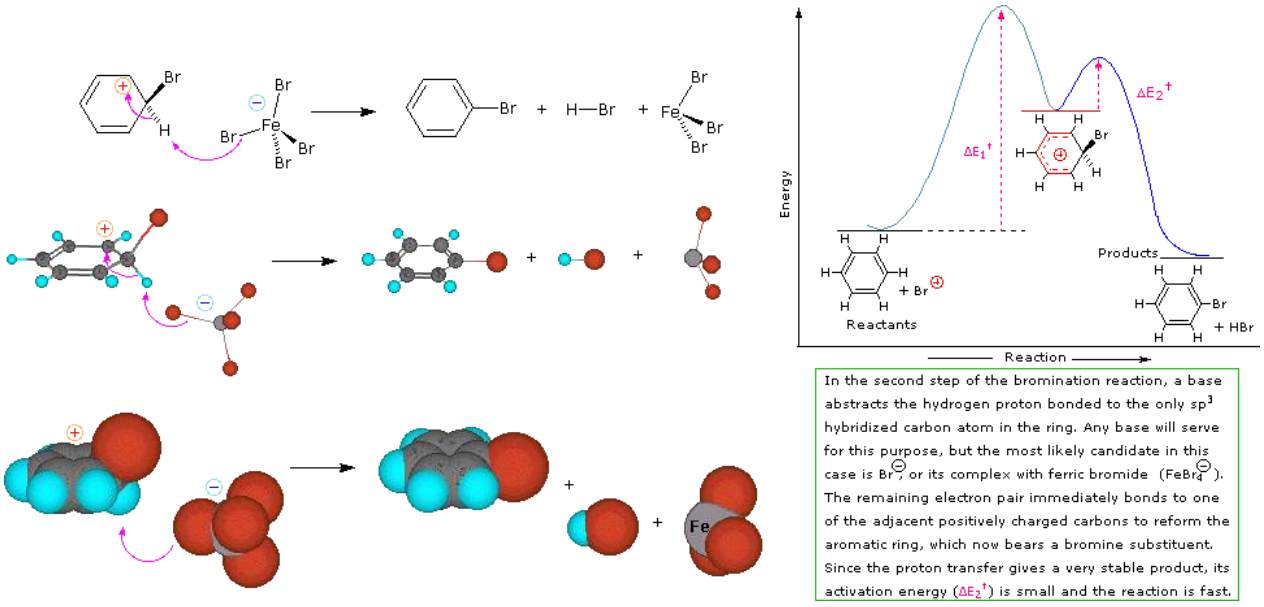
Preliminary step: Formation of the strongly electrophilic bromine cation



The π-electrons of the benzene ring are polarized by the electrophile, and two electrons are diverted to form a σ-bond to the bromine atom. The positive charge is thereby relocated on the six-carbon ring, where it is conjugated with the remaining double bonds. The resulting intermediate is a benzenonium cation. Since the aromatic character of benzene is lost, the activation energy ($\Delta E_1^{\ddagger}$) for this reaction is large. Note that the charge alternates so it is greatest *ortho* and *para* to the location of the bromine attack.

Step 1: The electrophile forms a sigma-bond to the benzene ring, generating a positively charged benzenonium intermediate

https://chem.libretexts.org/@go/page/31573



Step 2: A proton is removed from this intermediate, yielding a substituted benzene ring

This mechanism for electrophilic aromatic substitution should be considered in context with other mechanisms involving carbocation intermediates. These include S_N1 and E1 reactions of alkyl halides, and Brønsted acid addition reactions of alkenes.

To summarize, when carbocation intermediates are formed one can expect them to react further by one or more of the following modes:

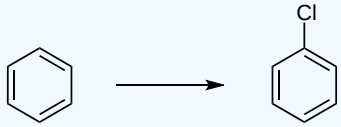
1. The cation may bond to a nucleophile to give a substitution or addition product.
2. The cation may transfer a proton to a base, giving a double bond product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

S_N1 and E1 reactions are respective examples of the first two modes of reaction. The second step of alkene addition reactions proceeds by the first mode, and any of these three reactions may exhibit molecular rearrangement if an initial unstable carbocation is formed. The carbocation intermediate in electrophilic aromatic substitution (the arenium ion) is stabilized by charge delocalization (resonance) so it is not subject to rearrangement. In principle it could react by either mode 1 or 2, but the energetic advantage of reforming an aromatic ring leads to exclusive reaction by mode 2 (*ie.* proton loss).

EXERCISES

? EXERCISE 16.1.1

What reagents would you need to get the given product?

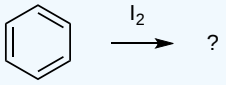


Answer

Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

? EXERCISE 16.1.2

What product would result from the given reagents?

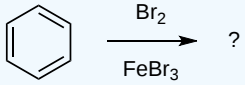


Answer

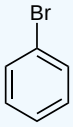
No Reaction

EXERCISE 16.1.3

What is the major product given the reagents below?



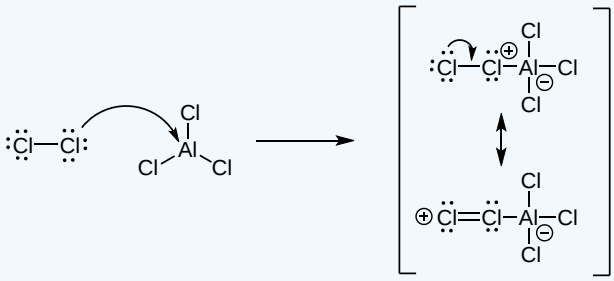
Answer



EXERCISE 16.1.4

Draw the formation of Cl^+ from $AlCl_3$ and Cl_2.

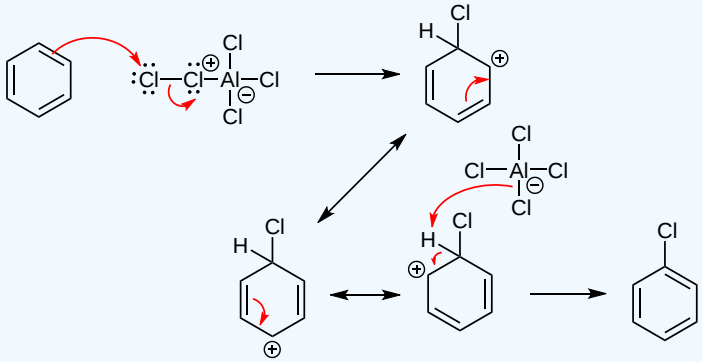
Answer



EXERCISE 16.1.5

Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer



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16.2: OTHER AROMATIC SUBSTITUTIONS

OBJECTIVES

After completing this section, you should be able to

1. write a balanced equation for the halogenation (F, Cl, Br, I) of benzene in the presence of a suitable catalyst or promoter.
2. draw the resonance contributors for the carbocation which is formed during the reaction of chlorine or bromine with benzene.
3. write the equation for the nitration and sulfonation of benzene.
4. write the detailed mechanism for the nitration and sulfonation of benzene.
5. write the equation for the reduction of an aromatic nitro compound to an amine.
6. identify aromatic sulfonation as being a reversible process, and describe the conditions under which the forward and reverse reactions are favoured.
7. write the equation for the desulfonation of an aromatic sulfonic acid.
8. identify aromatic sulfonic acids as being key intermediates in the manufacture of sulfa drugs.

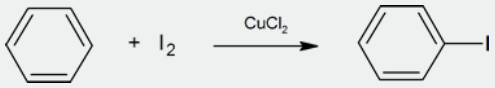
KEY TERMS

Make certain that you can define, and use in context, the key term below.

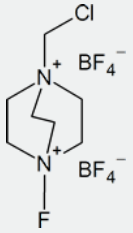
- nitronium ion, (NO^{+2})

STUDY NOTES

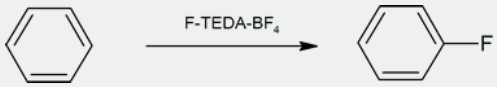
You should be careful to remember that iodine and fluorine cannot be introduced into an aromatic ring by the method used for bromine and chlorine. On its own, iodine is unreactive with aromatic rings, but one method for aromatic iodination is treatment in the presence of a copper salt such as copper(II)chloride where I2 is oxidized to the more electrophilic species I^+.



In contrast, fluorine is too reactive, so it cannot be used directly for aromatic flourination. However, fluorinating agents like 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate (also known as F-TEDA-BF_4) sold commercially as Sectfluor® offer convenient sources of "F^+" for this type of reaction.



F-TEDA-BF_4

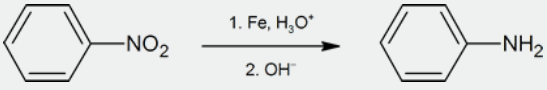


The overall equation for the formation of nitronium ions by the action of sulfuric acid on nitric acid is

$\ce{\sf{HNO3 + 2H2SO4 <=> H3O+ + NO2+ + HSO4- }}$

The ability of compounds such as nitronium tetrafluoroborate to bring about the nitration of aromatic compounds is good evidence in support of the proposed mechanism.

The nitration of an aromatic ring is an important synthetic pathway to generating arylamines. The reaction below shows one common method of reducing the nitro group. (Amines are examined in more detail in Chapter 24.)



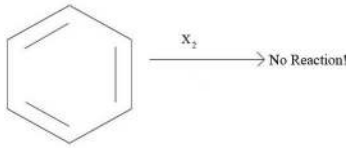
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HALOGENATION OF BENZENE

Halogenation is an example of electrophillic aromatic substitution. In electrophilic aromatic substitutions, a benzene is attacked by an electrophile which results in substition of hydrogens. However, halogens are not electrophillic enough to break the aromaticity of benzenes, which require a catalyst to activate.

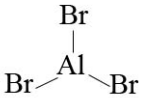
ACTIVATION OF HALOGEN

(where X= Br or Cl, we will discuss further in detail later why other members of the halogen family Flourine and Iodine are not used in halogenation of benzenes)

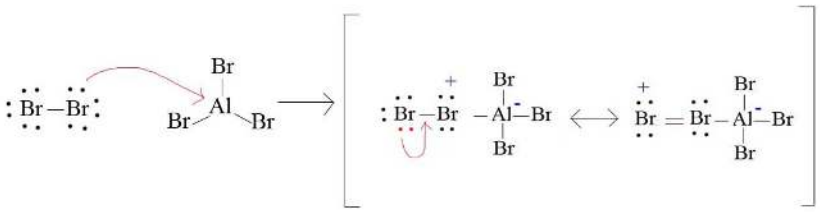


Hence, Halogen needs the help and aid of Lewis Acidic Catalysts to activate it to become a very strong electrophile. Examples of these activated halogens are Ferric Hallides (FeX_3) Aluminum Halides (AlX_3) where X= Br or Cl. In the following examples, the halogen we will look at is Bromine.

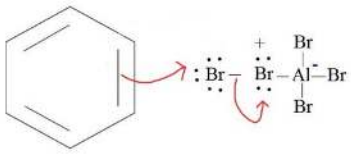
In the example of bromine, in order to make bromine electrophillic enough to react with benzene, we use the aid of an aluminum halide such as aluminum bromide.



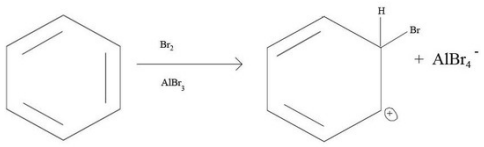
With aluminum bromide as a Lewis acid, we can mix Br_2 with $AlBr_3$ to give us Br^+. The presence of Br^+ is a much better electrophile than Br_2 alone. Bromination is acheived with the help of $AlBr_3$ (Lewis acid catalysts) as it polarizes the Br-Br bond. The polarization causes polarization causes the bromine atoms within the Br-Br bond to become more electrophillic. The presence of Br^+ compared to Br_2 alone is a much better electrophille that can then react with benzene.



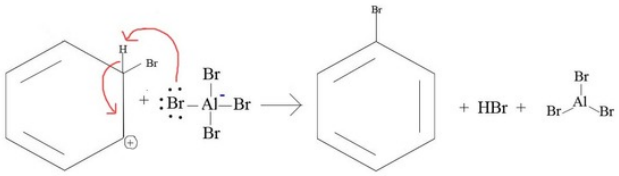
As the bromine has now become more electrophillic after activation of a catalyst, an electrophillic attack by the benzene occurs at the terminal bromine of Br-Br-$AlBr_3$. This allows the other bromine atom to leave with the $AlBr_3$ as a good leaving group, $AlBr_4$-.



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After the electrophilic attack of bromide to the benzene, the hydrogen on the same carbon as bromine substitutes the carbocation in which resulted from the attack. Hence it being an electrophilic aromatic SUBSTITUTION. Since the by-product aluminum tetrabromide is a strong nucleophile, it pulls of a proton from the Hydrogen on the same carbon as bromine.



In the end, $AlBr_3$was not consumed by the reaction and is regenerated. It serves as our catalyst in the halogenation of benzenes.

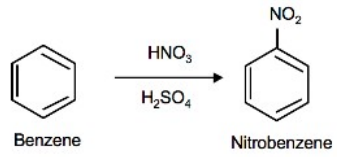
DISSOCIATION ENERGIES OF HALOGENS AND ITS EFFECT ON HALOGENATION OF BENZENES

The electrophillic bromination of benzenes is an exothermic reaction. Considering the exothermic rates of aromatic halogenation decreasing down the periodic table in the Halogen family. Flourination is the most exothermic and Iodination would be the least. Being so exothermic, a reaction of flourine with benzene is explosive! For iodine, electrophillic iodination is generally endothermic, hence a reaction is often not possible. Similar to bromide, chlorination would require the aid of an activating presence such as Alumnium Chloride or Ferric Chloride. The mechanism of this reaction is the same as with Bromination of benzene.

Nitration and sulfonation of benzene are two examples of electrophilic aromatic substitution. The nitronium ion (NO_2^+) and sulfur trioxide (SO_3) are the electrophiles and individually react with benzene to give nitrobenzene and benzenesulfonic acid respectively.

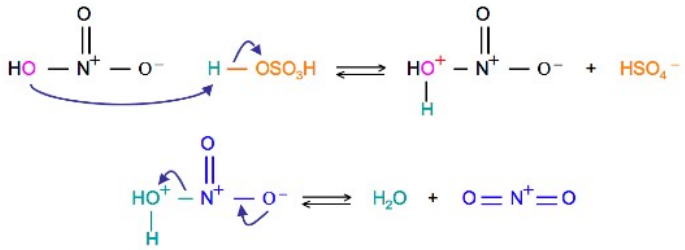
NITRATION OF BENZENE

The source of the nitronium ion is through the protonation of nitric acid by sulfuric acid, which causes the loss of a water molecule and formation of a nitronium ion.



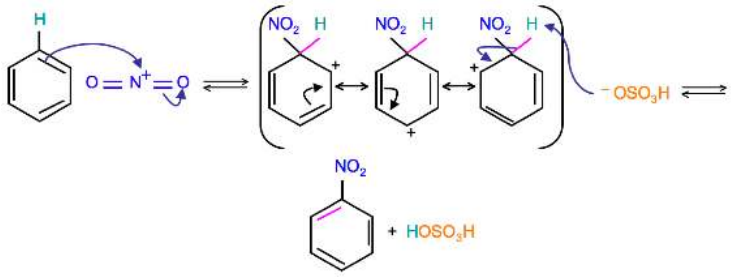
SULFURIC ACID ACTIVATION OF NITRIC ACID

The first step in the nitration of benzene is to activate $HNO_3$with sulfuric acid to produce a stronger electrophile, the nitronium ion.



Because the nitronium ion is a good electrophile, it is attacked by benzene to produce Nitrobenzene.

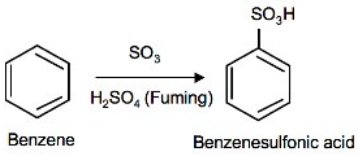
MECHANISM



(Resonance forms of the intermediate can be seen in the generalized electrophilic aromatic substitution)

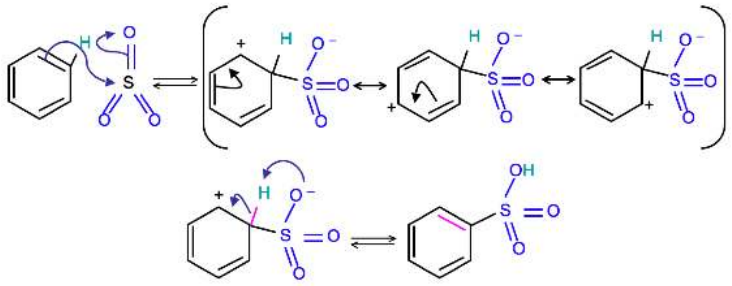
SULFONATION OF BENZENE

Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



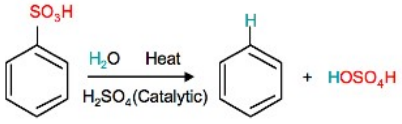
MECHANISM

To produce benzenesulfonic acid from benzene, fuming sulfuric acid and sulfur trioxide are added. Fuming sulfuric acid, also refered to as *oleum*, is a concentrated solution of dissolved sulfur trioxide in sulfuric acid. The sulfur in sulfur trioxide is electrophilic because the oxygens pull electrons away from it because oxygen is very electronegative. The benzene attacks the sulfur (and subsequent proton transfers occur) to produce benzenesulfonic acid.



REVERSE SULFONATION

Sulfonation of benzene is a reversible reaction. Sulfur trioxide readily reacts with water to produce sulfuric acid and heat. Therefore, by adding heat to benzenesulfonic acid in diluted aqueous sulfuric acid the reaction is reversed.



FURTHER APPLICATIONS OF NITRATION AND SULFONATION

Nitration is used to add nitrogen to a benzene ring, which can be used further in substitution reactions. The nitro group acts as a ring deactivator. Having nitrogen present in a ring is very useful because it can be used as a directing group as well as a masked amino group. The products of aromatic nitrations are very important intermediates in industrial chemistry.

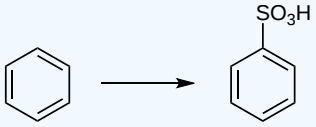
Because sulfonation is a reversible reaction, it can also be used in further substitution reactions in the form of a directing blocking group because it can be easily removed. The sulfonic group blocks the carbon from being attacked by other substituents and after the reaction is

completed it can be removed by reverse sulfonation. Benzenesulfonic acids are also used in the synthesis of detergents, dyes, and sulfa drugs. Bezenesulfonyl Chloride is a precursor to sulfonamides, which are used in chemotherapy.

EXERCISES

EXERCISE 16.2.1

1. What is/are the required reagent(s)for the following reaction:

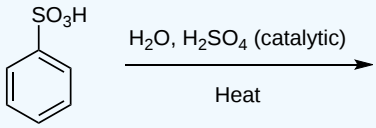


Answer

SO_3 and H_2SO_4 (fuming)

EXERCISE 16.2.2

What is the product of the following reaction:



Answer



EXERCISE 16.2.3

Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

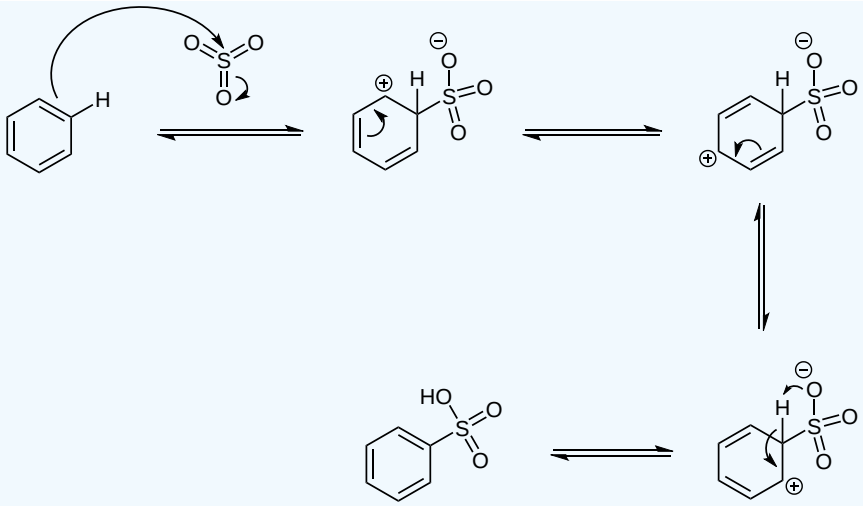
Answer

Sulfuric acid is needed in order for a good electrophile to form. Sulfuric acid protonates nitric acid to form the nitronium ion (water molecule is lost). The nitronium ion is a very good electrophile and is open to attack by benzene. Without sulfuric acid the reaction would not occur.

EXERCISE 16.2.4

Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

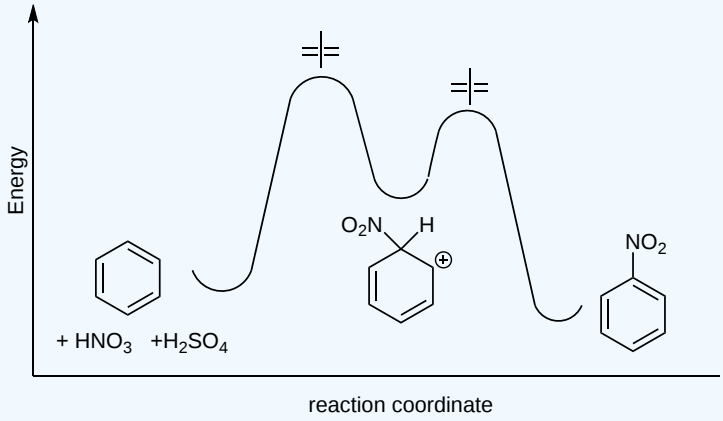
Answer



EXERCISE 16.2.5

Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

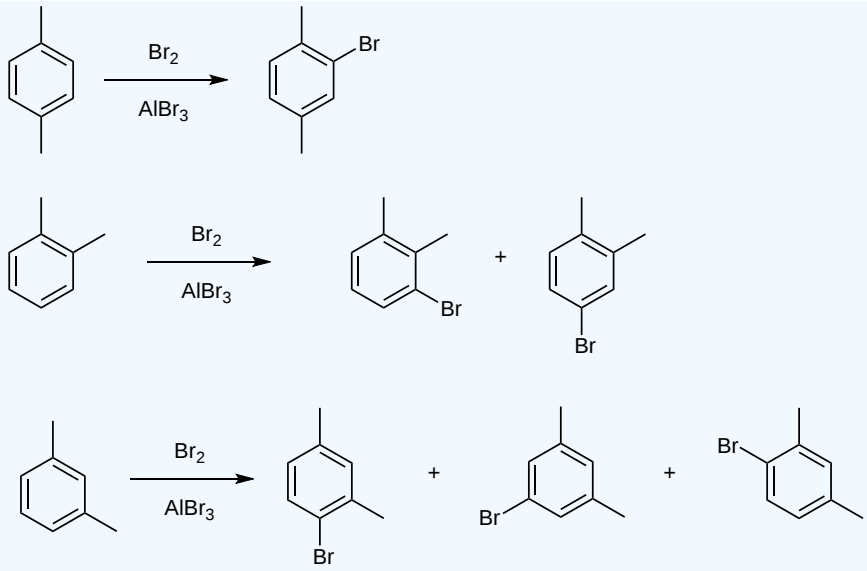
Answer



EXERCISE 16.2.6

In each case, how many products would be possible for the bromination of *p*-xylene, *o*-xylene, and *m*-xylene?

Answer

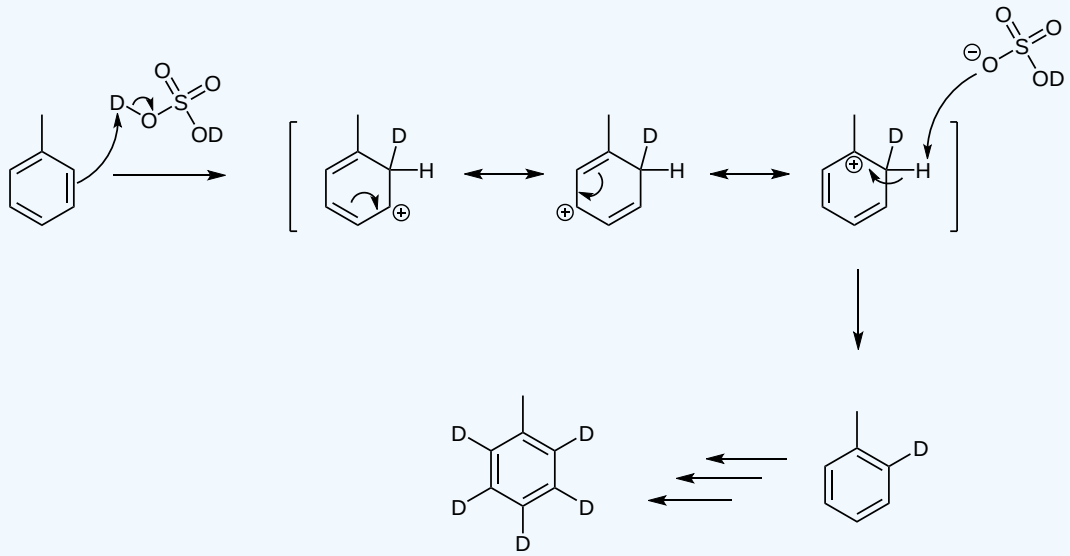


EXERCISE 16.2.7

If toluene is treated with D_2SO_4 all the hydrogen's are replaced with deuterium. Explain.

Answer

The deuterium is added to the ring. When the ring "re-aromatizes" the base scavenges the hydrogen before the deuterium and therefore is left on the ring. Continues for the rest of the hydrogen on the ring.



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3. Sauls, Thomas W., Walter H. Rueggeberg, and Samuel L. Norwood. "On the Mechanism of Sulfonation of the Aromatic Nucleus and Sulfone Formation." The Journal of Organic Chemistry 66 (1955): 455-465. American Chemical Society.
4. Vollhardt, Peter. Organic Chemistry : Structure and Function. 5th ed. Boston: W. H. Freeman & Company, 2007.

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16.3: ALKYLATION AND ACYLATION OF AROMATIC RINGS - THE FRIEDEL-CRAFTS REACTION

OBJECTIVES

After completing this section, you should be able to

- write the equation for the preparation of an alkylbenzene by a Friedel-Crafts alkylation reaction.
- identify the product formed from the Friedel-Crafts alkylation of a given aromatic compound.
- identify the aromatic compound needed to prepare a given arene by a Friedel-Crafts alkylation.
- identify the alkyl halide and catalyst needed to form a specified arene from a given aromatic compound.
- write the detailed mechanism for the Friedel-Crafts alkylation reaction, and identify the similarities between this reaction and those electrophilic aromatic substitution reactions you studied in Sections 16.1 and 16.2.
- show how alkyl halides and acylhalides can be used as alkylating agents in Friedel-Crafts alkylation reactions.
- discuss the limitations of the Friedel-Crafts alkylation reaction, paying particular attention to the structure of the alkyl halide, the structure of the aromatic substrate and the problem of polyalkylation.
- write an equation for a typical Friedel-Crafts acylation.
- write the detailed mechanism of the Friedel-Crafts acylation reaction.
- identify the product formed by the Friedel-Crafts acylation of a given aromatic compound.
- identify the aromatic compound, and the reagent and catalyst needed to prepare a given ketone through a Friedel-Crafts acylation reaction.
- Explain the following laws within the Ideal Gas Law

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- acyl group
- Friedel-Crafts acylation reaction
- Friedel-Crafts alkylation reaction
- polyalkylation

STUDY NOTES

A Friedel-Crafts alkylation reaction is an electrophilic aromatic substitution reaction in which a carbocation is attacked by a pi bond from an aromatic ring with the net result that one of the aromatic protons is replaced by an alkyl group. If you prefer, you may regard these reactions as involving an attack by an aromatic ring on a carbocation. The latter approach is the one used in the textbook, but the former approach is probably more common.

When more than one alkyl group is introduced into an aromatic ring during the course of a Friedel-Crafts alkylation reaction, polyalkylation is said to have occurred.

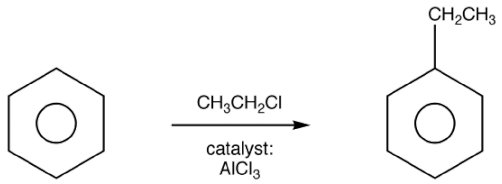
The four limitations on the use of Friedel-Crafts alkylations are as follows:

1. vinyl and aryl halides cannot be used to form carbocations.
2. the aromatic substrate must not contain a strongly deactivating group, or groups, such as NH_2, NHR or NR_2, which form complexes with the Lewis acid catalyst and in so doing become strongly deactivating.
3. polyalkylation, which can be overcome by using a large excess of the aromatic substrate.
4. carbocation rearrangements may occur in any reaction that involves a carbocation.

The reaction of an aromatic substrate with an acid chloride (or acid anhydride) in the presence of an aluminum chloride catalyst is used to introduce an acyl group (C=O) into the aromatic ring through an electrophilic aromatic substitution mechanism. Such reactions are Friedel-Crafts acylation reactions.

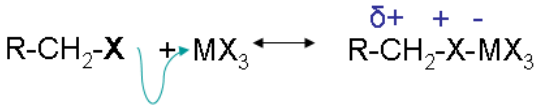
FRIEDEL-CRAFTS ALKYLATION

Friedel-Crafts Alkylation was first discovered by French scientist Charles Friedel and his partner, American scientist James Crafts, in 1877. This reaction allowed for the formation of alkyl benzenes from alkyl halides, but was plagued with unwanted supplemental activity that reduced its effectiveness.



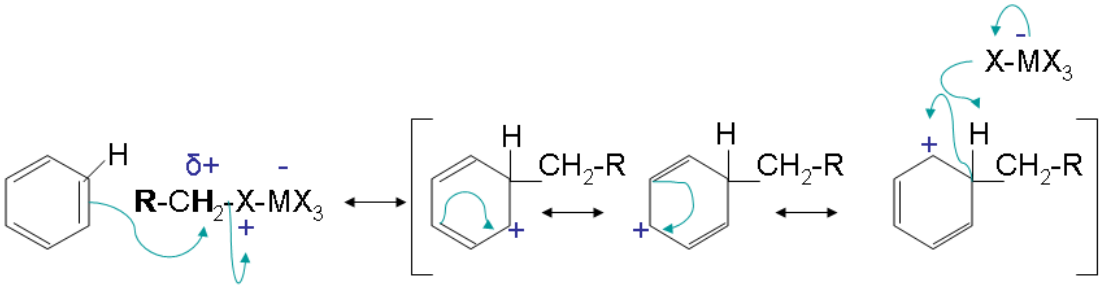
The mechanism takes place as follows:

Step 1:



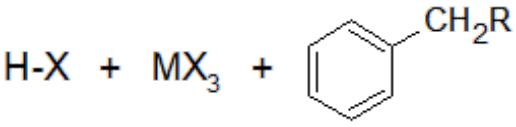
Step one creates a carbocation that acts as the electrophile in the reaction. This steps activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.

Steps 2 and 3:



Step 2 has an electron pair from the aromatic ring attack the carbocation forming a new C-C bond. The arenium ion intermediate results with stabilization from multiple resonance forms. The loss of a proton then gives the neutral alkylated substitution product.

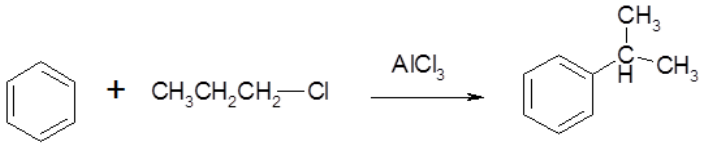
Final Products



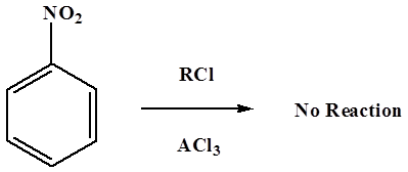
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen combinations such as BF_3, $SbCl_5$, $AlCl_3$, $SbCl_5$, and $AlBr_3$, all of which are commonly used in these reactions.

SOME LIMITATIONS OF FRIEDEL-CRAFTS ALKYLATION

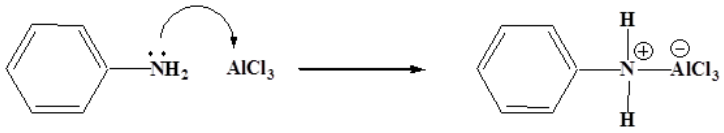
There are possibilities of carbocation rearrangements when you are trying to add a carbon chain greater than two carbons. The rearrangements occur due to hydride shifts and methyl shifts. For example, the product of a Friedel-Crafts Alkylation will show an iso rearrangement when adding a three carbon chain as a substituent. One way to resolve these problems is through Friedel-Crafts Acylation.



Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.

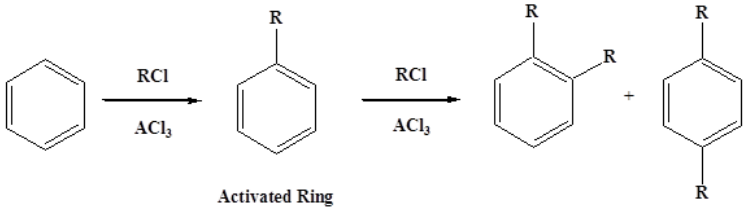


Friedel-Crafts reactions cannot be preformed then the aromatic ring contains a NH_2, NHR, or NR_2 substituent. The lone pair electrons on the amines react with the Lewis acid $AlCl_3$. This places a positive charge next to the benzene ring, which is so strongly activating that the Friedel-Crafts reaction cannot occur.



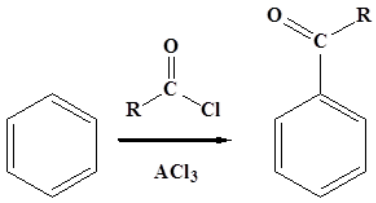
The positive charge strongly deactivates the benzene ring

Lastly, Friedel-Crafts alkylation can undergo polyalkylation. The reaction adds an electron donating alkyl group, which activates the benzene ring to further alkylation.



Activated Ring

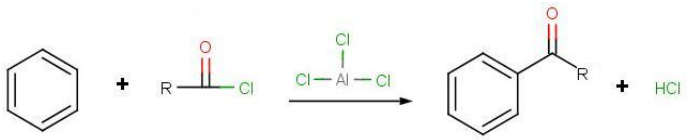
This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating, thus prevents further acylations.



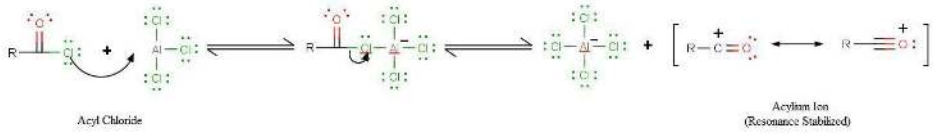
Dectivated Ring

FRIEDEL-CRAFTS ACYLATION

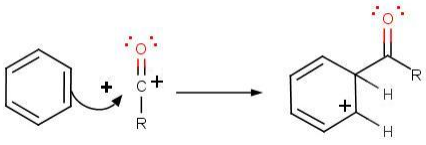
The goal of the reaction is the following:



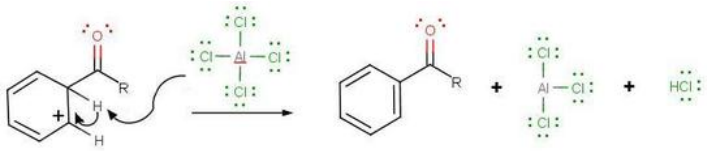
The very first step involves the formation of the acylium ion which will later react with benzene:



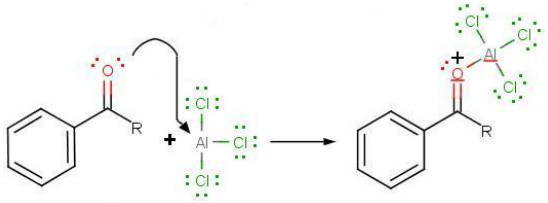
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



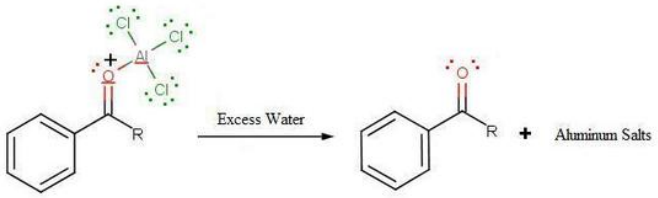
The third step involves the departure of the proton to reform aromaticity:



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the first part of the final product of the reaction, which is a ketone. Thie first part of the product is the complex with aluminum chloride as shown:



The final step involves the addition of water to liberate the final product as the acylbenzene:

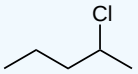
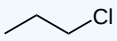


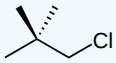
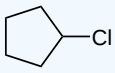
Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (unlike in Friedel-Crafts Alkylation reactions - see Limitation 1 above). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3 above from Friedel-Crafts Alkylation reactions). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

EXERCISES

? EXERCISE 16.3.1

Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?

A) CH_3Cl B)  C) 

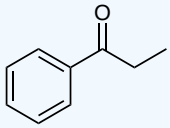
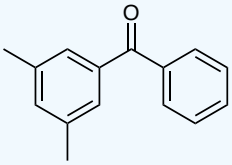
D)  E) 

Answer

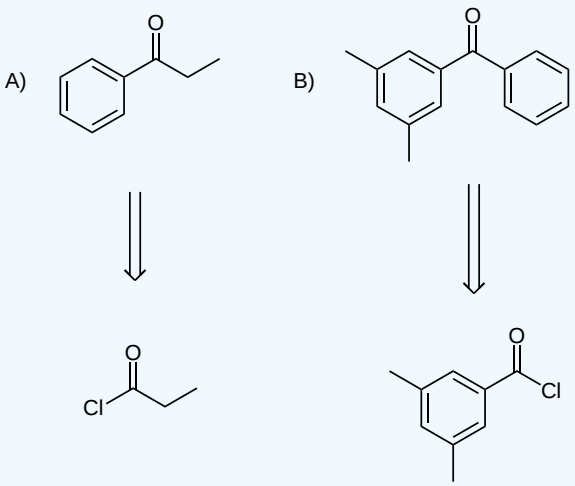
A and E will not undergo a rearrangement.

? EXERCISE 16.3.2

Suggest an acyl chloride that was used to make the following compounds:

A)  B) 

Answer



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16.4: SUBSTITUENT EFFECTS IN SUBSTITUTED AROMATIC RINGS

OBJECTIVES

After completing this section, you should be able to

1. describe the two ways in which a substituent influences the electrophilic substitution of a monosubstituted aromatic compound.
2. classify each of the following substituents as being either activating or deactivating with respect to electrophilic aromatic substitution: **—NH2**, **—OH**, **—NHR**, **—NR2**, **—OR**, **—NHCOR**, alkyl (R), phenyl, **R3N+**, **—NO2**, **—CN**, **—COR**, **—CO2H**, **—CO2R**, **—CHO**, halogens.
3. list a given series of substituents (selected from those given in Objective 2) in order of increasing or decreasing ability to activate or deactivate an aromatic ring with respect to electrophilic substitution.
4. explain, in general terms, the factors that determine whether a given substituent will activate or deactivate an aromatic ring with respect to electrophilic substitution.
5. list a given series of aromatic compounds in order of increasing or decreasing reactivity with respect to electrophilic substitution.
6. explain the inductive effects displayed by substituents such as nitro, carboxyl, alkyl and the halogens during electrophilic aromatic substitution reactions.
7. explain the resonance effects displayed by substituents such as nitro, carbonyl-containing, hydroxy, alkoxy and amino groups during electrophilic aromatic substitution reactions.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

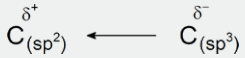
- inductive effect
- resonance effect

STUDY NOTES

On reading Objective 2 students may exclaim “How am I ever going to memorize all of this!”—or words to that effect. The answer is that if you are trying to memorize such things, you are taking the wrong approach to organic chemistry. What you should be doing is trying to understand the factors that determine whether a given substituent will activate or deactivate a benzene ring with respect to electrophilic substitution.

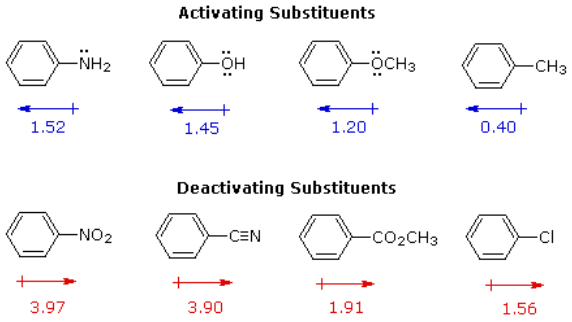
You may wish to review earlier material on to the inductive effect. If so, refer to Sections 2.1, 7.9 (paying particular attention to the “Study Notes”) and 14.5.

Note that one argument sometimes used to explain the ability of alkyl groups to donate electrons inductively to an aromatic ring is that sp^2-hybridized carbon atoms are more electronegative than sp^3-hybridized carbon atoms. Thus, a sigma bond between sp^2- and sp^3-carbon is slightly polarized, as follows:



When substituted benzene compounds undergo electrophilic substitution reactions of the kind discussed above, **two related features must be considered:**

I. The first is the relative reactivity of the compound compared with benzene itself. Experiments have shown that substituents on a benzene ring can influence reactivity in a profound manner. For example, a hydroxy or methoxy substituent increases the rate of electrophilic substitution about ten thousand fold, as illustrated by the case of anisole in the virtual demonstration (above). In contrast, a nitro substituent decreases the ring's reactivity by roughly a million. This **activation** or **deactivation** of the benzene ring toward electrophilic substitution may be correlated with the electron donating or electron withdrawing influence of the substituents, as measured by molecular dipole moments. In the following diagram we see that electron donating substituents (blue dipoles) activate the benzene ring toward electrophilic attack, and electron withdrawing substituents (red dipoles) deactivate the ring (make it less reactive to electrophilic attack).

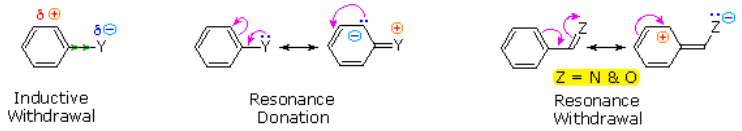


The influence a substituent exerts on the reactivity of a benzene ring may be explained by the interaction of two effects:

The first is the **inductive effect** of the substituent. Most elements other than metals and carbon have a significantly greater electronegativity than hydrogen. Consequently, substituents in which nitrogen, oxygen and halogen atoms form sigma-bonds to the aromatic ring exert an inductive electron withdrawal, which deactivates the ring (left-hand diagram below).

The second effect is the result of **conjugation** of a substituent function with the aromatic ring. This conjugative interaction facilitates electron pair donation or withdrawal, to or from the benzene ring, in a manner different from the inductive shift. If the atom bonded to the ring has one or more non-bonding valence shell electron pairs, as do nitrogen, oxygen and the halogens, electrons may flow into the aromatic ring by p-π conjugation (resonance), as in the middle diagram. Finally, polar double and triple bonds conjugated with the benzene ring may withdraw electrons, as in the right-hand diagram. Note that in the resonance examples all the contributors are not shown. In both cases the charge distribution in the benzene ring is greatest at sites ortho and para to the substituent.

In the case of the nitrogen and oxygen activating groups displayed in the top row of the previous diagram, electron donation by resonance dominates the inductive effect and these compounds show exceptional reactivity in electrophilic substitution reactions. Although halogen atoms have non-bonding valence electron pairs that participate in p-π conjugation, their strong inductive effect predominates, and compounds such as chlorobenzene are less reactive than benzene. The three examples on the left of the bottom row (in the same diagram) are examples of electron withdrawal by conjugation to polar double or triple bonds, and in these cases the inductive effect further enhances the deactivation of the benzene ring. Alkyl substituents such as methyl increase the nucleophilicity of aromatic rings in the same fashion as they act on double bonds.

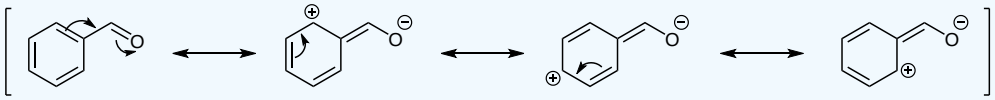


EXERCISES

EXERCISE 16.4.1

Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

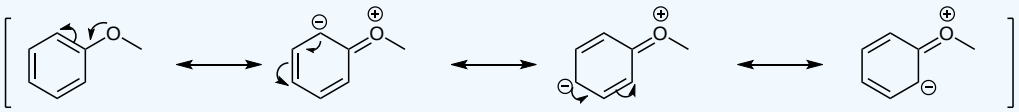
Answer



EXERCISE 16.4.2

Draw the resonance structures for methoxybenzene to show the electron-donating group.

Answer



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16.5: AN EXPLANATION OF SUBSTITUENT EFFECTS

OBJECTIVES

After completing this section, you should be able to

1. draw the resonance contributors for the carbocation intermediate formed during the reaction of a given monosubstituted benzene derivative with any of the electrophiles discussed in this chapter.
2. classify each of the substituents listed in Objective 2 of Section 16.4 as being either meta or ortho/para directing.
3. classify each of the substituents listed in Objective 2 of Section 16.4 as being ortho/para directing activators, ortho/para directing deactivators, or meta directing deactivators.
4. predict the product or products formed from the reaction of a given monosubstituted benzene derivative with each of the electrophiles discussed in this chapter.
5. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic substitution of an alkyl benzene results in a mixture of mainly ortho- and para- substituted products.
6. explain why the electrophilic substitution of phenols, amines and their derivatives proceeds more rapidly than the electrophilic substitution of benzene itself.
7. explain, by drawing the resonance contributors for the intermediate carbocation, why meta substitution predominates in electrophilic aromatic substitution reactions carried out on benzene derivatives containing one of the substituents R_3N^+, NO_2, CO_2H, CN, CO_2R, COR or CHO.
8. explain why electrophilic aromatic substitution of benzene derivatives containing one of the substituents listed in Objective 7, above, proceeds more slowly than the electrophilic substitution of benzene itself.
9. explain, by drawing the resonance contributors for the intermediate carbocation, why the electrophilic aromatic substitution of halobenzenes produces a mixture of mainly ortho- and para-substituted products.
10. explain why the electrophilic aromatic substitution of halobenzenes proceeds more slowly than does the electrophilic substitution of benzene itself.
11. use the principles developed in this chapter to predict in which of the three categories listed in Objective 3, above, a previously unencountered substituent should be placed.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- steric effect
- steric hindrance

STUDY NOTES

As you saw in Section 16.4, a substituent on a benzene ring can be an activator or a deactivator. At the same time, a substituent can also be a meta director or an ortho/para director. Of the four possible combinations, only three are known—there are no meta directing activators.

If you look at the data for the nitration of toluene, you will see that the yield of *o*-nitrotoluene is 63% and that of *p*-nitrotoluene is 34%. Statistically, we should expect to obtain twice as much ortho product as para product, because the former is produced by attack at either of two carbon atoms whereas the latter is produced by attack at only one carbon atom (see Figure below).

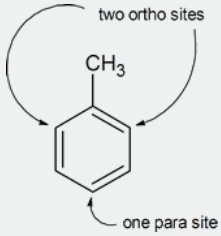


Figure **16.5.1**: Proportions of *o*-nitrotoluene and *p*-nitrotoluene produced by the nitration of toluene

In this instance, the observed ortho/para ratio is almost 2:1, as we might expect. However, if we study the ortho/para ratio found in the nitration of a number of other arenes, we see that this is not always the case. Note that the data for the nitration of toluene given in the

table below differ from those presented elsewhere. The variation may result from a difference in temperature, reaction conditions or reagent, and emphasizes the point that it is the trends which are important, not the numbers themselves.

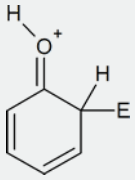
Substrate	% ortho	% para	ortho/para ratio
toluene	58	37	1.57:1
ethylbenzene	45	49	0.92:1
isopropylbenzene	30	62	0.48:1
tert-butylbenzene	16	73	0.22:1

[**Source:** These data were taken from the audiocassette *Some Organic Reaction Pathways*, by Peter Sykes. London: Educational Techniques Subject Group, The Chemical Society, 1975.]

Table 16.5.1: Nitration of arenes

The table above shows us that as the size of the alkyl substituent already present in the ring increases, attack at the ortho position becomes more difficult, and the percentage of ortho isomers in the mixture of products decreases. This is an example of a *steric effect*—an effect caused by the size of the substituent—and we would say that as the size of the alkyl group increases, attack at the ortho position becomes less favorable as a result of *steric hindrance*. Note that the size of the electrophile can also be a factor in determining the ortho/para ratio: the larger the electrophile, the less able it is to attack at the ortho position, particularly if the substituent already present in the ring is itself quite bulky.

When drawing the resonance contributors to the carbocation formed during an electrophilic aromatic substitution, bear in mind that those of the type



are particularly important, because in such structures each atom possesses a complete octet of electrons.

Note that, as do the hydroxyl and amino groups, the halogens have an inductive electron-withdrawing effect and a resonance electron-releasing effect on a benzene ring. The difference in behavior during electrophilic substitutions arises because, with the hydroxyl and amino groups, the resonance effect is much greater than the inductive effect, whereas with the halogens, there is a much finer balance. In the case of the latter, the inductive effect reduces the overall reactivity, but the resonance effect means that this reduction is felt less at the ortho and para positions than at the meta position.

Substituted rings are divided into two groups based on the type of the substituent that the ring carries:

- **Activated rings**: the substituents on the ring are groups that donate electrons.
- **Deactivated rings**: the substituents on the ring are groups that withdraw electrons.

INTRODUCTION

Examples of activating groups in the relative order from the most activating group to the least activating:

$$-NH_2, -NR_2 > -OH, -OR > -NHCOR > -CH_3 \text{ and other alkyl groups}$$

with R as alkyl groups (C_nH_{2n+1})

Examples of deactivating groups in the relative order from the most deactivating to the least deactivating:

$$-NO_2, -CF_3 > -COR, -CN, -CO_2R, -SO_3H > \text{Halogens}$$

with R as alkyl groups (C_nH_{2n+1})

The order of reactivity among Halogens from the more reactive (least deactivating substituent) to the least reactive (most deactivating substituent) halogen is:

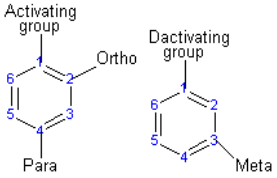
$$F > Cl > Br > I$$

The order of reactivity of the benzene rings toward the electrophilic substitution when it is substituted with a halogen groups, follows the order of electronegativity. The ring that is substituted with the most electronegative halogen is the most reactive ring (less deactivating substituent) and the ring that is substituted with the least electronegative halogen is the least reactive ring (more deactivating substituent),

when we compare rings with halogen substituents. Also the size of the halogen effects the reactivity of the benzene ring that the halogen is attached to. As the size of the halogen increase, the reactivity of the ring decreases.

THE DIRECTION OF THE REACTION

The activating group directs the reaction to the ortho or para position, which means the electrophile substitutes for the hydrogen that is on carbon 2 or carbon 4. The deactivating group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen that is on carbon 3 with the exception of the halogens which are deactivating groups but direct the ortho or para substitution.

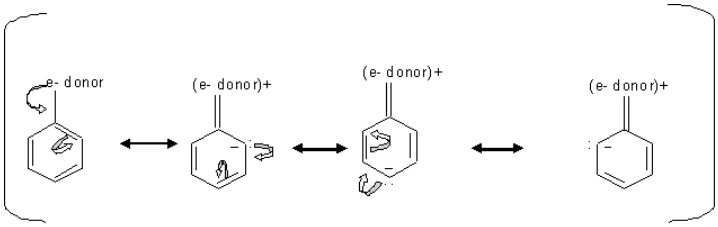


SUBSTITUENTS DETERMINE THE REACTION DIRECTION BY RESONANCE OR INDUCTIVE EFFECT

Resonance effect is the conjugation between the ring and the substituent, which means the delocalizing of the π electrons between the ring and the substituent. Inductive effect is the withdraw of the sigma (the single bond) electrons away from the ring toward the substituent, due to the higher electronegativity of the substituent compared to the carbon of the ring.

ACTIVATING GROUPS (ORTHO OR PARA DIRECTORS)

When substituents such as -OH have an unshared pair of electrons, the resonance effect is stronger than the inductive effect which make these substituents stronger activators, since this resonance effect direct the electron toward the ring. In cases where the subtituents is esters or amides, they are less activating because they form resonance structure that pull the electron density away from the ring.

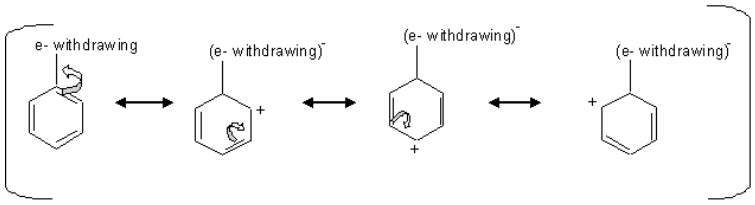


By looking at the mechanism above, we can see how electron donating groups direct electrophilic substitution to the ortho and para positions. Since the extra electron density is localized on the ortho and para carbons, these carbons are more likely to react with the electrophile.

Inductive effects of alkyl groups activate the direction of the ortho or para substitution, which is when s electrons gets pushed toward the ring.

DEACTIVATING GROUP (META DIRECTORS)

The deactivating groups deactivate the ring by the inductive effect in the presence of an electronegative atom that withdraws electron density away from the ring.



The mechanism above shows that when electron density is withdrawn from the ring, that leaves the carbons at the ortho, para positions with a parital positive charge which is unfavorable for the electrophile, so the electrophile attacks the carbon at the meta positions.

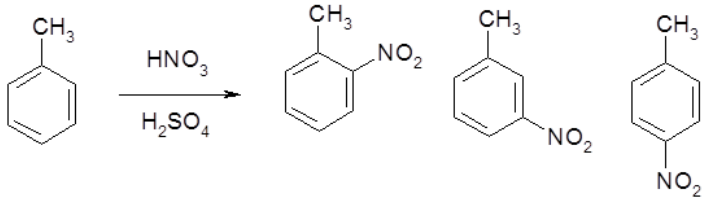
Halogens are an exception of the deactivating group that directs to the ortho or para substitution. The halogens deactivate the ring by inductive effect not by the resonance even though they have an unpaired pair of electrons. The unpaired pair of electrons gets donated to the ring, but the inductive effect pulls away the s electrons from the ring by the electronegativity of the halogens.

SUBSTITUENTS DETERMINE THE REACTIVITY OF RINGS

The reaction of a substituted ring with an activating group is faster than the same reaction wtih benzene. On the other hand, a substituted ring with a deactivated group reacts slower than benzene.

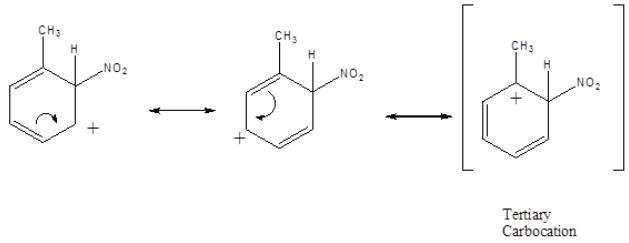
Activating groups speed up reaction with electrophiles due to increased electron density on the ring. This stabilizes the intermediate carbocation, which decreases the activation energy for the reaction. On the other hand, deactivating groups withdraw electron density away from the carbocation formed in the intermediate step, increasing the activation energy, which slows down the reaction.

THE CH_3 GROUP IS AN ORTHO, PARA DIRECTOR

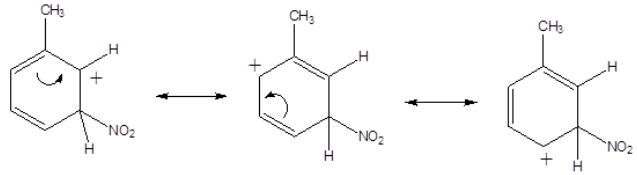


Alkyl groups are inductively donating, therefore are activators. This resulsts in o/p attack to form a tertiary arenium carbocation which speeds up the reaction.

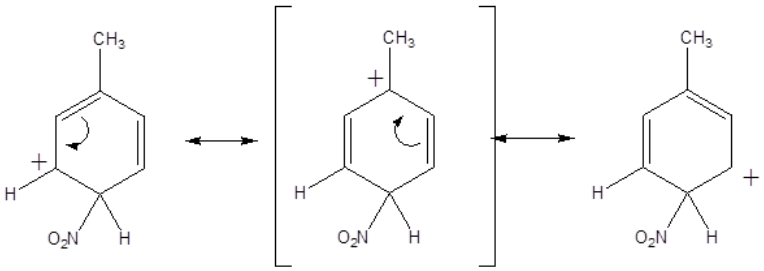
Ortho Attack



Meta Attack

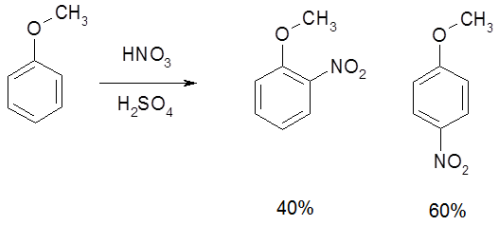


Para Attack



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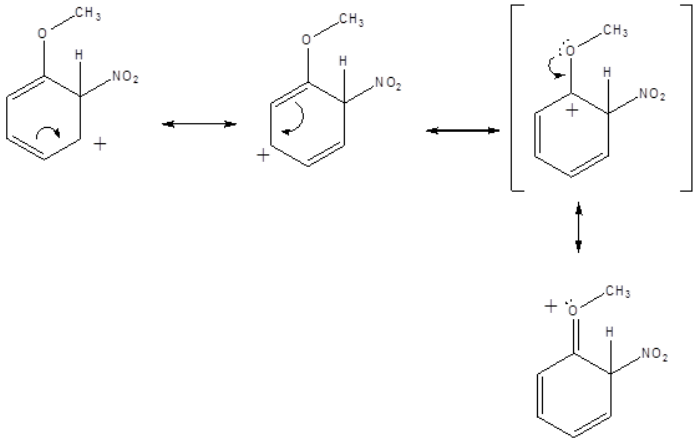
THE O-CH_3 GROUP IS AN ORTHO, PARA DIRECTOR



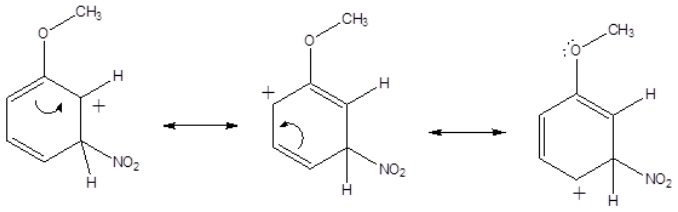
The methoxy group is an example of groups that are ortho, para directors by having and oxygen or nitrogen adjacent to the aromatic ring. This same activation is present with alcohols, amines, esters and amides (with the oxygen or nitrogen attached to the ring, not the carbonyl).

Groups with an oxygen or nitrogen attached to the aromatic ring are ortho and para directors since the O or N can push electrons into the ring, making the ortho and para positions more reactive and stabilizing the arenium ion that forms. This causes the ortho and para products to form faster than meta. Generally, the para product is preferred because of steric effects.

Ortho Attack

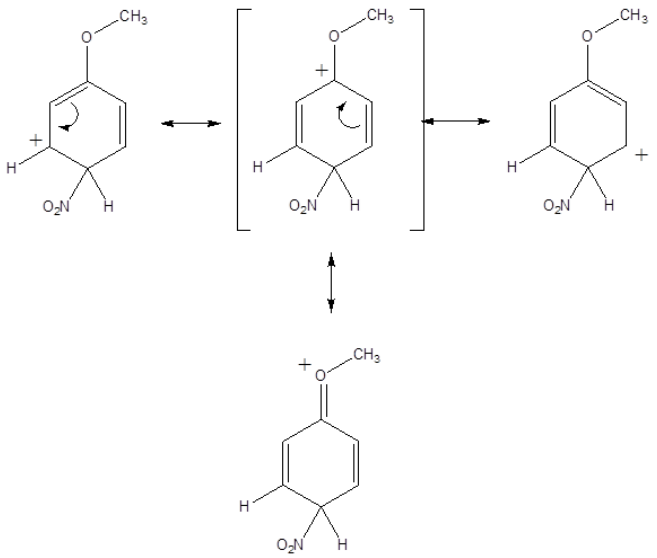


Meta Attack

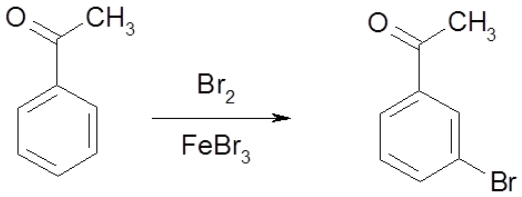


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Para Attack



ACYL GROUPS ARE META DIRECTORS

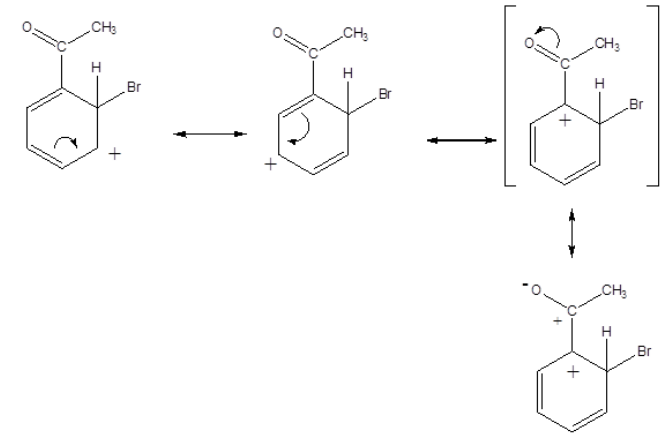


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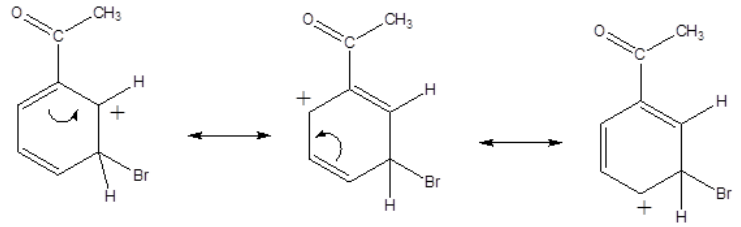
Ketones are an example of groups that deactivate an aromatic ring through resonance. Similar deactivation also occurs with ammonium ions, nitro groups, aldehydes, nitriles, sulfonic acids, and groups with a carbonyl attached to the ring (amides, esters, carboxylic acids, and anhydrides).

Acyl groups are resonance deactivators. Ortho and para attack produces a resonance structure which places the arenium cation next to an additional cation. This destabilizes the arenium cation and slows down ortho and para reaction. By default the meta product forms faster because it lacks this destabilizing resonance structure.

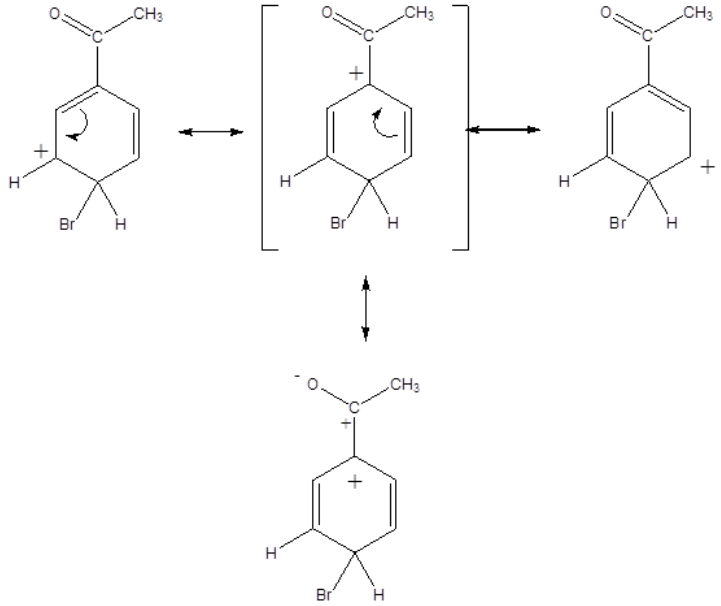
Ortho Attack



Meta Attack



Para Attack



HALOGENS

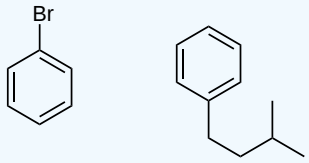
Halogens are an interesting hybrid case. They are ortho, para directors, but deactivators. Overall, they remove electron density from the ring, making it less reactive. However, due to their resonance donation to the ring, if it does react, it reacts primarily at ortho and para positions.

REFERENCES

1. Schore, N.E. and P.C. Vollhardt. 2007. *Organic Chemistry, structure and function*, 5th ed. New York,NY: W.H. Freeman and Company.
2. Fryhle, C.B. and G. Solomons. 2008. *Organic Chemistry*, 9th ed.Danvers,MA: Wiley.

? EXERCISE 16.5.1

Predict the pattern of the electrophilic substitution on these rings:



Answer

The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substitution is going to be ortho and/or para substitution also since we have an alkyl substituent.

EXERCISE 16.5.2

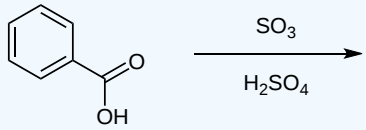
Which nitration product is going to form faster: nitration of aniline or nitration of nitrobenzene?

Answer

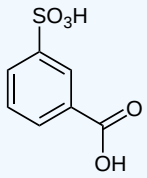
The nitration of aniline is going to be faster than the nitration of nitrobenzene, since the aniline is a ring with NH_2 substituent and nitrobenzene is a ring with NO_2 substituent. As described above NH_2 is an activating group which speeds up the reaction and NO_2 is a deactivating group that slows down the reaction.

EXERCISE 16.5.3

Predict the product of the following sulfonation reaction:



Answer



EXERCISE 16.5.4

Classify these two groups as activating or deactivating groups:

A. alcohol

B. ester

Answer

A. alcohol is an activating group.

B. Esters can be either. If the oxygen atom is next to the ring, esters are activating. However if the carbonyl is next to the ring, the ester is a deactivating group.

EXERCISE 16.5.5

Does a chloride substituent activate or deactivate an aromatic ring?

Answer

Chloride deactivate an aromatic ring due to the inductive effect.

EXERCISE 16.5.6

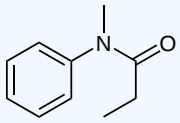
(Trichloromethyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Answer

The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

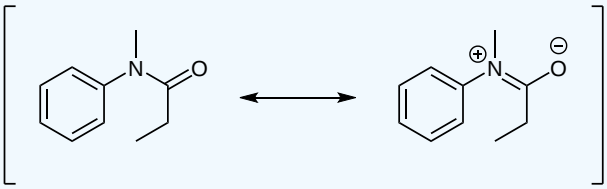
EXERCISE 16.5.7

The following compound is less reactive towards electrophilic substitution than aniline? Explain.



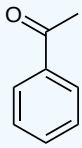
Answer

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.

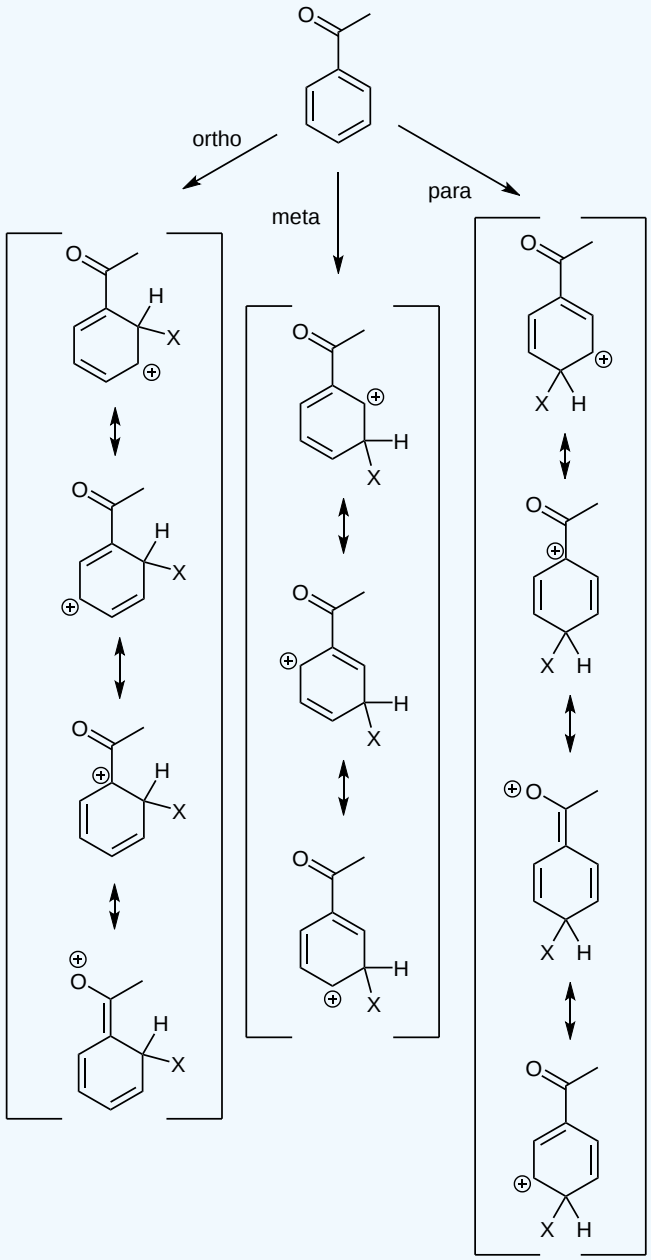


EXERCISE 16.5.8

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



Answer



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16.6: TRISUBSTITUTED BENZENES - ADDITIVITY OF EFFECTS

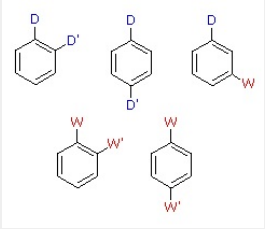
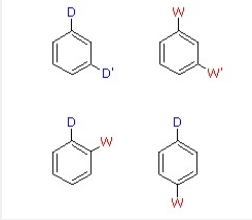
OBJECTIVES

After completing this section, you should be able to

1. predict the position or positions at which electrophilic substitution will occur when a third substituent is introduced into a disubstituted benzene ring.
2. explain the observed substitution pattern when a third substituent is introduced into a disubstituted benzene ring.

ORIENTATIONAL INTERACTION OF SUBSTITUENTS

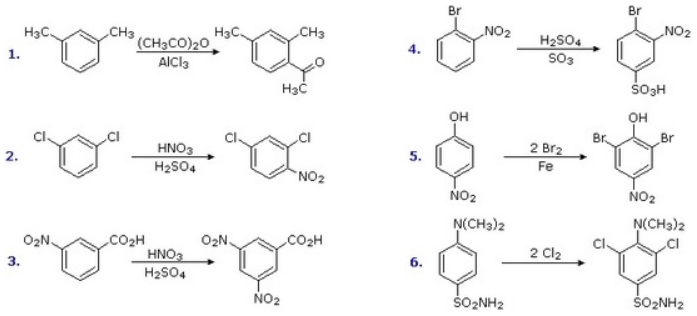
When a benzene ring has two substituent groups, each exerts an influence on subsequent substitution reactions. The activation or deactivation of the ring can be predicted more or less by the sum of the individual effects of these substituents. The site at which a new substituent is introduced depends on the orientation of the existing groups and their individual directing effects. We can identify two general behavior categories, as shown in the following table. Thus, the groups may be oriented in such a manner that their directing influences act in concert, reinforcing the outcome; or are opposed (antagonistic) to each other. Note that the orientations in each category change depending on whether the groups have similar or opposite individual directing effects.

Antagonistic or Non-Cooperative	Reinforcing or Cooperative
	

D = Electron Donating Group (ortho/para-directing)
W = Electron Withdrawing Group (meta-directing)

REINFORCING OR COOPERATIVE SUBSTITUTIONS

The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected manner. Symmetry, as in the first two cases, makes it easy to predict the site at which substitution is likely to occur. Note that if two different sites are favored, substitution will usually occur at the one that is least hindered by ortho groups.

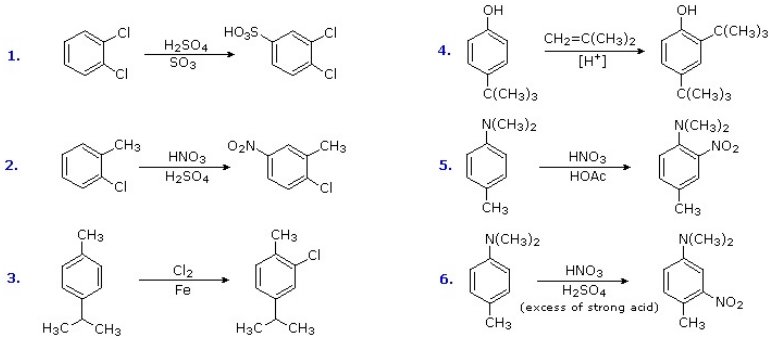


The first three examples have two similar directing groups in a meta-relationship to each other. In examples 4 through 6, oppositely directing groups have an ortho or para-relationship. The major products of electrophilic substitution, as shown, are the sum of the individual group effects. The strongly activating hydroxyl (–OH) and amino ($–NH_2$) substituents favor dihalogenation in examples 5 and 6.

ANTAGONISTIC OR NON-COOPERATIVE SUBSTITUTIONS

Substitution reactions of compounds having an antagonistic orientation of substituents require a more careful analysis. If the substituents are identical, as in example 1 below, the symmetry of the molecule will again simplify the decision. When one substituent has a pair of non-bonding electrons available for adjacent charge stabilization, it will normally exert the product determining influence, examples 2, 4 & 5, even though it may be overall deactivating (case 2). Case 3 reflects a combination of steric hindrance and the superior innate stabilizing

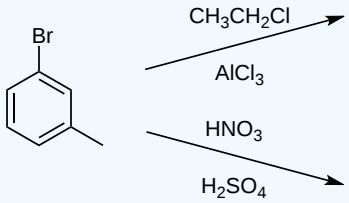
ability of methyl groups relative to other alkyl substituents. Example 6 is interesting in that it demonstrates the conversion of an activating ortho/para-directing group into a deactivating meta-directing "onium" cation [$-NH(CH_3)_2^{(+)}$] in a strong acid environment.

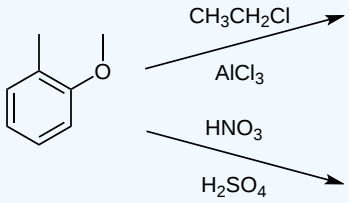


EXERCISES

? EXERCISE 16.6.1

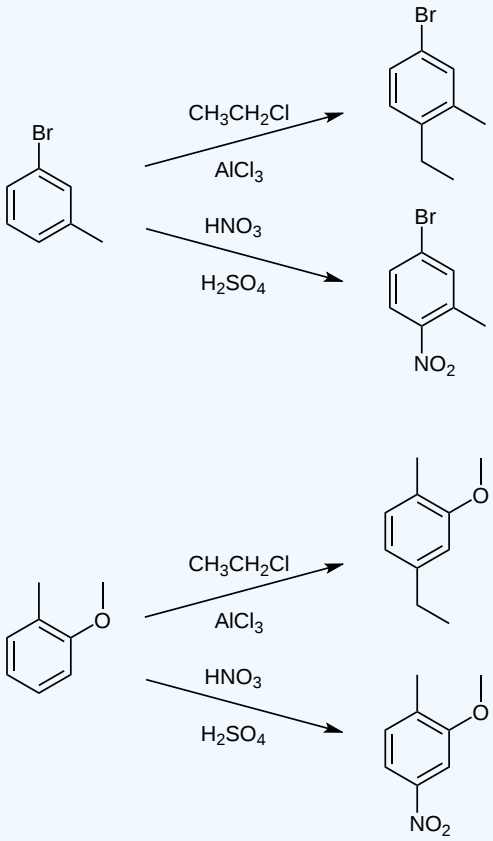
Predict the products of the following reactions:





Answer

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16.7: NUCLEOPHILIC AROMATIC SUBSTITUTION

OBJECTIVES

After completing this section, you should be able to

1. identify the conditions necessary for an aryl halide to undergo nucleophilic aromatic substitution, and give an example of such a reaction.
2. write the detailed mechanism for a nucleophilic aromatic substitution reaction.
3. compare the mechanism of a nucleophilic aromatic substitution reaction and the S_N1 and S_N2 mechanisms discussed earlier.
4. identify the product formed when a given nucleophile reacts with a given aryl halide in a nucleophilic aromatic substitution reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Meisenheimer complex
- nucleophilic aromatic substitution

STUDY NOTES

A *nucleophilic aromatic substitution reaction* is a reaction in which one of the substituents in an aromatic ring is replaced by a nucleophile.

A *Meisenheimer complex* is a negatively charged intermediate formed by the attack of a nucleophile upon one of the aromatic-ring carbons during the course of a nucleophilic aromatic substitution reaction. A typical Meisenheimer complex is shown in the reaction scheme below. Notice how this particular complex can be formed from two different starting materials by using a different nucleophile in each case.

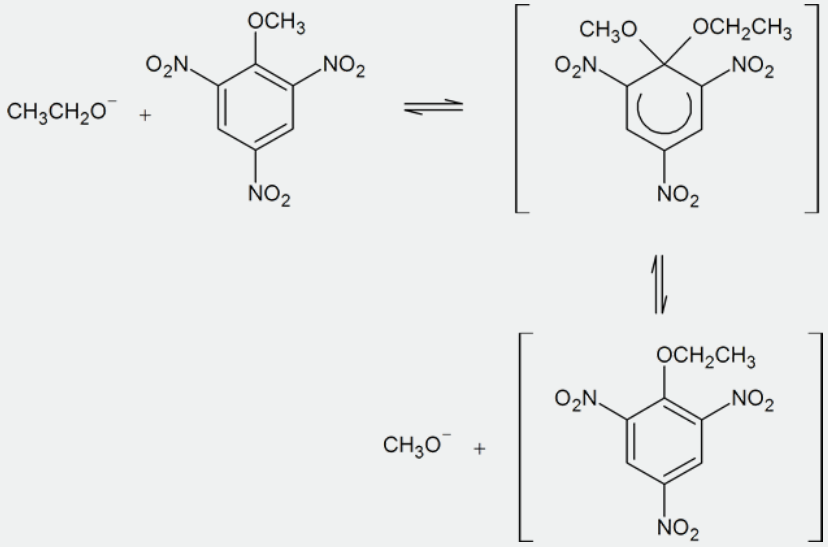


Figure **16.7.1**: The formation of a typical Meisenheimer complex

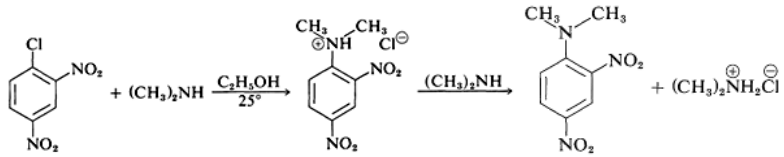
A NUCLEOPHILIC AROMATIC DISPLACEMENT REACTIONS OF ARYL HALIDES

The carbon-halogen bonds of aryl halides are like those of alkenyl halides in being much stronger than those of alkyl halides. The simple aryl halides generally are resistant to attack by nucleophiles in either S_N1 or S_N2 reactions. However, this low reactivity can be changed dramatically by changes in the reaction conditions and the structure of the aryl halide. In fact, nucleophilic displacement becomes quite rapid

a. when the aryl halide is activated by substitution with strongly electron-attracting groups such as NO_2, and
b. when very strongly basic nucleophilic reagents are used.

ADDITION-ELIMINATION MECHANISM OF NUCLEOPHILIC SUBSTITUTION OF ARYL HALIDES

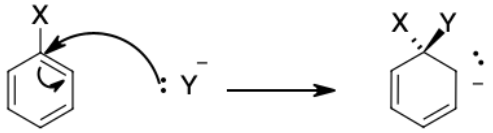
Although the simple aryl halides are inert to the usual nucleophilic reagents, considerable activation is produced by strongly electron-attracting substituents provided these are located in either the ortho or para positions, or both. For example, the displacement of chloride ion from 1-chloro-2,4-dinitrobenzene by dimethylamine occurs readily in ethanol solution at room temperature. Under the same conditions chlorobenzene completely fails to react; thus the activating influence of the two nitro groups amounts to a factor of at least 108:



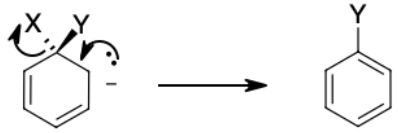
A related reaction is that of 2,4-dinitrofluorobenzene with the amino groups of peptides and proteins, and this reaction provides a means for analysis of the N-terminal amino acids in polypeptide chains.

In general, the reactions of activated aryl halides closely resemble the S_N2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., $CH_3O^{\ominus}$, $HO^{\ominus}$, and RNH_2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the more nucleophilic the attacking reagent, the faster the reaction. However, there must be more than a subtle difference in mechanism because an aryl halide is unable, to pass through the same type of transition state as an alkyl halide in S_N2 displacements.

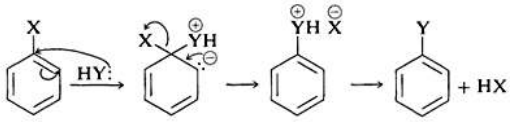
The generally accepted mechanism of nucleophilic aromatic substitution of aryl halides carrying activating groups involves two steps. The first step involves attack of the nucleophile $Y:^{\ominus}$ at the carbon bearing the halogen substituent to form an intermediate carbanion. The aromatic system is destroyed on forming the anion, and the carbon at the reaction site changes from planar (sp^2 bonds) to tetrahedral (sp^3 bonds).



In the second step, loss of an anion, $X^{\ominus}$ or $Y^{\ominus}$, regenerates an aromatic system, and, if $X^{\ominus}$ is lost, the overall reaction is nucleophilic displacement of X by Y.

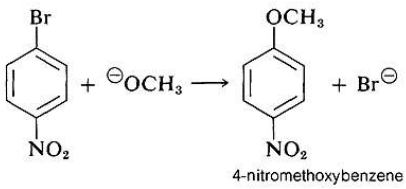


In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



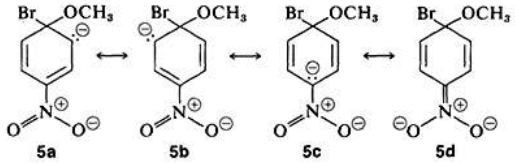
Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the intermediate is too high in energy to be formed at any practical rate. Not only has it lost the aromatic stabilization of the benzene ring, but its formation results in transfer of a negative charge to the ring carbons, which themselves are not very electronegative.

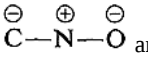
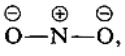
However, when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. As an example, consider the displacement of bromine by methoxid (OCH_3) in the reaction of 4-bromonitrobenzene and methoxide ion:



4-nitromethoxybenzene

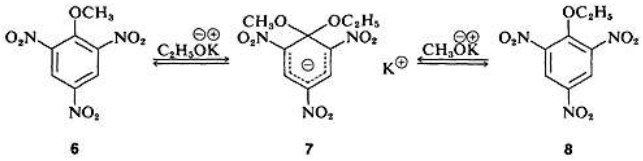
The anionic intermediate formed by addition of methoxide ion to the aryl halide can be described by the valence-bond structures 5a-5d. Of these structures 5d is especially important because in it the charge is transferred from the ring carbons to the oxygen of the nitro substituent:



Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and  ,



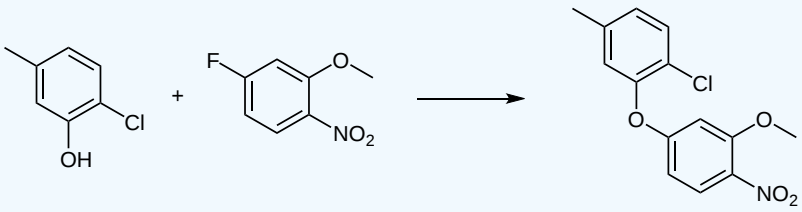
In a few instances, stable compounds resembling the postulated reaction intermediate have been isolated. One classic example is the complex 7 (isolated by J. Meisenheimer), which is the product of the reaction of either the methyl aryl ether 6 with potassium ethoxide, or the ethyl aryl ether 8 and potassium methoxide:



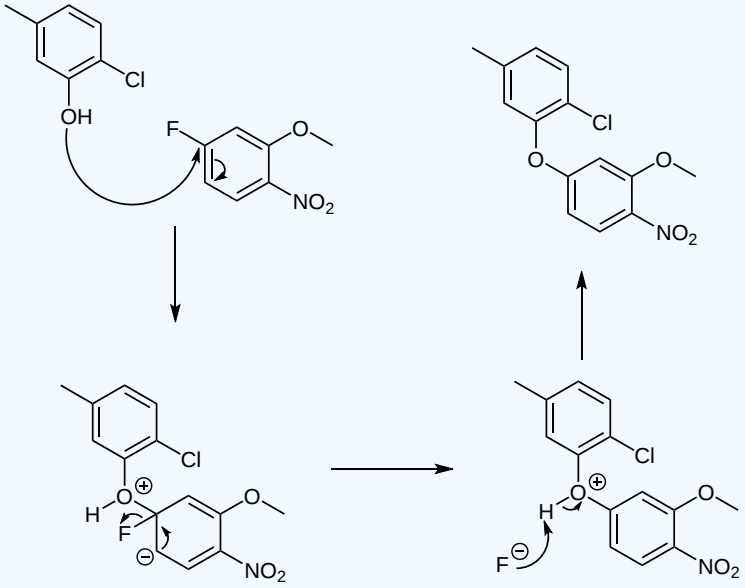
EXERCISES

? EXERCISE 16.7.1

Propose a mechanism for the following reaction:



Answer



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16.8: BENZYNE

OBJECTIVES

After completing this section, you should be able to

1. identify the reagents and conditions required to produce phenol from chlorobenzene on an industrial scale.
2. write the mechanism for the conversion of an alkyl halide to a phenol through a benzyne intermediate.
3. discuss the experimental evidence which supports the existence of benzyne intermediates.
4. discuss the bonding in benzyne, and hence account for its high reactivity.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- benzyne
- elimination-addition mechanism

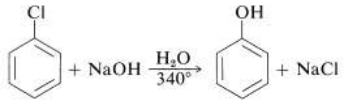
STUDY NOTES

An elimination-addition mechanism involves the elimination of the elements of a small molecule from a substrate to produce a highly reactive intermediate, which then undergoes an addition reaction.

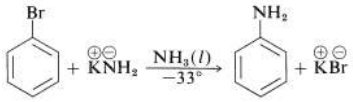
The elimination-addition mechanism of nucleophilic aromatic substitution involves the remarkable intermediate called benzyne or arynes.

ELIMINATION-ADDITION MECHANISM OF NUCLEOPHILIC AROMATIC SUBSTITUTION. ARYNES

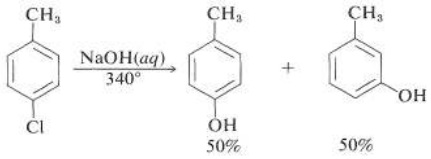
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect substitution with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, chlorobenzene reacts with sodium hydroxide solution at temperatures around **340°** and this reaction was once an important commercial process for the production of benzenol (phenol):



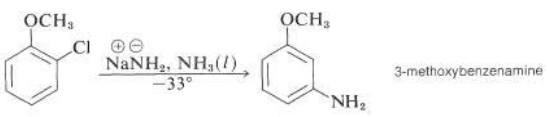
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines **$ArNH_2$** by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as **−33°** with liquid ammonia as solvent:



However, substitution reactions of this type differ from the previously discussed substitutions of activated aryl halides in that rearrangement often occurs. That is, *the entering group does not always occupy the same position on the ring as that vacated by the halogen substituent*. For example, the hydrolysis of 4-chloromethylbenzene at **340°** gives an equimolar mixture of 3- and 4-methylbenzenols:



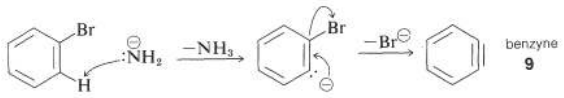
Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change:



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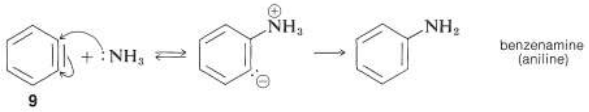
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (**HX**) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination

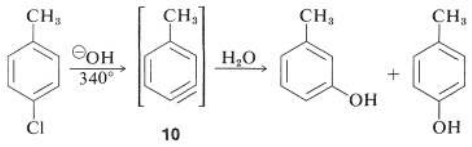


The product of the elimination reaction is a highly reactive intermediate **9** called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

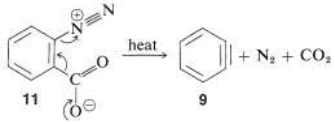
Addition



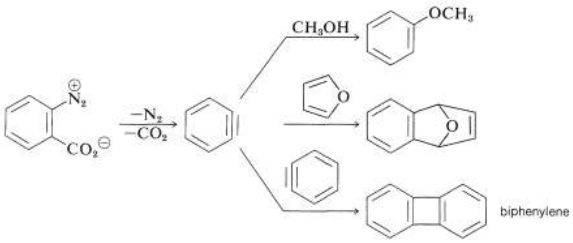
The rearrangements in these reactions result from the attack of the nucleophile at one or the other of the carbons of the extra bond in the intermediate. With benzyne the symmetry is such that no rearrangement would be detected. With substituted benzynes isomeric products may result. Thus 4-methylbenzyne, **10**, from the reaction of hydroxide ion with 4-chloro-1-methylbenzene gives both 3- and 4-methylbenzenols:



In the foregoing benzyne reactions the base that produces the benzyne in the elimination step is derived from the nucleophile that adds in the addition step. This need not always be so, depending on the reaction conditions. In fact, the synthetic utility of aryne reactions depends in large part of the success with which the aryne can be generated by one reagent but captured by another. One such method will be discussed in Section 14-10C and involves organometallic compounds derived from aryl halides. Another method is to generate the aryne by thermal decomposition of a 1,2-disubstituted arene compound such as **11**, in which both substituents are leaving groups - one leaving with an electron pair, the other leaving without:



When **11** decomposes in the presence of an added nucleophile, the benzyne intermediate is trapped by the nucleophile as it is formed. Or, if a conjugated diene is present, benzyne will react with it by a [4 + 2] cycloaddition. In the absence of other compounds with which it can react, benzyne will undergo [2 + 2] cycloaddition to itself:

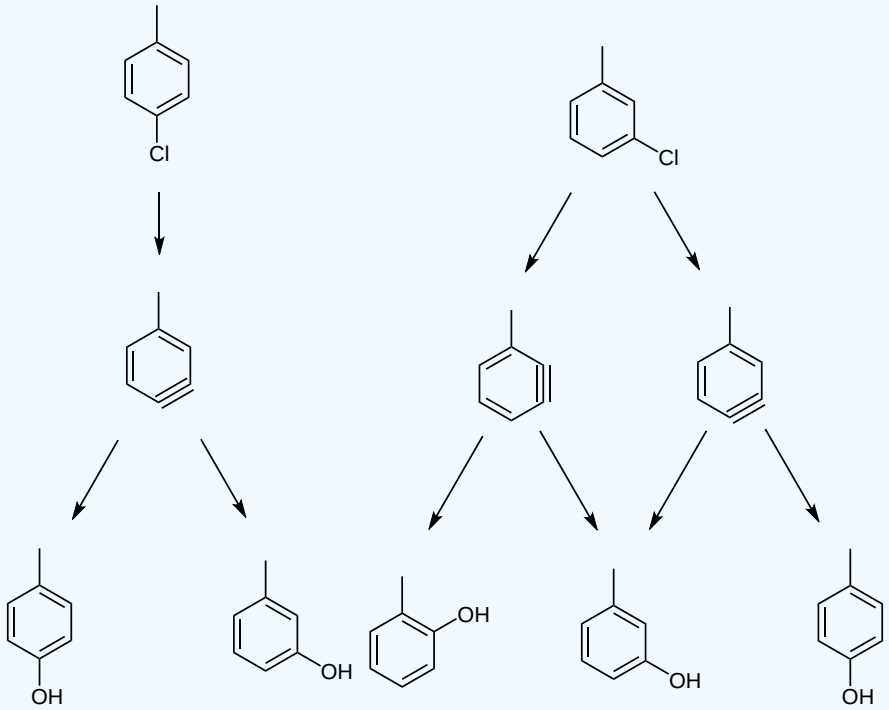


? EXERCISE 16.8.1

When *p*-chlorotoluene is reacted with NaOH, two products are seen. While when *m*-chlorotoluene is reacted with NaOH, three products are seen. Explain this.

Answer

You need to look at the benzyne intermediates. The para substituted only allows for two products, while the para produces two different alkynes which give three different products.



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16.9: OXIDATION OF AROMATIC COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

- write an equation to describe the oxidation of an alkylbenzene to a carboxylic acid.
- identify the reagents required to oxidize a given alkylbenzene to a carboxylic acid.
- identify the product formed from the side-chain oxidation of a given alkylbenzene.
- identify the aromatic compound needed to produce a given carboxylic acid through side-chain oxidation.
- write the equation for the bromination of an alkylbenzene side chain.
- identify the reagents and conditions necessary to bring about bromination in the side chain of an alkylbenzene.
- identify the product formed when a given alkylbenzene undergoes side-chain bromination.
- identify the alkylbenzene needed to prepare a given benzylic bromide by radical substitution.
- write the mechanism for the radical substitution at the benzylic position of an alkylbenzene.
- explain the stability of benzylic radicals in terms of resonance, and draw the resonance contributors of a given benzyl radical.
- explain, and illustrate with appropriate examples, the importance of benzylic bromides as intermediates in organic syntheses.
- arrange a given series of radicals (including benzylic type radicals) in order of increasing or decreasing stability. (Review Section 10.3 if necessary.)

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- benzylic oxidation
- benzylic position
- side-chain oxidation

STUDY NOTES

As you can see from the examples, no matter what the length of the alkyl group in the arene substrate, the product is always a one-carbon carboxyl group. Thus, the benzylic carbon atom has been oxidized and the term *benzylic oxidation* is appropriate. The term *side-chain oxidation* is also commonly used.

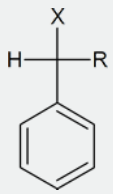
In alkylbenzenes, the carbon atom which is attached to the aromatic ring is particularly reactive. Reactions taking place at this carbon atom are said to occur at the *benzylic position*.

You may wish to review Section 10.3 to remind yourself about allylic bromination using N-bromosuccinimide.

Benzylic halides undergo the typical reactions of alkyl halides; thus, you can expect to see such compounds used frequently in multistep syntheses.

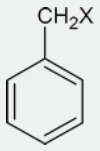
Note that we have adopted the terminology given below.

Any compound of the type



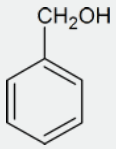
(where X = halogen) will be referred to as a “benzylic halide.”

Compounds of the type



are actually called benzyl chloride, benzyl bromide, etc.

The compound



is called benzyl alcohol.

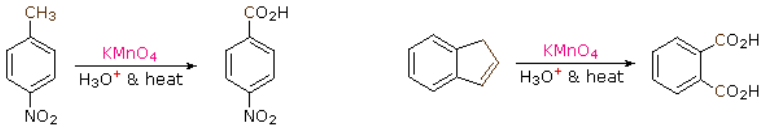
OXIDATION OF ALKYL SIDE-CHAINS

The benzylic hydrogens of alkyl substituents on a benzene ring are activated toward free radical attack, as noted earlier. Furthermore, S_N1 S_N2 and E1 reactions of benzylic halides, show enhanced reactivity, due to the adjacent aromatic ring. The possibility that these observations reflect a general benzylic activation is supported by the susceptibility of alkyl side-chains to oxidative degradation, as shown in the following examples (the oxidized side chain is colored). Such oxidations are normally effected by hot acidic permanganate solutions, but for large scale industrial operations catalyzed air-oxidations are preferred. Interestingly, if the benzylic position is completely substituted this oxidative degradation does not occur.

$$\mathbf{C_6H_5{-}CH_2CH_2CH_2CH_3 + KMnO_4 + H_3O^+ + heat \longrightarrow C_6H_5{-}CO_2H + CO_2}$$

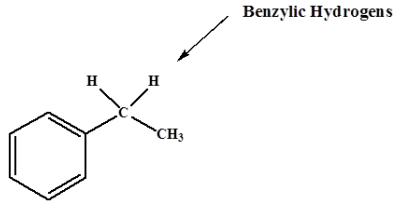
$$\mathbf{\textit{p}\text{-}(CH_3)_3C{-}C_6H_4{-}CH_3 + KMnO_4 + H_3O_6{+} + heat \longrightarrow \textit{p}\text{-}(CH_3)_3C{-}C_6H_4{-}CO_2H}$$

These equations are not balanced. The permanganate oxidant is reduced, usually to Mn(IV) or Mn(II). Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.

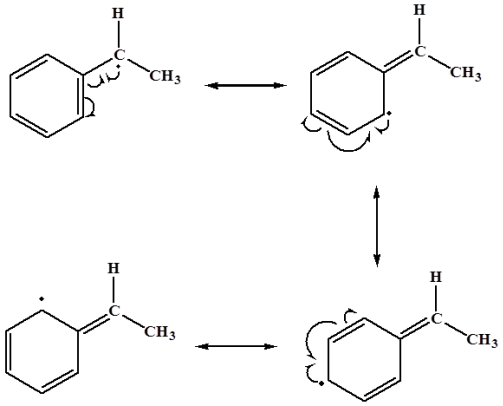


BROMINATION OF THE BENZYLIC CARBON

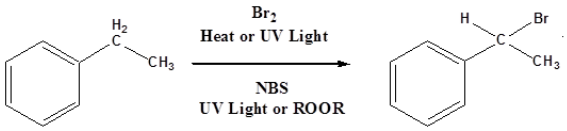
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

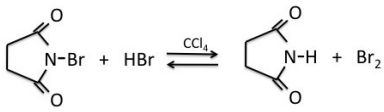


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS AS A BROMINE SOURCE

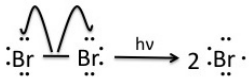
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



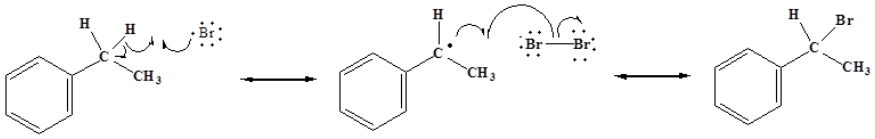
ALLYLIC BROMINATION MECHANISM

Step 1: Initiation

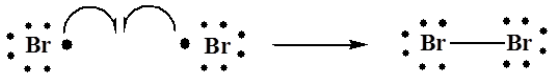
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation

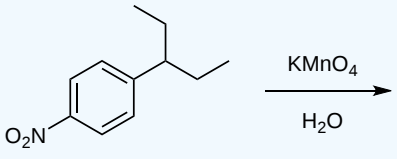


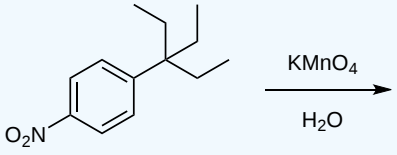
Step 4: Termination



? EXERCISE 16.9.1

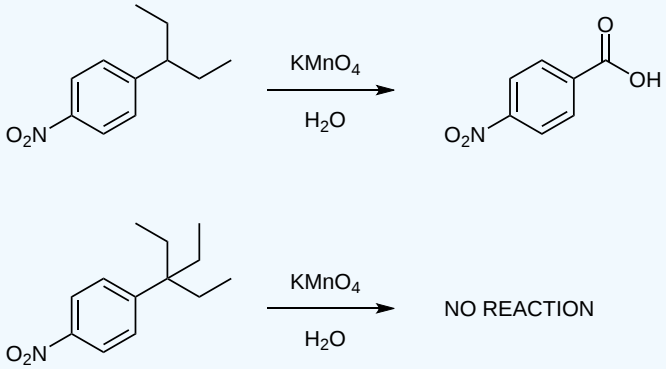
Predict the products of the following two reactions.





Answer

The second one leads to no reaction because it requires a hydrogen just off the phenyl ring.



EXERCISE 16.9.2

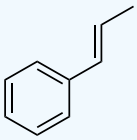
Consider a benzyl radical. Would it be more stable than an alkyl radical? Explain.

Answer

Yes it would be more stable than an alkyl radical. The benzyl radical is stabilized through several resonance structures where the radical is moved through the ring via the pi system there.

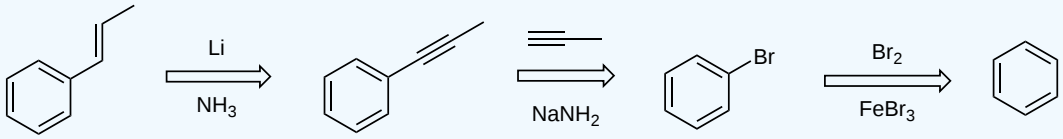
EXERCISE 16.9.3

How would you make the following molecule?



Answer

The following is just one possibility.



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16.10: REDUCTION OF AROMATIC COMPOUNDS

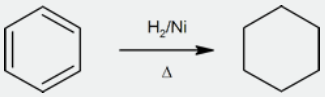
OBJECTIVES

After completing this section, you should be able to

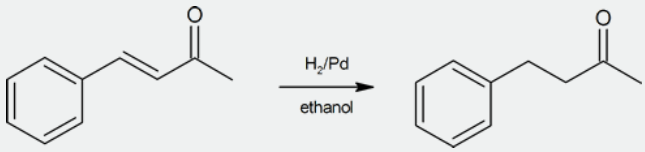
- write an equation to represent the reduction of a substituted benzene to a substituted cyclohexane.
- identify the catalyst and reagents used to reduce aromatic rings.
- compare the ease of reduction of alkenes with the difficulty in reducing benzene rings, and show how this difference in reactivity can be used in organic synthesis.
- write an equation to illustrate the reduction of an aromatic ketone to an arene.
- explain why Friedel-Crafts acylation, followed by reduction, provides a better route to primary alkylbenzenes than does direct alkylation.
- show how a specified alkylbenzene may be prepared by a Friedel-Crafts acylation, followed by reduction. Specify all reagents, the structure of the intermediate ketone, and the necessary starting material.

STUDY NOTES

Catalytic hydrogenation of aromatic rings requires forcing conditions (high heat and hydrogen pressure).

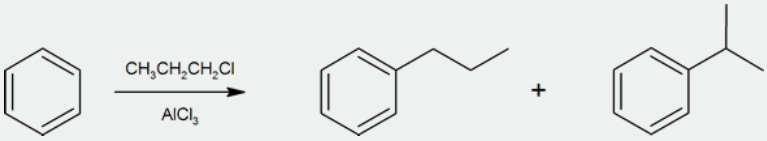


Under milder conditions it is possible to reduce the double-bond of an alkene without reducing the aromatic ring.

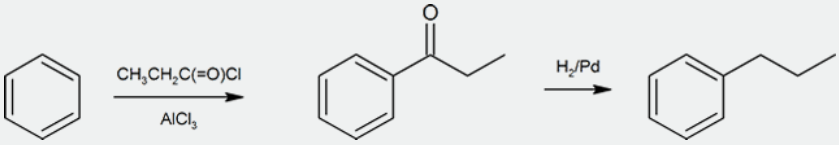


Notice in the above equation that H_2/Pd does not reduce the keto-carbonyl group. Remember, however, that H_2/Pd will reduce a keto-carbonyl group when it is directly attached to an aromatic ring (see equations 4 and 5 under Carbonyl Reductions).

This reduction of the (C=O) group next to an aromatic ring is an important synthetic tool. Recall the Friedel-Crafts alkylation from Section 16.3. When attaching larger alkyl groups to arenes there is a possibility of rearrangement of the alkyl group structure.

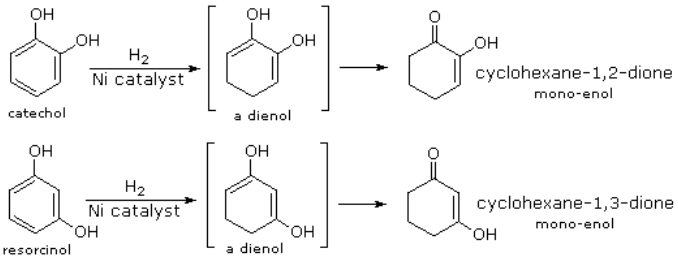


To generate the target compound (in this case *n*-propylbenzene) in a more controlled fashion, one can simply use the equivalent Friedel-Crafts acylation and then reduce the keto-carbonyl group next to the ring as a final step.

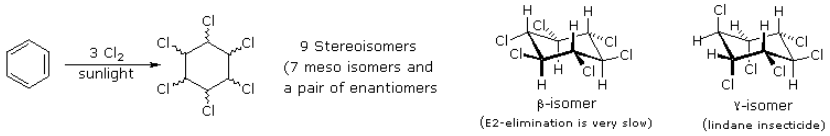


AROMATIC REDUCTION REACTIONS

Although it does so less readily than simple alkenes or dienes, benzene adds hydrogen at high pressure in the presence of Pt, Pd or Ni catalysts. The product is cyclohexane and the heat of reaction provides evidence of benzene's thermodynamic stability. Substituted benzene rings may also be reduced in this fashion, and hydroxy-substituted compounds, such as phenol, catechol and resorcinol, give carbonyl products resulting from the fast ketonization of intermediate enols. Nickel catalysts are often used for this purpose, as noted in the following equations.

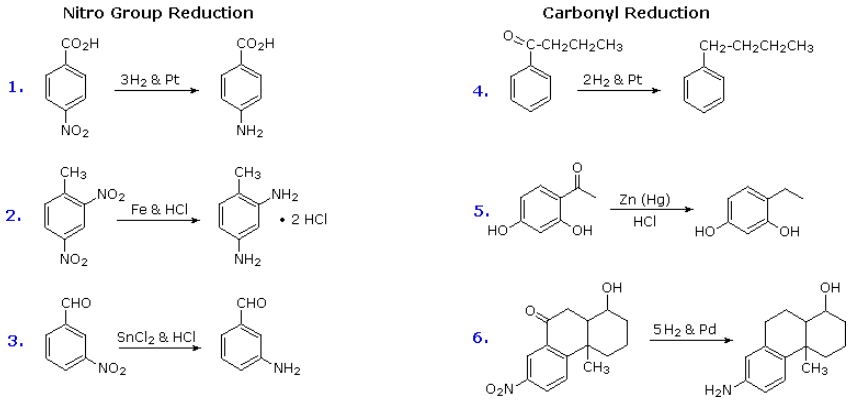


Benzene is more susceptible to radical addition reactions than to electrophilic addition. We have already noted that benzene does not react with chlorine or bromine in the absence of a catalyst and heat. In strong sunlight or with radical initiators benzene adds these halogens to give hexahalocyclohexanes. It is worth noting that these same conditions effect radical substitution of cyclohexane, the key factors in this change of behavior are the pi-bonds array in benzene, which permit addition, and the weaker C-H bonds in cyclohexane. The addition of chlorine is shown below on the left; two of the seven meso-stereoisomers are displayed to the right.



REDUCTION OF NITRO GROUPS AND ARYL KETONES

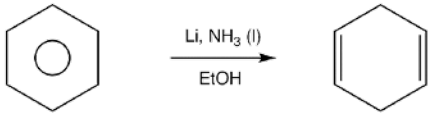
Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction is easily achieved either by catalytic hydrogenation (H_2 + catalyst), or with reducing metals in acid. Examples of these reductions are shown here, equation 6 demonstrating the simultaneous reduction of both functions. Note that the butylbenzene product in equation 4 cannot be generated by direct Friedel-Crafts alkylation due to carbocation rearrangement. The zinc used in ketone reductions, such as 5, is usually activated by alloying with mercury (a process known as amalgamation).



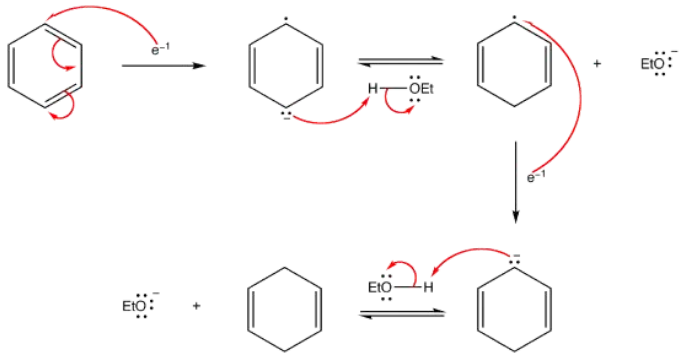
Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

THE BIRCH REDUCTION

Another way of adding hydrogen to the benzene ring is by treatment with the electron rich solution of alkali metals, usually lithium or sodium, in liquid ammonia. See examples of this reaction, which is called the **Birch Reduction.** The Birch reduction is the dissolving-metal reduction of aromatic rings in the presence of an alcohol.



MECHANISM:

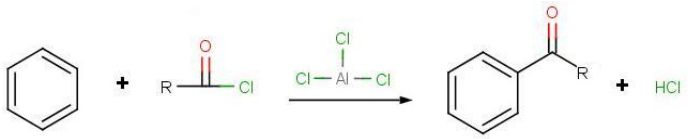


LIMITATIONS OF FRIEDEL-CRAFTS ALKYLATION

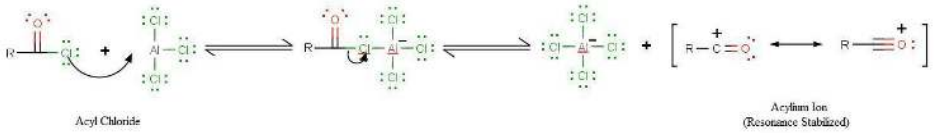
1. Carbocation Rearrangement - Only certain alkylbenzenes can be made due to the tendency of cations to rearrange.
2. **Compound Limitations** - Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.
3. **Polyalkylation** - Products of Friedel-Crafts are even more reactive than starting material. Alkyl groups produced in Friedel-Crafts Alkylation are electron-donating substituents meaning that the products are more susceptible to electrophilic attack than what we began with. For synthetic purposes, this is a big dissapointment.

To remedy these limitations, a new and improved reaction was devised: The Friedel-Crafts Acylation, also known as Friedel-Crafts Alkanoylation.

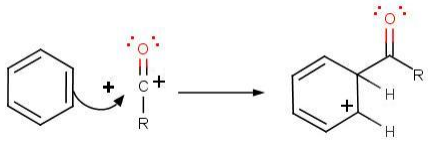
The goal of the reaction is the following:



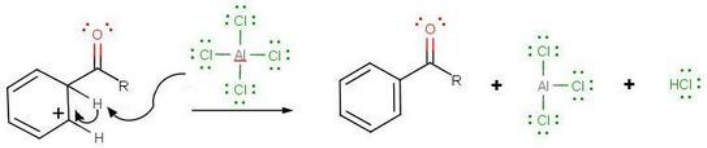
The very first step involves the formation of the acylium ion which will later react with benzene:



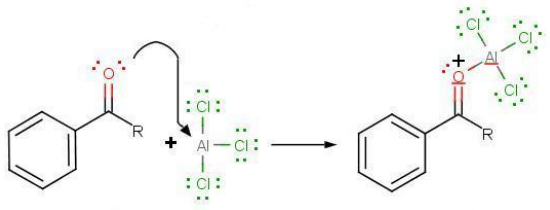
The second step involves the attack of the acylium ion on benzene as a new electrophile to form one complex:



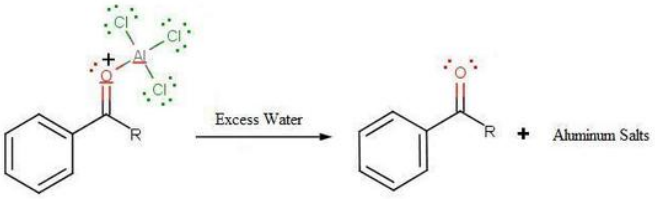
The third step involves the departure of the proton in order for aromaticity to return to benzene:



During the third step, $AlCl_4$ returns to remove a proton from the benzene ring, which enables the ring to return to aromaticity. In doing so, the original $AlCl_3$ is regenerated for use again, along with HCl. Most importantly, we have the first part of the final product of the reaction, which is a ketone. Thie first part of the product is the complex with aluminum chloride as shown:



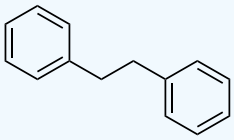
The final step involves the addition of water to liberate the final product as the acylbenzene:



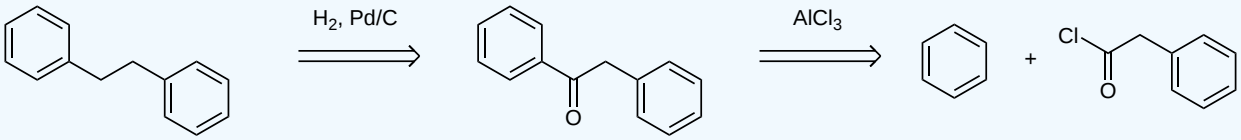
Because the acylium ion (as was shown in step one) is stabilized by resonance, no rearrangement occurs (Limitation 1). Also, because of of the deactivation of the product, it is no longer susceptible to electrophilic attack and hence, is no longer susceptible to electrophilic attack and hence, no longer goes into further reactions (Limitation 3). However, as not all is perfect, Limitation 2 still prevails where Friedel-Crafts Acylation fails with strong deactivating rings.

? EXERCISE 16.10.1

How would you make the following from benzene and an acid chloride?



Answer



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16.11: SYNTHESIS OF POLYSUBSTITUTED BENZENES

OBJECTIVES

After completing this section, you should be able to

- Design a multistep synthesis which may involve reactions in the alkyl side chain of an alkylbenzene and the electrophilic substitution reactions discussed in this chapter. You should pay particular attention to
  - carrying out the reactions in the correct order.
  - using the most appropriate reagents and conditions.
  - the limitations of certain types of reactions.
- Analyze a proposed multistep synthesis involving aromatic substitution to determine its feasibility, point out any errors in the proposal and identify possible problem areas.

STUDY NOTES

As you can see, designing a multistep synthesis requires an analytical mind and an ability to think logically, as well as a knowledge of organic reactions. The best way to become an expert in designing such syntheses is to get lots of practice by doing plenty of problems.

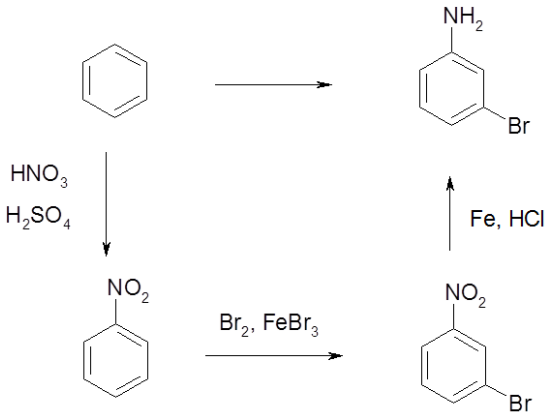
The ability to plan a successful multi step synthesis of complex molecules is one of the goals of organic chemists. It requires a working knowledge of the uses and limitations of many organic reactions - not only which reactions to use, but when. A few examples follow:

FROM BENZENE MAKE *M*-BROMOANILINE

In this reaction three reactions are required.

1. A nitration
2. A conversion from the nitro group to an amine
3. A bromination

Because the end product is meta a meta directing group must be utilized. Of the nitro, bromine, and amine group, only the nitro group is meta direction. This means that the first step need to be the nitration and not the bromination. Also, the conversion of the nitro group to an amine must occur last because the amine group is ortho/para direction.



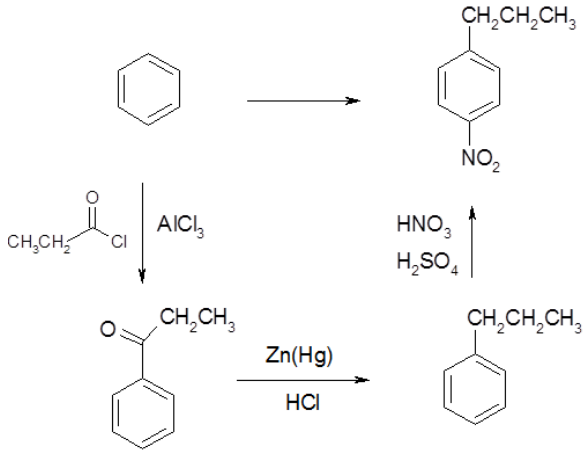
FROM BENZENE MAKE *P*-NITROPROPYLBENZENE :

In this reaction three reactions are required.

1. A Friedel Crafts acylation
2. A conversion from the acyl group to an alkane
3. A nitration

Because the propyl group has more than two carbons, it must be added in two steps. A Friedel Crafts acylation followed by a Clemmensen Reduction. Remember that Friedel Crafts reactions are hindered if the benzene ring is strongly deactivated. This means that the acyl group

must go on first. Because the end product is para a para directing group must be utilized. Of the nitro, acyl, and alkane group, only the alkane group is meta direction. This means that the acyl group must be converted to an alkane prior to the nitration step.



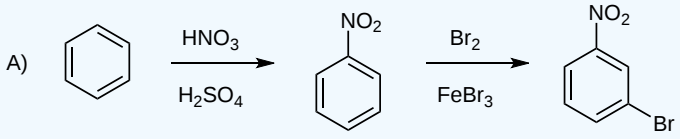
EXERCISE 16.11.1

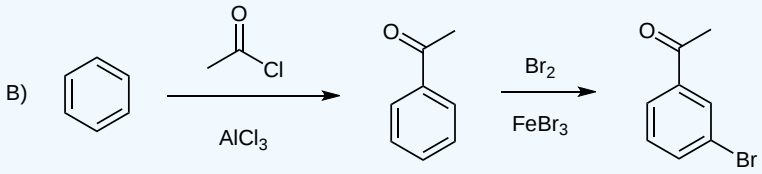
How would make the following compounds from benzene?

a. *m*-bromonitrobenzene
b. *m*-bromoethylbenzene

Answer

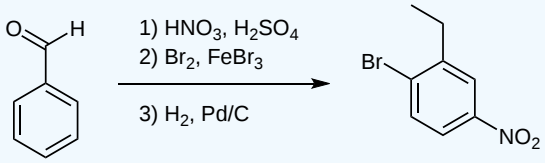
Only one possible synthesis is shown for each compound. There are multiple possibilities.





EXERCISE 16.11.2

There is something wrong with the following reaction, what is it?



Answer

The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.

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16.S: CHEMISTRY OF BENZENE - ELECTROPHILIC AROMATIC SUBSTITUTION (SUMMARY)

CONCEPTS & VOCABULARY

16.0 Introduction

- Aromatic compounds don't typically undergo addition reactions.
- Aromatic compounds typically undergo substitution reactions.

16.1 Electrophilic Aromatic Substitution Reactions: Bromination

- Aromatic molecules only react with strong electrophiles.
- The first step in many electrophilic aromatic substitution mechanisms is activation or formation of the electrophile.
- The electrophilic aromatic substitution mechanism occurs in two steps. The first is addition of the electrophile to the ring and the second is elimination of a hydrogen from the ring to re-form the pi bond and restore aromaticity.
- In bromination of an aromatic ring, molecular bromine (Br_2) is reacted with iron tribromide ($FeBr_3$) to form the strongly electrophilic bromine cation and $FeBr_4$. Following this, the aromatic ring is reacted with the bromine cation and adds to the ring to form a benzenonium cation. This molecule then reacts with one of the bromine atoms from $FeBr_4$ to lose a hydrogen forming the product and HBr as well as reforming the iron tribromide.

16.2 Other Aromatic Substitutions

- Aluminum bromide ($AlBr_3$) can be used in place of $FeBr_3$ to create the bromine cation. Also the chlorides of alumnium and iron can also be used to create a chlorine cation which will also undergo electrophilic aromatic substitution.
- Reacting nitric acid and sulfuric acid forms nitronium (NO_2^+), which will react with aromatics for form nitro compounds.
- Sulfonation of aromatics can be accomplished by reacting with sulfur trioxide and sulfuric acid to yield sulfonic acids.

16.3 Alkylation and Acylation of Aromatic Rings - The Friedel-Crafts Reaction

- Friedel-Crafts reactions incorporate activation of alkyl and acyl halides by reacting them with a Lewis Acid catalyst, $AlCl_3$.
- Friedel-Crafts alkylations allow for adding alkyl chains to aromatic rings.
- After activation with aluminum chloride, alkyl carbocations can undergo rearrangement if it leads to a more stable intermediate.
- Friedel-Crafts acylations add alkyl ketones to aromatic rings.

16.4 Substituent Effects in Substituted Aromatic Rings

- Aromatic inductive effects are caused by differences in electronegativity between atoms bonded to the ring and the ring carbons.
- Most common heteroatoms (N, O, halogens) donate electron density toward the ring inductively.
- Aromatic resonance effects are caused by conjugation of substituents with the pi bonds of the ring.
- Substituents that increase the electron density of the ring activate the ring (make more reactive) toward electrophilic substitution.
- Substituents that decrease the electron density of the ring deactivate the ring (make less reactive) toward electrophilic substitution.

16.4b An Explanation of Substituent Effects

- Steric effects can increase para substitution as ortho/para directors become larger.
- Activating groups are ortho/para (o, p) directors.
- Deactivating groups are meta directors.
- Alkyl groups inductively donate electron density to the ring making them o, p directors.
- Groups with an O or N attached to the aromatic ring are activators and o, p directors due to resonance.
- Groups with a pi bond attached to the aromatic ring are deactivators and m directors due to resonance.
- Halogens are o, p directors, but are deactivators.

16.5 Trisubstituted Benzenes: Additivity of Effects

- When there is more than one group attached to an aromatic ring, these groups may reinforce directing effects (cooperative) or have opposing directing effects (non-cooperative).

16.6 Nucleophilic Aromatic Substitution

- Highly activated aromatic rings can react with strong nucleophiles through a substitution mechanism.
- The mechanism typically begins with addition of a nucleophile followed by elimination of a leaving group.

16.7 Benzyne

- Under highly reactive conditions, a mechanism that begins with elimination for form a benzyne molecule intermediate followed by addition of a nucleophile resulting in nucleophilic aromatic substitution.

16.8 Oxidation of Aromatic Compounds

- Alkyl side-chains can be oxidized to benzoic acid (or a benzoic acid derivative if there are other groups present on the ring) by potassium permanganate ($KMnO_4$) as long as the benzylic carbon has at least one hydrogen attached.
- Radical halogenation will occur at the benzylic carbon, due to stabilization of radical intermediates.

16.9 Reduction of Aromatic Compounds

- Catalytic hydrogenation (H_2 and a catalyst) can be used to reduce many aromatic side-chains.
- Nitro groups can be selectively reduced to amines with $SnCl_2$ and HCl or with Fe and HCl.
- Carbonyls adjacent to the ring can be reduced by either Clemmensen reduction (Zn(Hg) and HCl.
- Birch reductions can reduce aromatic rings.

16.10 Synthesis of Polysubstituted Benzenes

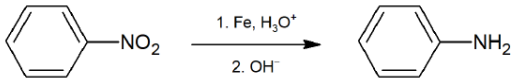
- Multistep synthesis requires a combination of forward (from the starting material) and backward (from the target compound) thinking.

SKILLS TO MASTER

- Skill 16.1 Write detailed electrophilic aromatic substitution mechanisms (halogentation, nitration, sulfonation, Friedel-Crafts alkyation and acylation).
- Skill 16.2 Write detailed mechanisms for formation of reactive electrophiles.
- Skill 16.3 Predict and explain rearrangements that can occur during Friedel-Crafts alkylation.
- Skill 16.4 Explain activation and deactivation of aromatic rings toward electrophilic aromatic substitution.
- Skill 16.5 Explain ortho, para vs. meta directing during electrophilic aromatic substitution reactions.
- Skill 16.6 Combine activation and deactivation and directing effects to predict products of reactions of substituted aromatic molecules.
- Skill 16.7 Write detailed nucleophilic aromatic substitution mechanisms through addition-elimination.
- Skill 16.8 Write detailed nucleophilic aromatic substitution mechanisms through benzyne elimination-addition.
- Skill 16.9 Draw products of oxidation of aromatic molecules.
- Skill 16.10 Draw products of reduction of aromatic side-chains.
- Skill 16.11 Draw mechanisms for reduction of aromatic rings.
- Skill 16.12 Solve multistep synthesis problems incorporating directing effects and side-chain reactions.

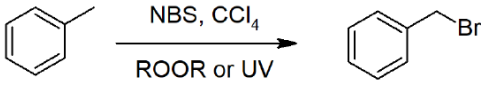
SUMMARY OF REACTIONS

Reduction of Nitro Group



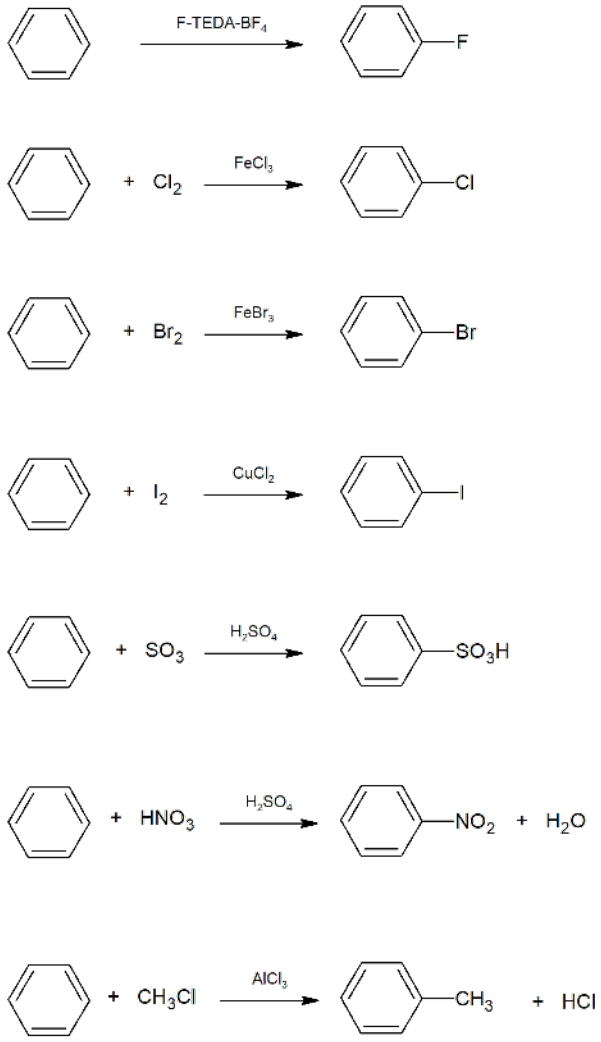
Oxidation of Alkylbenzene

Benzylic Bromination of Alkylbenzene



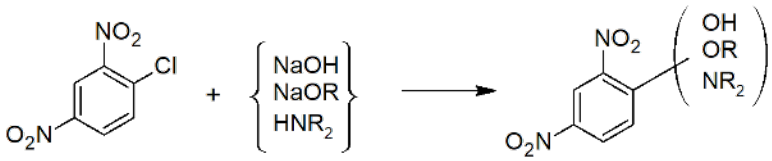
Reduction of Aromatic Compounds

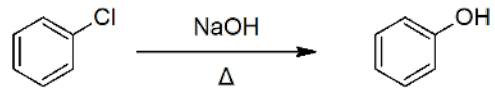
Electrophilic Aromatic Substitution

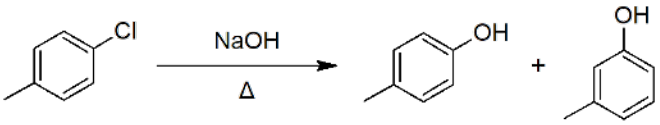


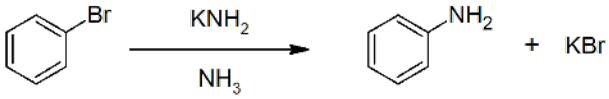
Nucleophilic Aromatic Substitution

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CHAPTER OVERVIEW

17: ALCOHOLS AND PHENOLS

LEARNING OBJECTIVES

When you have completed Chapter 17, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed in *Chemistry 350*.
3. solve "road-map" problems that require a knowledge of the chemistry of alcohols and phenols, in addition to the chemistry of the other classes of compounds discussed in *Chemistry 350*.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

17.0: Introduction to Alcohols and Phenols
17.1: Naming Alcohols and Phenols
17.2: Properties of Alcohols and Phenols
17.3: Preparation of Alcohols- A Review
17.4: Alcohols from Carbonyl Compounds- Reduction
17.5: Alcohols from Carbonyl Compounds - Grignard Reagents
17.6: Reactions of Alcohols
17.7: Oxidation of Alcohols
17.8: Protection of Alcohols
17.9: Phenols and Their Uses
17.10: Reactions of Phenols
17.11: Spectroscopy of Alcohols and Phenols
17.S: Alcohols and Phenols (Summary)

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17.0: INTRODUCTION TO ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. describe the structural differences among alcohols, phenols and enols.
2. write equations describing the industrial preparation of the two simplest alcohols: methanol and ethanol.

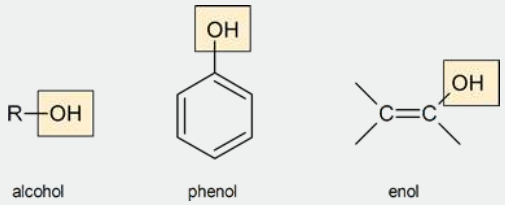
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alcohol
- enol
- phenol

STUDY NOTES

Alcohols and phenols are organic compounds with at least one hydroxyl group attached to a saturated or an aryl carbon, respectively. Enols are a related third class of compounds, with the hydroxyl group attached to a vinylic carbon. We will discuss enols in more detail in Chapter 22.



The reading correctly points out the toxicity of methanol, and describes the adverse effects of its consumption. These effects have not been exaggerated; you may recall reading about the deaths of six residents of Peerless Lake, Alberta, in 1986, brought about by drinking photocopier fluid which contained methanol (or methyl hydrate as it is often called in press reports). In 2000, more than 100 people died in El Salvador after black marketeers sold discarded liquor bottles that had been refilled with a methanol mixture. Indeed the problem has repeated itself globally and so often that in 2014 the World Health Organization released an information note warning of methanol poisoning outbreaks which "occur when methanol is added to illicitly- or informally-produced alcoholic drinks."

Almost everyone is aware that the alcohol present in alcoholic beverages is ethanol (also called ethyl alcohol or grain alcohol). However, many people do not realize that in its pure state, or in solutions of high concentration, this substance is poisonous. In the laboratory one may find containers labelled "absolute ethanol," "95% ethanol" and "denatured ethanol." The acquisition of ethanol by laboratories, and its subsequent disposal, is carefully monitored by provincial authorities. On no account should one consider drinking laboratory ethanol, even after it has been diluted to a concentration equivalent to that found in beer. Denatured alcohol is ethanol to which appropriate quantities of poisonous or nauseating substances (such as methanol) have been added.

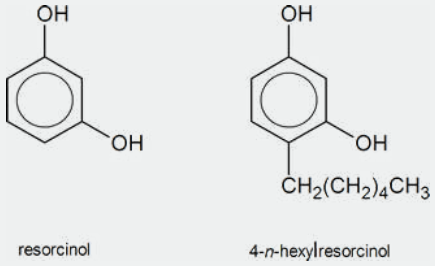
A third commonly encountered alcohol, isopropyl alcohol ("rubbing alcohol" or 2-propanol), is also toxic. It has the ability to kill germs and has a temporary lubricating effect during the rubbing process. Unlike methanol, 2-propanol is not absorbed through the skin; therefore it poses less of a health hazard.

The use of alcohols as fuels is well established. In 2010, the Canadian federal government joined several of the provinces in requiring that all gasoline must include an average of five per cent ethanol. Some gasoline producers, notably Husky/Mohawk, average ten per cent ethanol content in their products. Some especially modified vehicles can use fuel that consists of 85 per cent ethanol (E85).

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring.

Until the late nineteenth century, a person undergoing surgery had to face the fact that he or she might suffer the consequences of what we now know to be bacterial infection, contracted during the course of the operation. The physicians of the time did not know that bacteria existed, and had no way to counter the problems that bacteria caused. In 1867, Joseph Lister, who had learned of the existence of bacteria as a result of research done by Louis Pasteur, began using solutions of phenol to clean wounds and surgical instruments. The phenol solution was an effective antiseptic, killing bacteria, and as a result, a patient's chances of surviving surgery improved greatly.

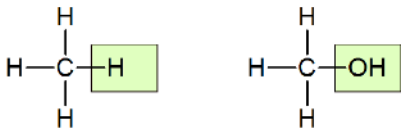
Phenol itself was rather strong for these purposes—it burns healthy tissue—and substitutes were eventually found. One such substitute, used today in throat lozenges and mouthwashes, is 4-*n*-hexylresorcinol.



resorcinol 4-*n*-hexylresorcinol

ALCOHOLS

Molecules of alcohols contain one or more hydroxyl groups (OH groups) substituted for hydrogen atoms along the carbon chain. The structure of the simplest alcohol, methanol (methyl alcohol), can be derived from that of methane by putting an OH in place of one of the H's:



methane methanol

The name, too, is derived from the name methane by replacing the final *e* with *ol* (for alcoh*ol*). The general formula for an alcohol may be written as R—OH, where R represents the hydrocarbon (alkane) portion of the molecule and is called an **alkyl group**. In methanol, R is the methyl group CH_3.

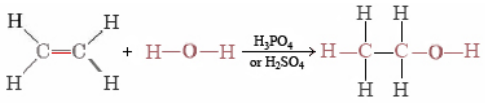
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. The effect of polarity and especially hydrogen bonding due to the OH group is evident when this is compared with the temperature of –85°C at which ethane, C_2H_6, boils. Both molecules contain 18 electrons and are nearly the same size, and so London forces should be about the same, but the OH group in one methanol molecule can form strong hydrogen bonds with an OH in another molecule. Methanol is an important industrial chemical—nearly 3×10^{10} kg was produced worldwide in 2003[1]. Some was made by destructive distillation, but most was synthesized from hydrogen and carbon monoxide:

$$2\,H_2\,(g) + CO\,(g) \longrightarrow CH_3OH\,(l)$$

This reaction is carried out at pressures several hundred times normal atmospheric pressure, using metal oxides as catalysts. Methanol is mainly used to make other compounds from which plastics are manufactured, but some is consumed as fuel in jet engines and racing cars. Methanol is also a component of nonpermanent antifreeze and automobile windshield-washer solvent.

The second member of the alcohol family is ethanol (ethyl alcohol)— the substance we commonly call *alcohol*. Ethanol is also known as grain alcohol because it is obtained when grain or sugar ferments. **Fermentation** refers to a chemical reaction which is speeded up by enzymes and occurs in the absence of air. (Enzymes, catalysts which occur naturally in yeasts and other living organisms, are discussed in more detail elsewhere.)

Ethanol can also be synthesized by adding H_2O to ethene, obtained during petroleum refining:



This is a typical example of an **addition reaction**. The H and OH from H_2O are added to the ethene molecule and held there by electrons made available when one-half of the double bond breaks.

Ethanol is used as a solvent, in some special fuels, in antifreeze, and to manufacture a number of other chemicals. You are probably most familiar with it as a component of alcoholic beverages. Ethanol makes up 3 to 6 percent of beer, 12 to 15 percent of most wines, and 49 to 59 percent of distilled liquor. (The "proof" of an alcoholic beverage is just twice the percentage of ethanol.) Alcohol's intoxicating effects are well known, and it is a mild depressant. Prolonged overuse can lead to liver damage. Methanol also produces intoxication but is much more poisonous than ethanol—it can cause blindness and death. Denatured alcohol is ethanol to which methanol or some other poison has

been added, making it unfit for human consumption. Most of the ethanol not used in alcoholic beverages is denatured because in that form its sale is taxed at a much lower rate.

PHENOLS

Compounds in which a hydroxyl group is bonded to an aromatic ring are called phenols. The chemical behavior of phenols is different in some respects from that of the alcohols, so it is sensible to treat them as a similar but characteristically distinct group. A corresponding difference in reactivity was observed in comparing aryl halides, such as bromobenzene, with alkyl halides, such as butyl bromide and tert-butyl chloride. Thus, nucleophilic substitution and elimination reactions were common for alkyl halides, but rare with aryl halides. This distinction carries over when comparing alcohols and phenols, so for all practical purposes substitution and/or elimination of the phenolic hydroxyl group does not occur.

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17.1: NAMING ALCOHOLS AND PHENOLS

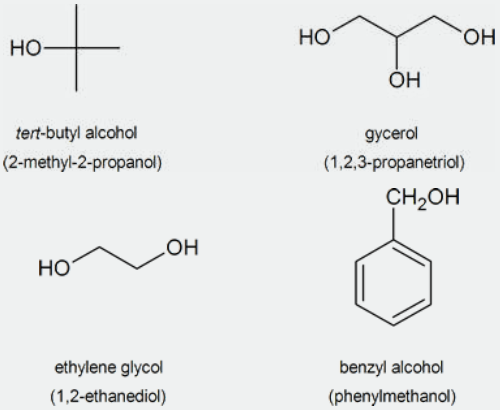
OBJECTIVES

After completing this section, you should be able to

1. identify an alcohol as being primary, secondary or tertiary, given its structure, its IUPAC name or its trivial name.
2. write the IUPAC name of an alcohol or phenol given its Kekulé, condensed or shorthand structure.
3. draw the structure of an alcohol or phenol given its IUPAC name.
4. identify a number of commonly occurring alcohols (e.g., benzyl alcohol, *tert*-butyl alcohol) by their trivial names.

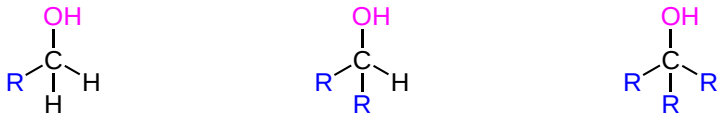
STUDY NOTES

The following are common names of some alcohols (with IUPAC name).



ALCOHOL CLASSIFICATIONS

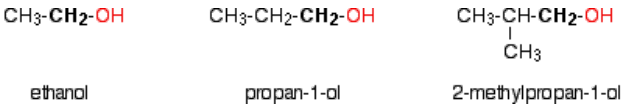
Alcohols can be classified as primary (**1º**), secondary (**2º**), or tertiary (**3º**) depending on the number of alkyl substituents attached to the carbon bonded to the O-H group.



Primary (1º) Alcohol **Secondary (2º) Alcohol** **Tertiary (3º) Alcohol**

PRIMARY ALCOHOLS

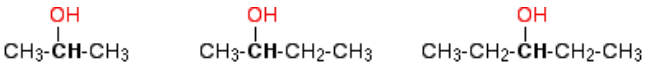
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case there is only one linkage to an alkyl group from the CH_2 group holding the -OH group. There is an exception to this. Methanol, CH_3OH, is counted as a primary alcohol even though there are no alkyl groups attached to the carbon with the -OH group on it.

SECONDARY ALCOHOLS

In a secondary (2°) alcohol, the carbon with the -OH group attached is joined directly to two alkyl groups, which may be the same or different. Examples:



propan-2-ol butan-2-ol pentan-3-ol

TERTIARY ALCOHOLS

In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:



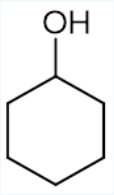
2-methylpropan-2-ol 2-methylbutan-2-ol

? EXERCISE 17.1.1

Indicate if the following molecules are 1º, 2º, or 3º alcohols:

1)

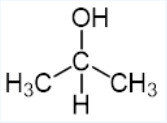
a)



b) $(CH_3)_3COH$

c) $CH_3CH_2CH_2OH$

d)



Answer

1)

a) Secondary

b) Tertiary

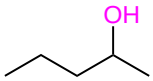
c) Primary

d) Secondary

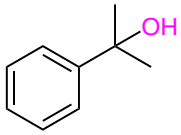
NAMING ALCOHOLS

The IUPAC naming of alcohols is based off the name of the parent alkane chain:

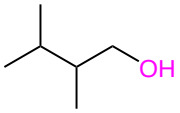
1. The longest chain containing the hydroxyl group (OH) is considered the parent chain. Remove the final **-e** from the parent alkane chain name and add the suffix **-ol**.
2. Number the parent alkane chain such that the hydroxyl group get the lowest possible number. Older IUPAC rules origianlly place the hydroxyl group number before the name of the parent chain. However, the newer rules places the number before the **-ol** suffix.
3. Number the substituents according to their position on the parent chain. Then list the substituents in alphabetical order.



2-Pentanol
(New: Pentan-2-ol)



2-Phenyl-2-propanol
(New: 2-Phenylpropan-2-ol)

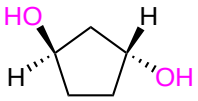


2,3-Dimethyl-1-butanol
(New: 2,3-Dimethylbutan-1-ol)

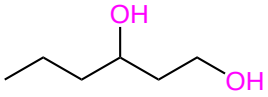
4. When naming a cyclic structure with a hydroxyl group, the -OH is assumed to be on the first carbon.

5. When multiple alcohols are present use **di, tri,** et.c before the **ol,** after the parent name. Also, when a prefix is used the **-e** is not removed from the parent chain name ex. 2,3-hexanediol

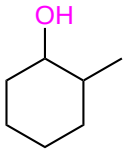
6. When an alkene and alcohol are present in a molecule it is named as follows **(location of the alkene)-(prefix for the parent chain + en)-(location of the hydroxyl)-ol**



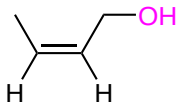
trans-1,3-Cyclopentanediol
(trans-Cyclopentane-1,3-diol)



1,3-Hexanediol
(Hexane-1,3-diol)



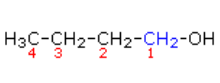
2-Methylcyclohexanol



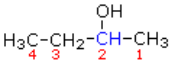
(Z)-2-Buten-1-ol

COMMON NAMES OF ALCOHOLS

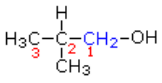
The common system of naming is often used when the alcohol only contains a few carbons. As discussed in **Section 3-3**, the common system names alcohols as if the hydroxyl group (-OH) is attached to a single substituent with the word alcohol added at the end **(Name of the substituent + Alcohol)**. Also, some simple alcohols are given their own generic name such ethylene glycol or glycerol.



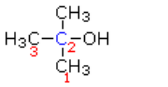
1-butanol
(butyl alcohol)



2-butanol
(*sec*-butyl alcohol)



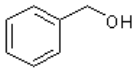
2-methyl-1-propanol
(isobutyl alcohol)



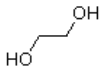
2-methyl-2-propanol
(*tert*-butyl alcohol)



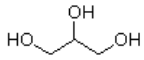
2-propen-1-ol
(allyl alcohol)



phenylmethanol
(benzyl alcohol)



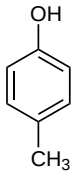
1,2-ethanediol
(ethylene glycol)



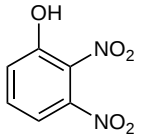
1,2,3-propanetriol
(glycerol)

NAMING PHENOLS

Phenols are named using the rules for aromatic compounds discussed in **Section 15-1**. Note that *-phenol is used* as the ending rather than *-benzene*.



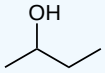
p-methylphenol

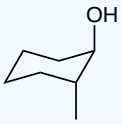


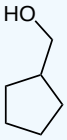
2,3-dinitrophenol

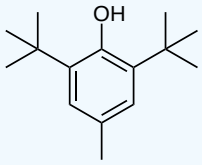
? EXERCISE 17.1.1

Give IUPAC names for the following structures.

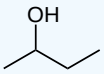




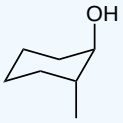




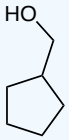
Answer



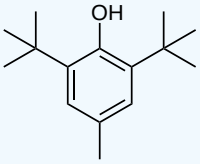
butan-2-ol



(1*R*, 2*R*)-2-mthylcyclohexan-1-ol



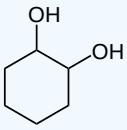
cyclopentylmethanol

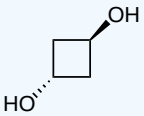


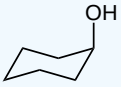
2,6-di-tert-butyl-4-methylphenol

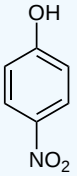
? EXERCISE 17.1.2

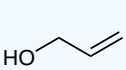
Name the following structures.







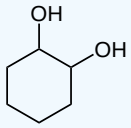




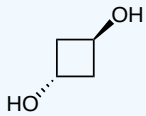


Answer

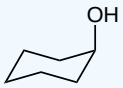
https://chem.libretexts.org/@go/page/36345



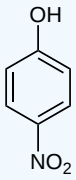
cyclohexane-1,2,-diol



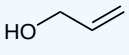
trans-cyclobutane-1,3-diol



cyclohexanol



4-nitrophenol



prop-2-en-1-ol



cycloproanol

EXERCISE 17.1.3

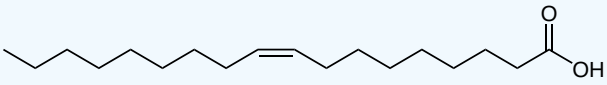
Draw and name all the alcohol isomers of C_3H_9O

Answer

Add texts here. Do not delete this text first.

EXERCISE 17.1.4

Oleic acid, a commonly occurring fatty acid in vegetable oils, has the following structure. Name the compound, making sure to give the correct alkene geometry.

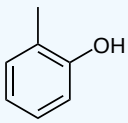


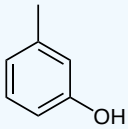
Answer

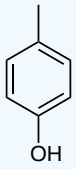
(9*Z*)-Octadec-9-enoic acid

EXERCISE 17.1.5

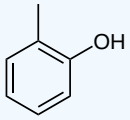
Creosols are naturally occurring compounds used building blocks for many molecules, they occur as three different isomers. Name each of the following isomers.



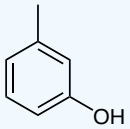




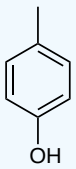
Answer



2-methylphenol



3-methylphenol



4-methylphenol

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17.2: PROPERTIES OF ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

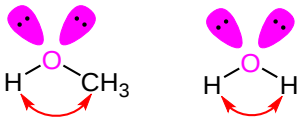
- acid ionization constant (K_a)
- alkoxide ion (RO^-)
- phenoxide ion (ArO^-)

STUDY NOTES

You may wish to review the concept of hydrogen bonding, which should have been discussed in your first-year general chemistry course.

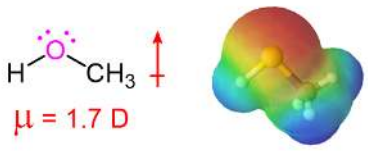
BOILING POINTS OF ALCOHOLS

The oxygen in alcohols and phenols is sp^3 hybridized which gives the roughly the same tetrahedral geometry as water. The bond angle of methanol (108.5 ^{o}) is slightly less than the tetrahedral value mainly due to the presence of its lone pair electrons.



108.5 ^{o} **Methanol** 104.5 ^{o} **Water**

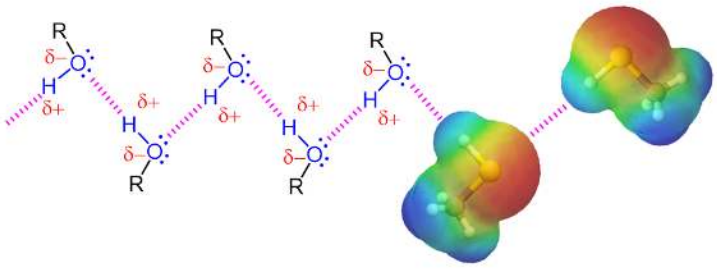
The presence of a highly electronegative oxygen confers a measure of polar character to alcohols. Much of the electron density of an alcohol is drawn towards the oxygen, giving alcohols a relatively high dipole momeny (1.7 D for Methanol).



The Dipole Moment of Methanol

Alcohols contain an extremely polar covalent O-H bond. The electrons in this bond are strongly drawn towards the oxygen giving it a partial negative charge (delta-) while the electrons are drawn away from the hydrogen giving is a partial positive charge (delta+). The polar character of this bond leads to an interaction between alcohol molecules where the positively polarized hydrogen of one alcohol molecule is attracted to the lone pair electrons on the electronegative oxygen atom of a different alcohol molecule. This creates a type of intramolecular attraction is called “hydrogen bonding.” Although the strength of such attractions are much less than most conventional chemical bonds, they are still significant (about 5 to 10 kcal per bond). For an alcohol to vaporize, these intramolecular hydrogen bonding attractions must be

broken making alcohols substantially less volatile, have higher boiling points, and greater water solubility than molecules with a similar molecular weight (Table **17.2.1**). An example of this is seen when comparing 1-propanol (MW = 60.1), Chloroethane (MW = 64.5), and butane (MW = 58.1) which have boiling points of 94.7 ^{o}C, 12.3 ^{o}C, and -1 ^{o}C respectively.



A Representation of Hydrogen Bonding in Alcohols

This table shows that alcohols (in blue) have higher boiling points than haloalkanes and alkanes with the equivalent molecular weight. It also shows that the boiling points of alcohols increase with the number of carbon atoms.

Table **17.2.1**: Physical Properties of Selected Alcohols, Haloalkanes, and Alkanes

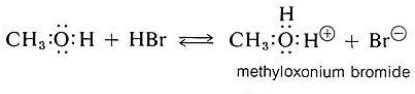
Compound	IUPAC Name	Molecular Weight (g/mol)	Melting Point (^{o}C)	Boiling Point (^{o}C)
CH_3OH	Methanol	32.0	-97.8	65.0
CH_3Cl	Chloromethane	50.5	-97.7	-24.2
CH_3CH_2OH	Ethanol	46.1	-114.7	78.5
$CH_3CH_2CH_2CH_3$	Butane	58.1	-140.	-1
$CH_3CH_2CH_2OH$	1-Propanol	60.1	-126.5	97.4
CH_3CH_2Cl	Chloroethane	64.5	-136.4	12.3
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72.2	-130	36.3
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74.1	-89.5	117.3
$CH_3(CH_2)_4OH$	1-Pentanol	88.1	-79	138

SOLUBILITY OF ALCOHOLS IN WATER

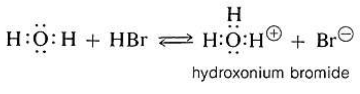
Alcohols and water have the ability to form hydrogen bonds with one another which tends to make the two liquids miscible. Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

BASIC PROPERTIES OF ALCOHOLS

Alcohols are weak bases similar in strength to water and can accept protons from strong acids to form the conjugate acid called oxonium ions (ROH_2^+). An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide from the reaction of hydrogen bromide and water:



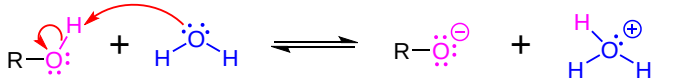
methyloxonium bromide



hydroxonium bromide

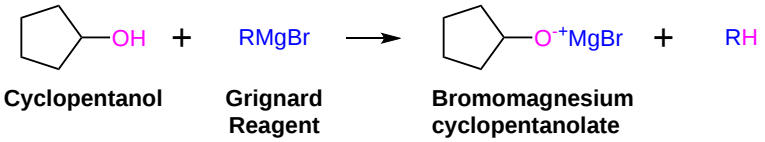
ACIDIC PROPERTIES OF ALCOHOLS

Alcohols, like water, are both weak bases and weak acids. In aqueous solutions, alcohols dissociate slightly by donating a hydrogen to water. This creates the alcohol's conjugate base, called an alkoxide ion (RO^-), along with hydronium (H_3O^+). The acid ionization constant (K_a) of ethanol is about 10^{-18}, which is slightly less than that of water. Alcohols, such as ethanol, can be deprotonated to form its conjugate base by reaction with a stronger base, such as sodium amide ($NaNH_2$), sodium hydride (NaH), or Grignard reagents (RMgBr). Alkoxides can also be formed using sodium or potassium metal which reacts vigorously but controllably with alcohols.

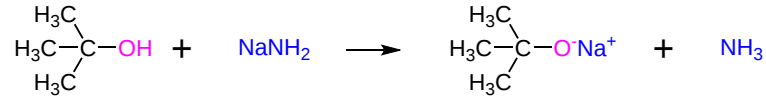


Alcohol **Alkoxide** **Hydronium**

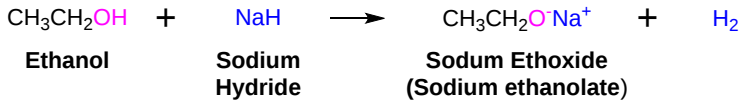
Once created, alkoxides act as bases and are often used as reagents in organic chemistry. Alkoxide's systematic names are based of the corresponding alcohol with the suffix *-ate* added. For example, ethanol becomes ethanolate. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance. Common names are often used for small alkoxides. Common names are generated as: (Name of the positive counter ion) (Prefix for the parent chain + oxide). Example: ethanol becomes ethoxide.



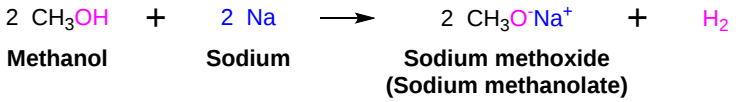
Cyclopentanol **Grignard Reagent** **Bromomagnesium cyclopentanolate**



***tert*-Butyl Alcohol (2-Methyl-2-propanol)** **Sodium Amide** **Sodium *tert*-Butoxide (Sodium 2-Methyl-2-proanolate)**



Ethanol **Sodium Hydride** **Sodum Ethoxide (Sodium ethanolate)**



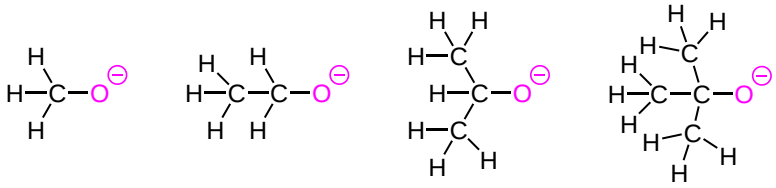
Methanol **Sodium** **Sodium methoxide (Sodium methanolate)**

As discussed in Section 2.8, the strength of an acid in water can be expressed either by its K_a or its pK_a. Compounds with a lower K_a and a higher pK_a are considered less acidic than compound with a higher K_a and a lower pK_a.

$$K_a = \frac{[A^-][H_3O^+]}{[HA]} \tag{17.2.1}$$

$$pK_a = -\log K_a$$

In general, alcohols in aqueous solution are slightly less acidic than water. The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the pK_a is increased as R is changed from primary to secondary to tertiary; therefore, *tert*-butyl alcohol is less acidic than ethanol. This trend is explained by the importance of solvation in equilibrium. In solution, the larger alkoxide ions, are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions. Acidity of alcohols therefore decreases as the size of the conjugate base increases. This trend can be clearly seen when comparing alkoxide size to the pKa of the corresponding alcohol listed in Table **17.2.2**.



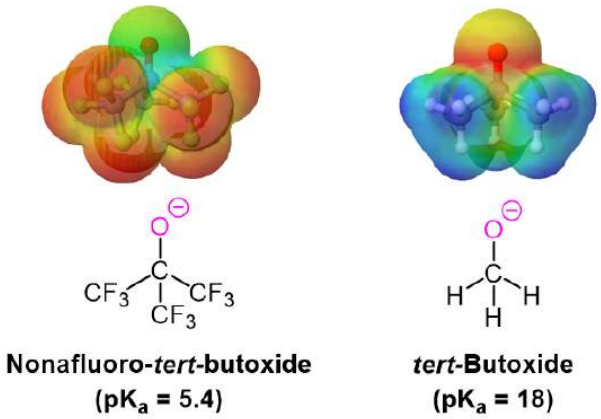
Methoxide **Ethoxide** **Isopropoxide** ***tert*-Butoxide**

$$ROH + OH^- \rightleftharpoons RO^- + HOH$$

Table **17.2.2**: The pKa's of various alcohols

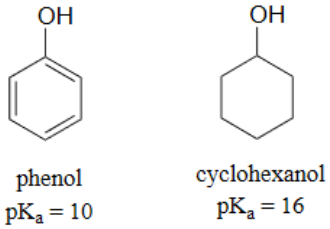
R	Name	pK_{a1}
H	water	14.0
CH_3	methanol	15.5
CH_3CH_2	ethanol	15.9
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5
$(CH_3)_3C$	2-methylpropan-2-ol (*tert*-butanol)	17
C_6H_5 (phenyl)	phenol	9.95

The addition of an electron-withdrawing group, such as an electronegative halogen, can increase the acid strength of an alcohol by stabilizing its alkoxide conjugate base through induction (Section 2.10). The electron-withdrawing group helps to spread out the electron density of the alkoxide's negative charge, which has a stabilizing effect. The inductive effect is cumulative such that the acid strength of an alcohol becomes stronger (Lower pK_a) as the number of halogens increases. The presence of nine fluorines in nonafluoro-*tert*-butyl alcohol decreases its pK_a to 5.4 which is significantly more acidic than *tert*-butyl alcohol (pK_a = 18). The electron-withdrawing effect of the fluorines is clearly seen when comparing the electrostatic potential maps of the corresponding alkoxides. In *tert*-butoxide the molecule's electron density is firmly centered around the oxygen as shown by the orange/yellow color. In nonafluoro-*tert*-butoxide the molecule's electron density is almost completely removed from the oxygen and shifted to the fluorines.

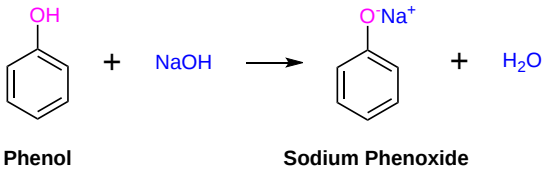


ACIDITY OF PHENOL

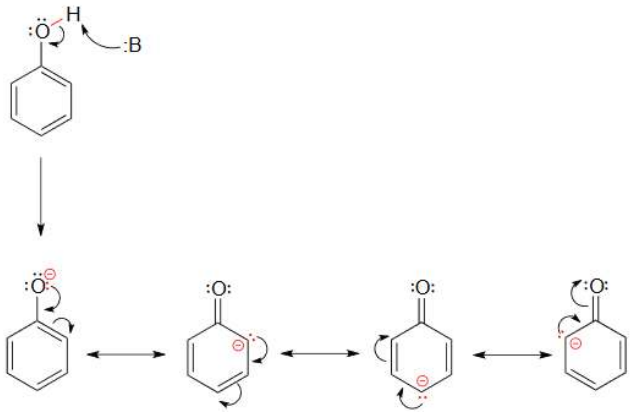
Another method for increasing acidity is through stabilizing a conjugate base through resonance effects. An excellent example of this effect is shown through phenol being roughly a million times more acidic than cyclohexanol.



Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion.

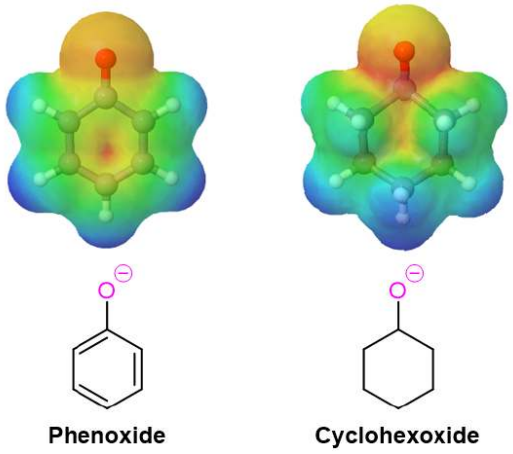


The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion allowing it to be highly stabilized.



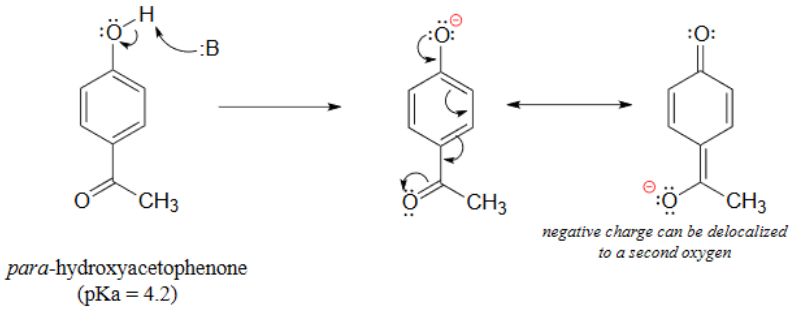
Although these are all minor resonance contributors (negative charge is placed on a carbon rather than the more electronegative oxygen), they nonetheless have a significant effect on the acidity of the phenolic proton. Essentially, the benzene ring is acting as an electron-withdrawing group by resonance.

The electrostatic potential maps below compare the phenoxide ion to an unconjugated alkoxide. The negative charge of the phenoxide ion, show as a yellow/orange color, is delocalized from oxygen into the aromatic ring (seen by the growing red color in the phenoxide ring).



ACIDITY OF SUBSTITUTED PHENOLS

Phenolic acidity is further enhanced by the presence of an additional electron-withdrawing substituent, such as a nitro or carbonyl, on the aromatic ring. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



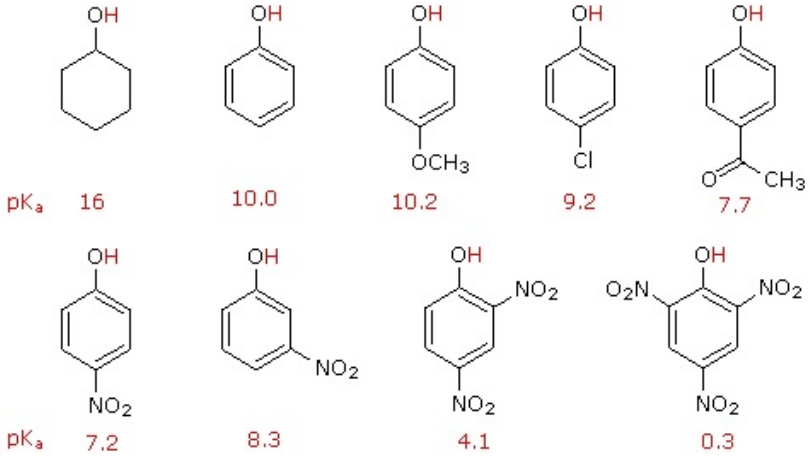
para-hydroxyacetophenone
(pKa = 4.2)

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen

atoms. The ketone group on the aromatic ring is acting as an electron withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

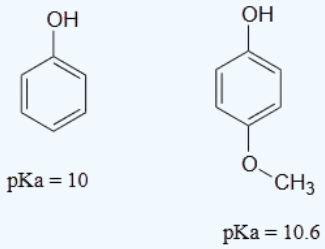
It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron donating group is attached to aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized which causes a decrease in acidity in the corresponding phenol.



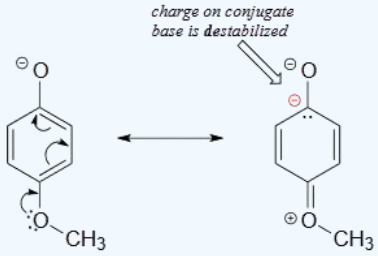
WORKED EXAMPLE 17.2.1

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



Answer

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.

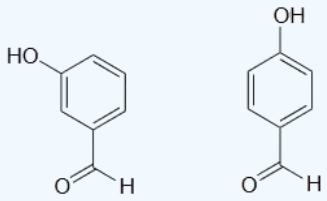


Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

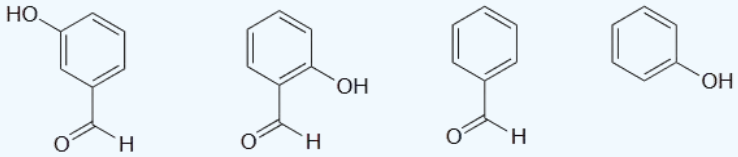
EXERCISE 17.2.1

1.

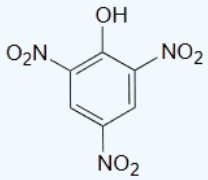
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



2) Rank the four compounds below from most acidic to least.



3) Use a resonance argument to explain why picric acid has such a low pKa.



picric acid
pKa = 0.25

4) Predict which compound of each pair is more soluble in water and explain your reasoning.

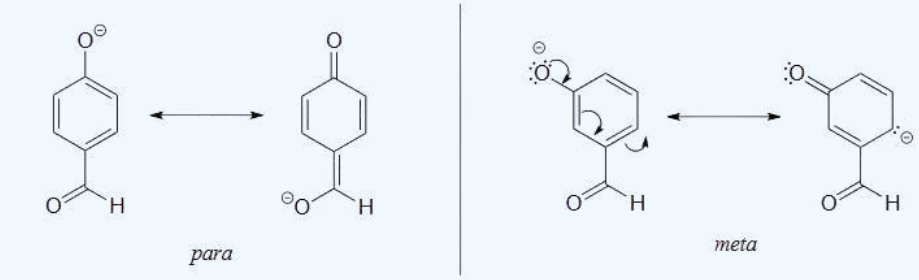
a. Butan-1-ol or pentan-1-ol
b. Phenol or cyclohexanol
c. Octan-1,3-diol or octan-1-ol
d. 1-Chlorohexane or hexan-1-ol

5) Predict which compound has the higher boiling point and explain your reasoning.

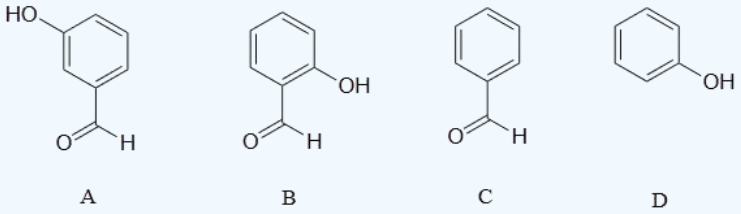
a. Water or ethanol
b. Butan-1-ol or octan-1-ol
c. Hexan-2-ol or hexan-2-one

Answer

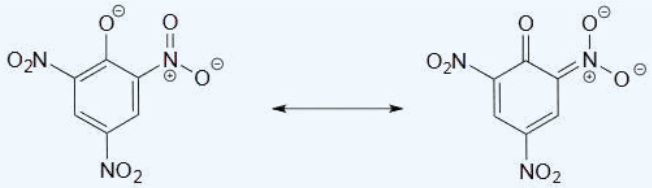
1) The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position



2) Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.



3) The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



4)

a. Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
b. Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
c. Octan-1,3-diol is more soluble in water as it has two hydroxy groups, allowing it to form more hydrogen bonds and interact with water better than octan-1-ol.
d. Hexan-1-ol is more soluble in water as it can hydrogen bond compared to alkyl halides, such as 1-chlorohexane, which are insoluble in water.

5)

a. Water has a higher boiling point compared to ethanol as it participates in more hydrogen bonding with other water molecules, thus requiring more energy to break the intermolecular attractions between water molecules.
b. Octan-1-ol has the higher boiling point compared to butan-1-ol. Both alcohols can H-bond, however the longer hydrophobic carbon chain tail of octan-1-ol experiences more van der Waal interactions compared to the shorter hydrophobic region of butan-1-ol leading to a higher boiling point.
c. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

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17.3: PREPARATION OF ALCOHOLS- A REVIEW

OBJECTIVES

After completing this section, you should be able to describe in detail the methods of preparing alcohols and diols, which you encountered in previous chapters.

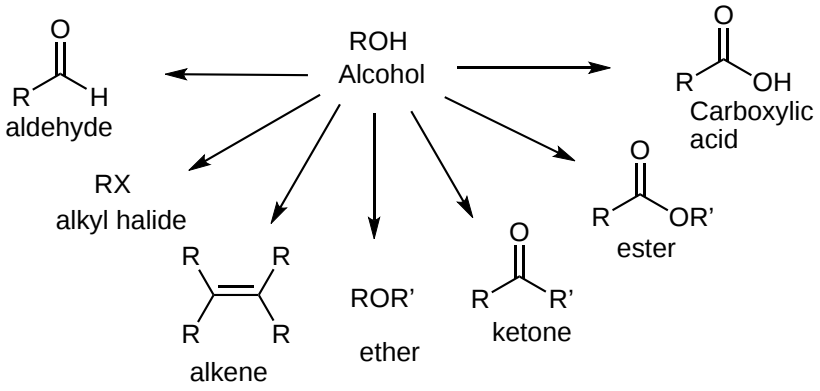
STUDY NOTES

If necessary, you should review Sections 8.4 and 8.5 describing direct hydration of alkenes, and Section 8.7 describing preparation of cis and trans diols from alkenes. Section 8.7 also gives more details on the formation of the respective osmate and epoxide intermediates of these reactions.

INTRODUCTION

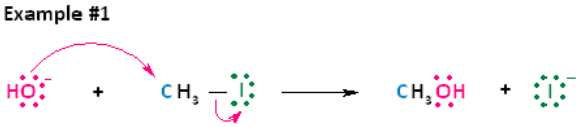
Alcohols are considered on of the more important functional groups in organic chemistry. They can be prepared from compounds containing a wide assortment of functional groups. Also, the can be used to create compounds with a wide variety of functional groups such as: alkenes, ketones, carboxylic acids, and others. Many functional group conversions can be accomplished through the preparation of an alcohol giving them an important central position in organic synthesis. ex. Alkene → Alcohol → Ketone.

Many methods for the preparation of alcohols have been discussed in previous chapter of this textbook and will be review in this section.



ALCOHOLS FROM SUBSTITUTION REACTIONS

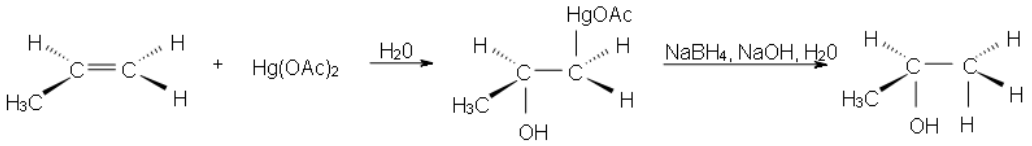
Methyl and primary alkyl halides can be converted to alcohols by using an S_N2 reaction with OH^- as a nucleophile (Section 11.5). Also, secondary and tertiary alkyl halides can be converted to alcohols by an S_N1 reaction using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents (Section 11.7).



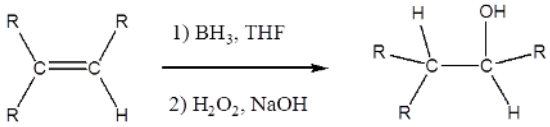
The Synthesis of Methanol Using an S_N2 Reaction

ALCOHOLS FROM ALKENES

Oxymercuration - demercurationis a special electrophilic addition (Section 8.5). It is anti-stereospecific and regioselective. This reaction involves mercury undergoing electrophilic addition to the alkene double bond forming a *Mercurinium Ion Bridge*. A water molecule then attacks the most substituted carbon to open the mercurium ion bridge, followed by proton transfer to form a hydroxyl group (-OH). The organomercury intermediate is then reduced by sodium borohydride. Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's Regioselectivity with the OH group attached to the most substituted carbon and the H is attached to the least substituted carbon. Also, the H and OH species will be anti to each other in the product.

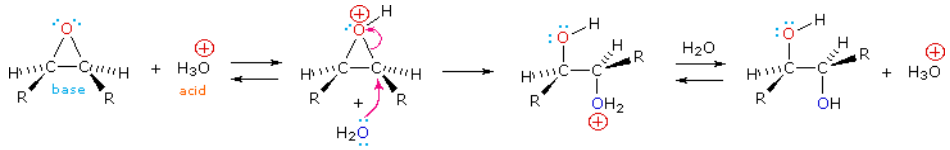


Hydroboration-Oxidation is a two step pathway used to produce alcohols (Section 8.6). It is syn-stereospecific and regioselective. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. The organoborane intermediate is then converted to an alcohol by reaction with hydrogen peroxide (H_2O_2) and sodium hydroxide (NaOH). The hydroboration mechanism has the elements of both hydrogenation and electrophilic addition and it is a stereospecific ***(syn addition)***, meaning that the addition of the H and OH species takes place on the same face of the double bond leading to their ***cis*** configuration in the product. Because the BH_3 can attack either face of the alkene, this reaction can product a racemic mixture of enantiomers in the product.

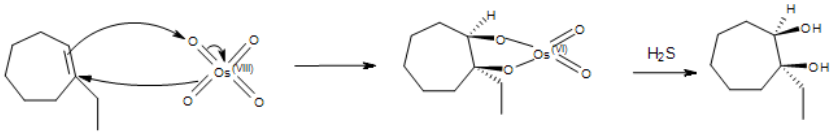


DIOLS FROM ALKENES

Epoxides may be cleaved by aqueous acid to give anti-1,2-diols which are also called glycols. Proton transfer from the acid catalyst generates the conjugate acid of the epoxide, which is attacked by a water nucleophile. Because the nucleophilic attach utilizes an S_N2 mechanism the result is an anti-stereospecific configuration of the diol product. The water nucleophile prefers to attack the more substituted carbon on the epoxide which allows for regioselectivity in the reaction.



Osmium tetroxide oxidizes alkenes to give 1,2-diols through syn addition. The reaction with OsO_4 is a concerted process that creates a cyclic intermediate with no rearrangements. The intermediate osmium compound is reduced to the diol product by reduction with H_2S or $NaHSO_4$ with H_2O.

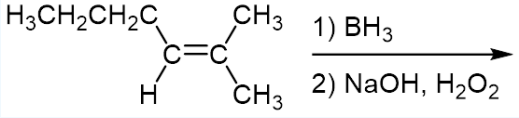


This *syn*-dihydroxylation complements the epoxide-hydrolysis sequence which creates an *anti*-dihydroxylation product. This reaction lack regioselectivity so an alkene reacts with osmium tetroxide there is a possibility of a reaction producing a racemic mixture as the product. In general for this reaction, cis alkenes produce a meso product while trans alkenes produce a racemic mixture as the product.

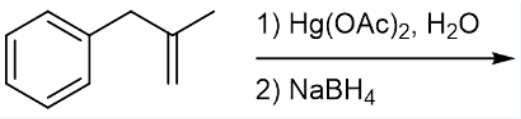
? EXERCISE 17.3.1

1) Predict the products of the following reactions:

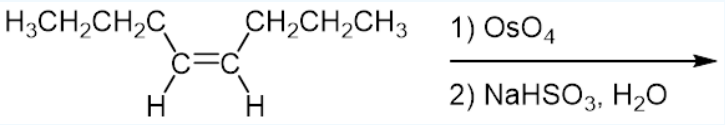
a)



b)



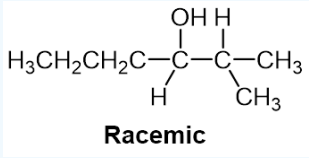
c)



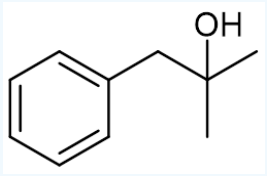
Answer

1)

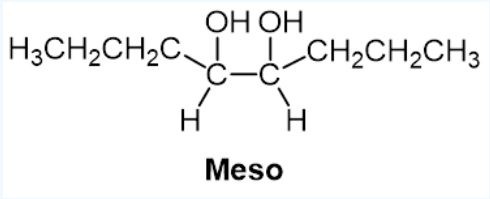
a)



b)



c)



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17.4: ALCOHOLS FROM CARBONYL COMPOUNDS- REDUCTION

OBJECTIVES

After completing this section, you should be able to

1. determine whether a given reaction should be classified as an oxidation or a reduction.
2. write an equation to represent the reduction of an aldehyde or ketone using sodium borohydride or lithium aluminum hydride.
   a. discuss the relative advantages and disadvantages of using sodium borohydride or lithium aluminum hydride to reduce aldehydes or ketones to alcohols.
   b. identify the product formed from the reduction of a given aldehyde or ketone.
   c. identify the aldehyde or ketone that should be used to produce a given alcohol in a reduction reaction.
   d. identify the best reagent to carry out the reduction of a given aldehyde or ketone.
3. write an equation to represent the reduction of an ester or a carboxylic acid to an alcohol.
   a. identify the product formed from the reduction of a given ester or carboxylic acid.
   b. identify the esters or carboxylic acids that could be reduced to form a given alcohol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- (organic) oxidation
- (organic) reduction

STUDY NOTES

In your course in first-year general chemistry, you probably discussed oxidation-reduction reactions in terms of the transfer of electrons and changes in oxidation numbers (oxidation states). In organic chemistry, it is often more convenient to regard reduction as the gain of hydrogen or loss of oxygen, and oxidation as the gain of oxygen or the loss of hydrogen. There is no contradiction in using these various definitions. For example, when hydrogen is added across the double bond of ethene to reduce it to ethane, the oxidation number of the doubly bonded carbon atoms decreases from −II to −III. Similarly, when 2-propanol



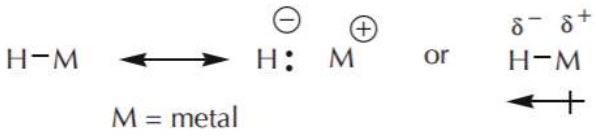
is oxidized to acetone



hydrogen is removed from the compound and the oxidation number of the central carbon atom increases from 0 to +II. If necessary, review the concept of oxidation number.

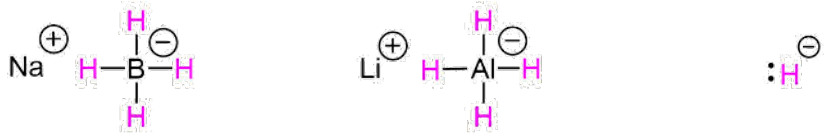
REDUCTION OF ALDEHYDES AND KETONES

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion (⁻:H).** How much of the negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.



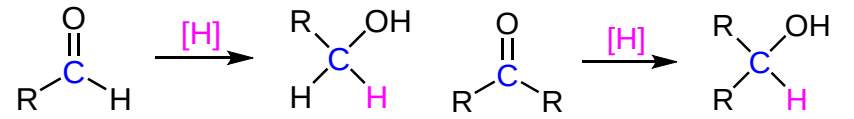
The most common sources of the hydride nucleophile are lithium aluminum hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$). Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-

hydrogen bond. Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.



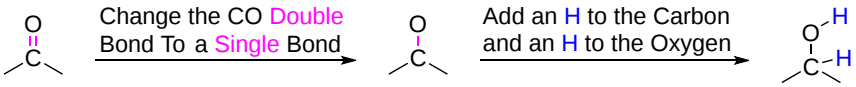
Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 1º-alcohols and ketones produce 2º-alcohols. These reactions will be discussed in more detail in **Chapter 19**.



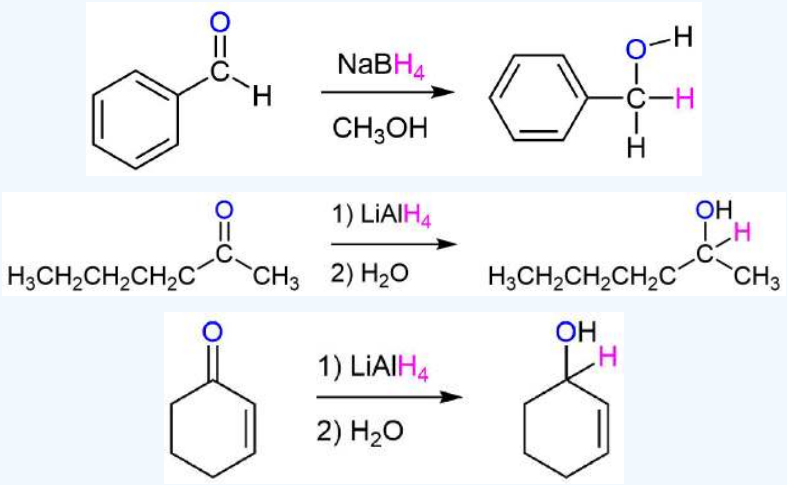
Aldehyde **1º Alcohol** **Ketone** **2º Alcohol**

PREDICTING THE PRODUCT OF A HYDRIDE ADDITION TO A CARBONYL



During the reduction the C=O double bond in the reactant and forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which originally in the carbonyl. Both of these single bonds will be attached to an "H" in the product formed.

EXAMPLE 17.4.1

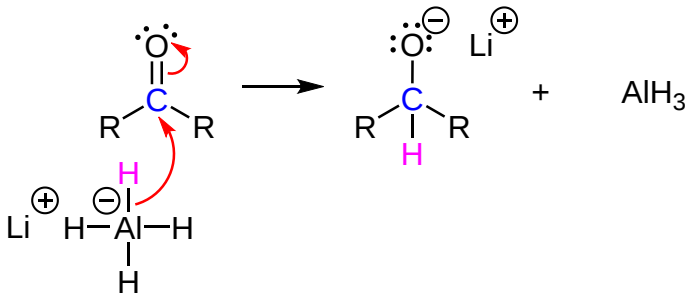


MECHANISM

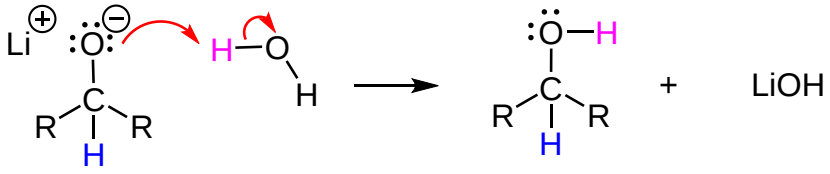
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of the hydride anion nucleophile. They hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source. In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding..

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate



2) Protonation to form an alcohol

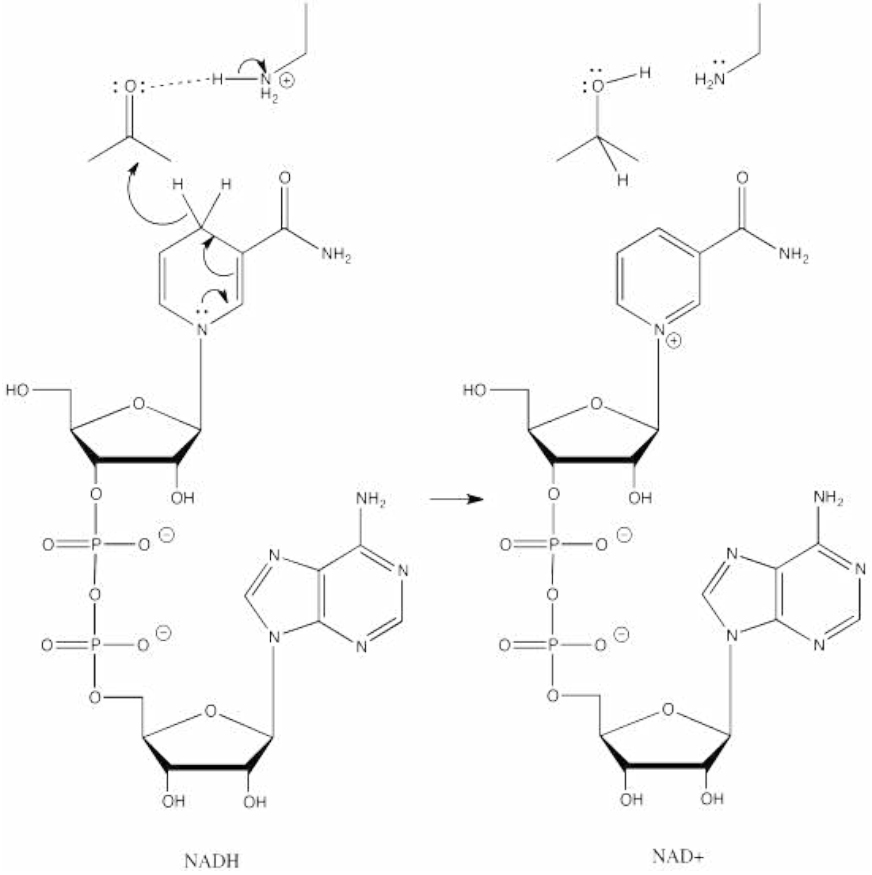


In metal hydride reductions the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

BIOLOGICAL REDUCTION

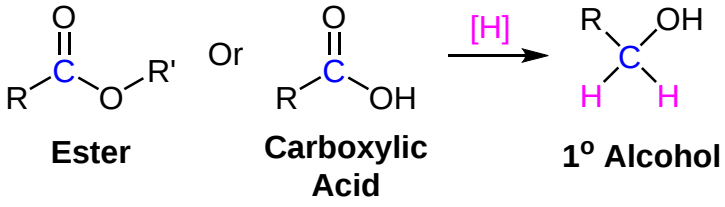
Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; it was not aromatic in NADH.

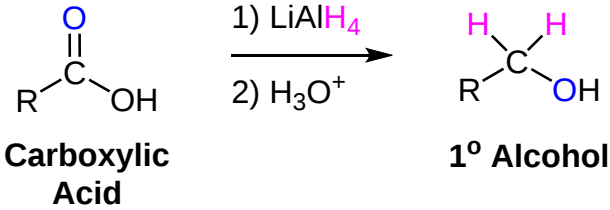


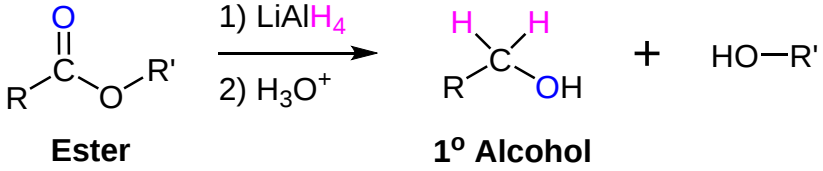
REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids and esters can be converted to 1º alcohols using Lithium aluminum hydride ($LiAlH_4$).



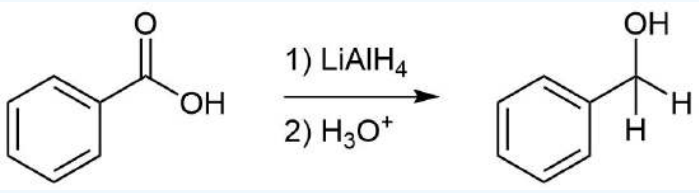
Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. Notice that during these reaction two hydrogen atoms are added the to carbonyl carbon whereas only one hydrogen atom was added during aldehyde and ketone reductions. These reactions will be discussed in more detail in **Chapter 21**.

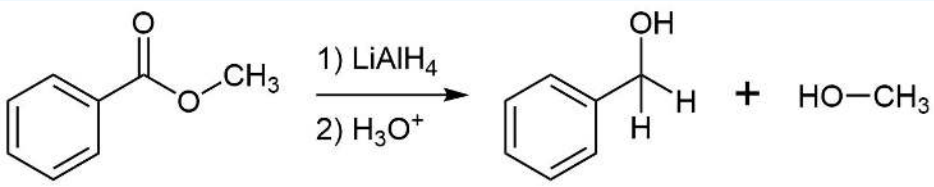




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EXAMPLE 17.4.2

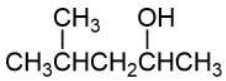




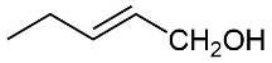
WORKED EXAMPLE

How would you prepare the following molecules using a hydride reduction?

a)



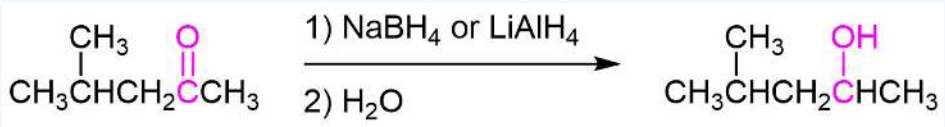
b)



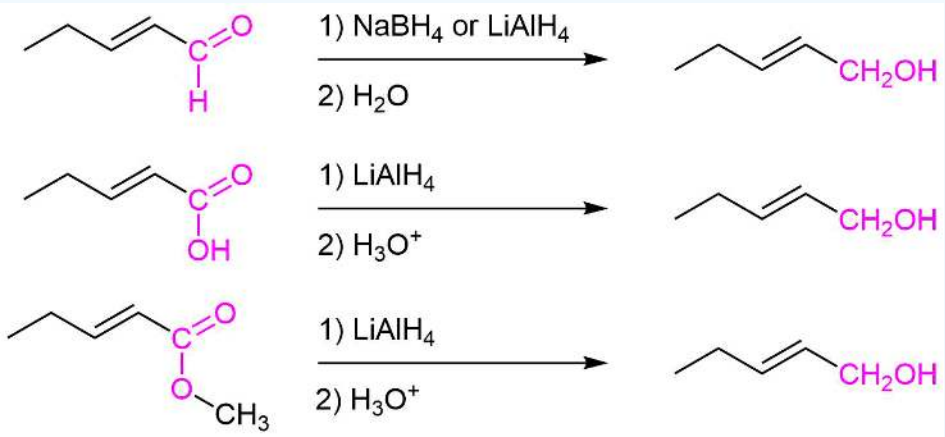
Answer

Analysis: The first step is to note if the target molecule is a 1° or 2° alcohol. Primary alcohols can be made by the hydride reduction of an aldehyde, carboxylic acid, or ester while secondary alcohols are made by the reduction of ketones. A 3° alcohol cannot be made by a hydride reduction. Also, it is important to remember than aldehydes and ketones can be reduced by both $NaBH^4$ and $LiAlH_4$ whereas carboxylic acids and ester can only be reduced by $LiAlH_4$.

a) Because the target molecule is a secondary alcohol the starting material must be a ketone.



b) Because the target molecule is a primary alcohol the starting material could be an aldehyde, a carboxylic acid, or an ester.

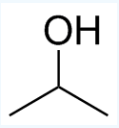


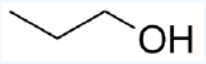
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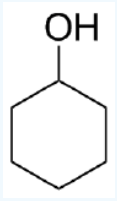
EXERCISES

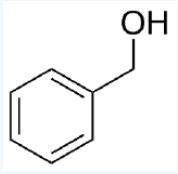
EXERCISE 17.4.1

1) Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

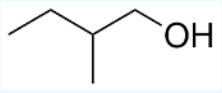
a) 

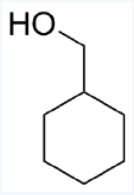
b) 

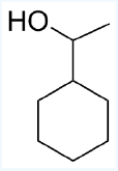
c) 

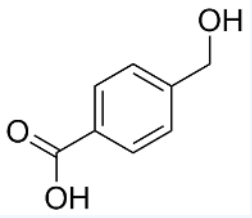
d) 

2) Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

a) 

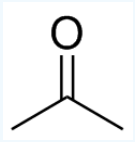
b) 

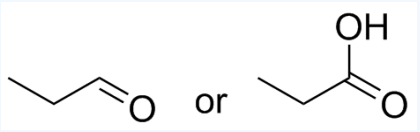
c) 

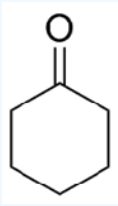
d) 

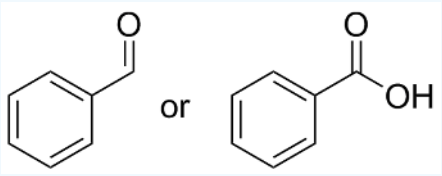
Answer

1)

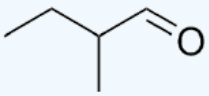
a) 

b) 

c) 

d) 

2) Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.

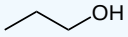
a) 

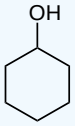
b)

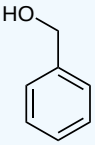
EXERCISE 17.4.2

Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

A) 

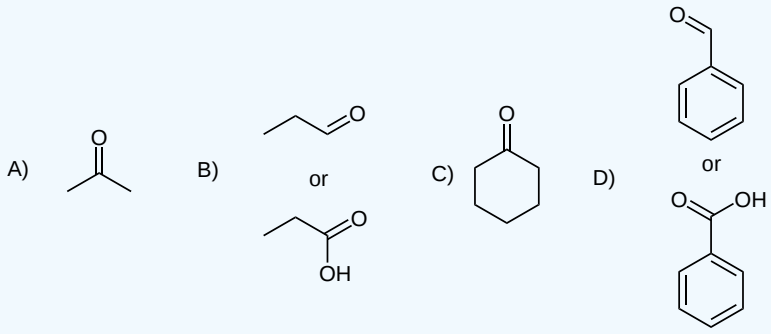
B) 

C) 

D) 

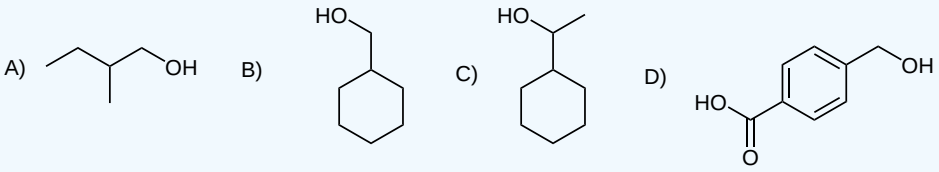
Answer

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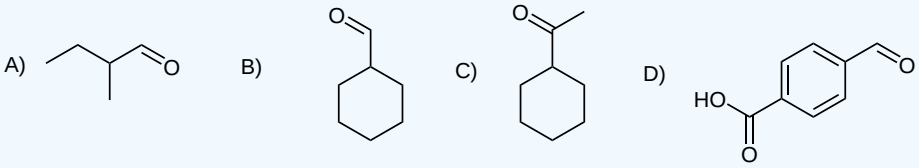
EXERCISE 17.4.3

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$.



Answer

Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



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17.5: ALCOHOLS FROM CARBONYL COMPOUNDS - GRIGNARD REAGENTS

OBJECTIVES

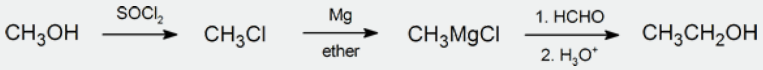
After completing this section, you should be able to

1. write an equation to illustrate the formation of a Grignard reagent.
2. write a general equation to represent the reaction of an aldehyde or ketone with a Grignard reagent.
3. write the detailed mechanism for the reaction of an aldehyde or ketone with a Grignard reagent.
4. identify the product formed from the reaction of a given aldehyde or ketone with a given Grignard reagent.
5. identify the carbonyl compound, the Grignard reagent, or both, needed to prepare a given alcohol.
6. write the equation to describe the reaction of an ester with a Grignard reagent.
7. identify the product formed from the reaction of a given ester with a given Grignard reagent.
8. discuss the limitations of Grignard reagent formation, and determine whether a given compound can be used to form such a reagent.

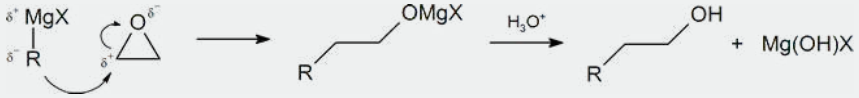
STUDY NOTES

Before you begin this section, you may wish to review Section 10.8 which discusses the formation of Grignard reagents. Link to section 10.8

Grignard reagents are among the most frequently used reagents in organic synthesis. They react with a wide variety of substrates; however, in this section, we are concerned only with those reactions that produce alcohols. Notice that in a reaction involving a Grignard reagent, not only does the functional group get changed, but the number of carbon atoms present also changes. This fact provides us with a useful method for ascending a homologous series. For example:



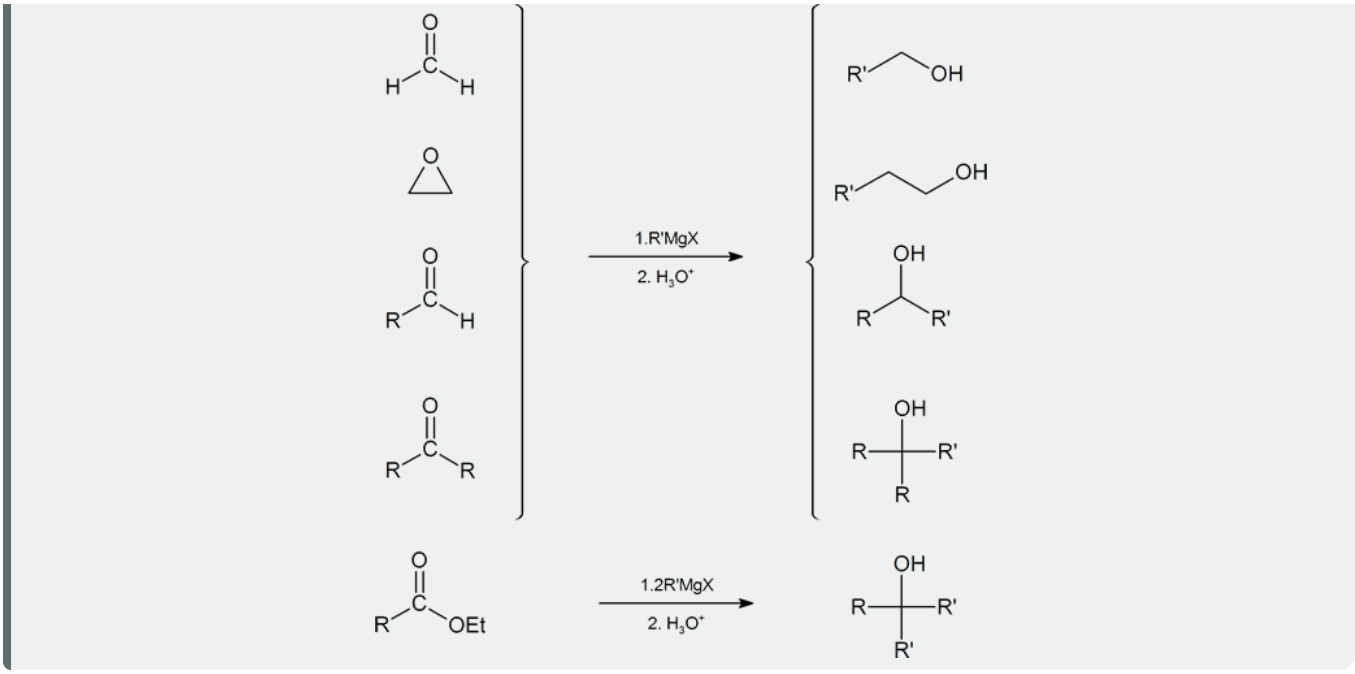
One important route for producing an alcohol from a Grignard reagent has been omitted from the discussion in the reading. It involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.



As mentioned in the reading, both organolithium and Grignard reagents are good nucleophiles. They also act as strong bases in the presence of acidic protons such as $-CO_2H$, $-OH$, $-SH$, $-NH$ and terminal alkyne groups. Not only do acidic protons interfere with the nucleophilic attack on the carbonyl of these organometallic reagents, if the starting materials possess any acidic protons, reagents cannot be generated in the first place. They are also the reason these reactions must be carried out in a water-free environment.

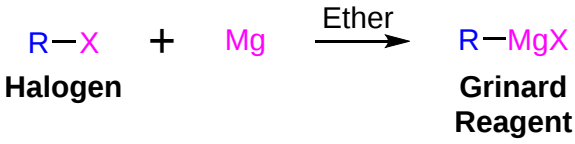
Another limitation of preparing Grignard and organolithium reagents is that they cannot already contain a carbonyl group (or other electrophilic multiple bonds like C=N, nitriles, N=O, S=O) because it would simply react with itself.

A summary of the methods used to prepare alcohols from Grignard reagents is provided below.



FORMATION OF GRIGNARD REAGENTS

Grignard reagents (RMgX) can be prepared through the reaction of halogens with magnesium metal (Section 10-6). Grignard reagents are a source of carbanion nucleophiles (R:$^{-}$ $^{+}$MgX) which add to carbonyl compounds to yield alcohols. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent. This complex helps stabilize the organometallic and increases its ability to react.



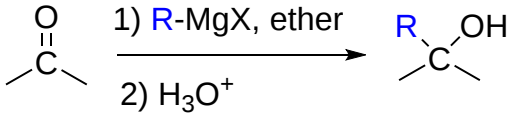
R = 1°, 2°, or 3° alkyl, aryl, or vinylic groups

X = Cl, Br, or I

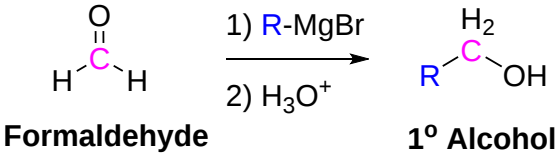
REACTION OF GRIGNARD REAGENTS WITH CARBONYLS

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes, ketones, and other carbonyl containing compounds will undergo nucleophilic addition with Grignard reagents. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation by an acid. The type of alcohol produced depends on the number of alkyl substituents attached to the electrophilic carbonyl carbon. Reacting a Grignard reagent with formaldehyde ($H_2C=O$) produces 1° alcohols, aldehydes produce 2° alcohols, and ketones produce 3° alcohols. These reactions will be discussed in greater detail in **Section 19.7**.

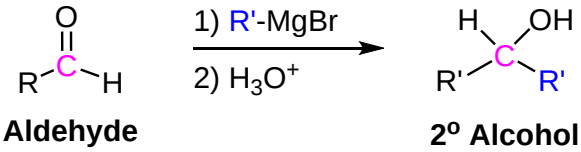
GENERAL REACTION



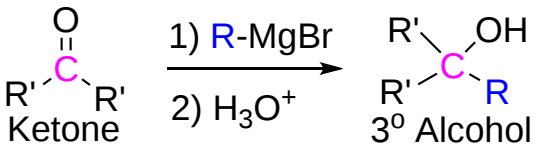
ADDITION TO FORMALDEHYDE GIVES 1^{O} ALCOHOLS



ADDITION TO ALDEHYDES GIVES 2^{O} ALCOHOLS

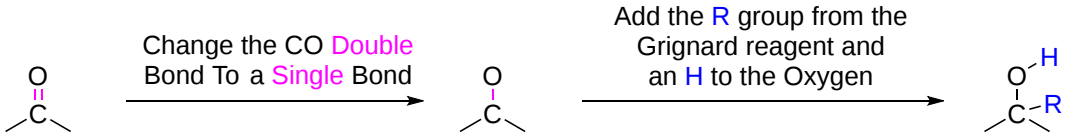


ADDITION TO KETONES GIVES 3° ALCOHOLS

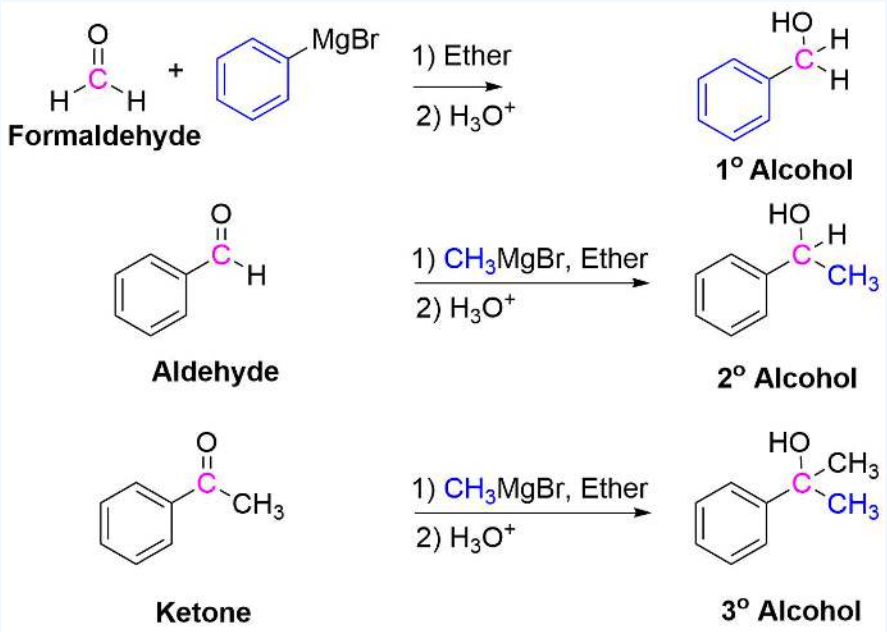


PREDICTING THE PRODUCT OF THE ADDITION OF GRIGNARD REAGENT TO CARBONYL

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was contained in the Grignard reagent and the oxygen will gain a hydrogen.



EXAMPLE 17.5.1

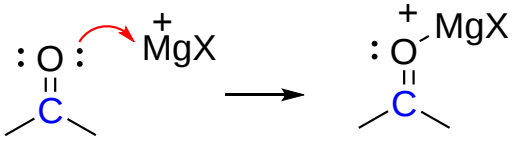


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MECHANISM FOR THE ADDITION OF GRIGNARD REAGENTS TO CARBONYLS

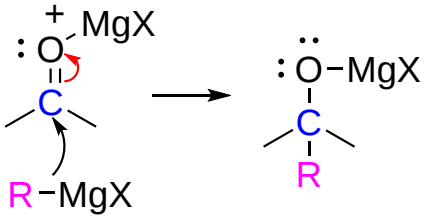
The mechanism starts with the formation of a acid-base complex between $^{+}$MgX and the carbonyl oxygen. The $^{+}$MgBr of the Grignard reagent acts as a Lewis acid and accepts a set of lone pair electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing its susceptibility to nucleophilic attack.

Step 1: Lewis acid-base formation



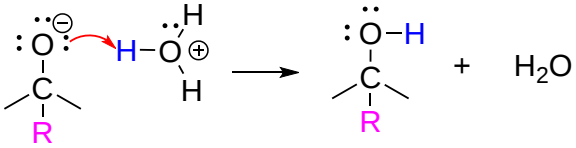
Step 2: Nucleophilic attack

The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral Magnesium alkoxide intermediate.



Step 3: Protonation

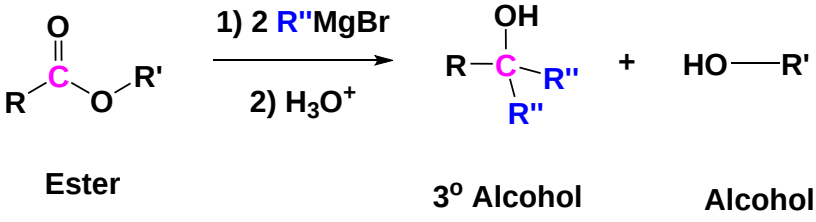
The alkoxide intermediate is converted to an alcohol through addition of a acidic aqueous solution. The $^{+}$MgX ion is also converted to HOMgX.'



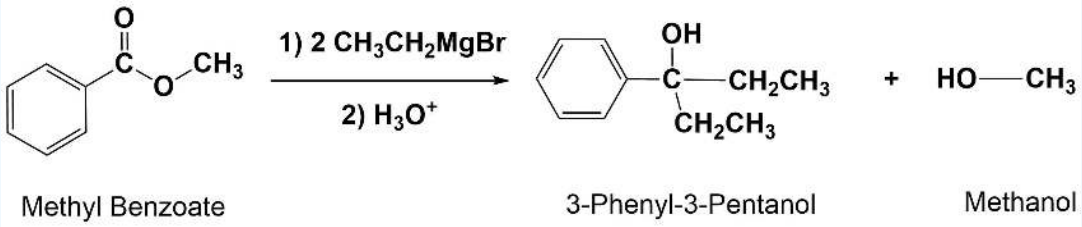
GRIGNARD REAGENTS CONVERT ESTERS TO 3° ALCOHOLS

With esters, after the first Grignard reaction, the carbonyl reforms creating a ketone which can then react with a second molecule of the Grignard. In effect, the Grignard reagent adds twice. This reaction will be discussed in greater detail in **Section 21.6**.

GENERAL REACTION

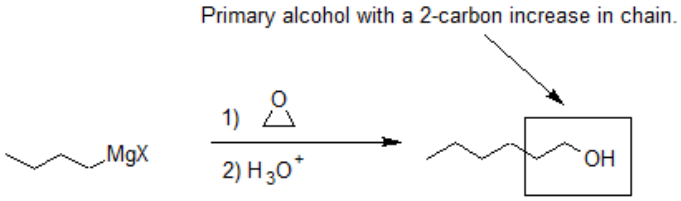


EXAMPLE 17.5.2

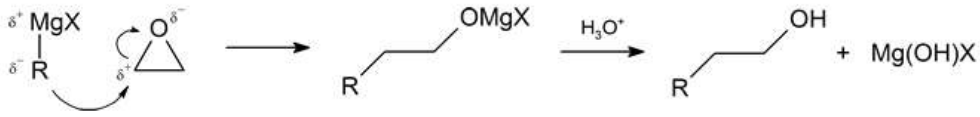


GRIGNARD REAGENTS CONVERT EPOXIDES TO 1O ALCOHOLS

Another important route for producing an alcohol from a Grignard reagent involves the reaction of the Grignard reagent with ethylene oxide to produce a primary alcohol containing two more carbon atoms than the original Grignard reagent. This reaction will be discussed in greater detail in **Section 18.6**.

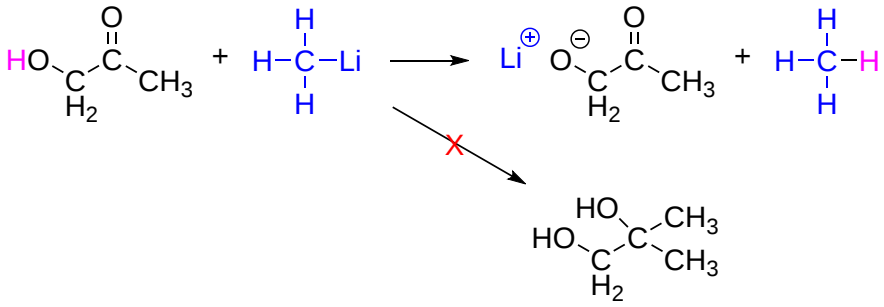


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section.



LIMITATION OF ORGANOMETALLIC REAGENTS

Grignard and organolithium reagents are powerful bases. Because of this they cannot be prepared using halogen compounds which contain an additional functional group that has acidic hydrogens. If there are acidic hydrogens present, the organometallic reagent will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used are: alcohols (ROH), carboxylic acids (RCO_2H), thiols (RSH), and terminal alkynes (RCCH). Additionally, amides ($RCONH_2$) and amines (RNH_2) that have NH bonds cannot be used with organometallic reagents.

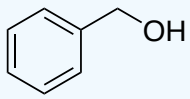


PLANNING AN ALCOHOL SYNTHESIS USING A GRIGNARD REACTION

The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

? WORKED EXAMPLE 17.5.1

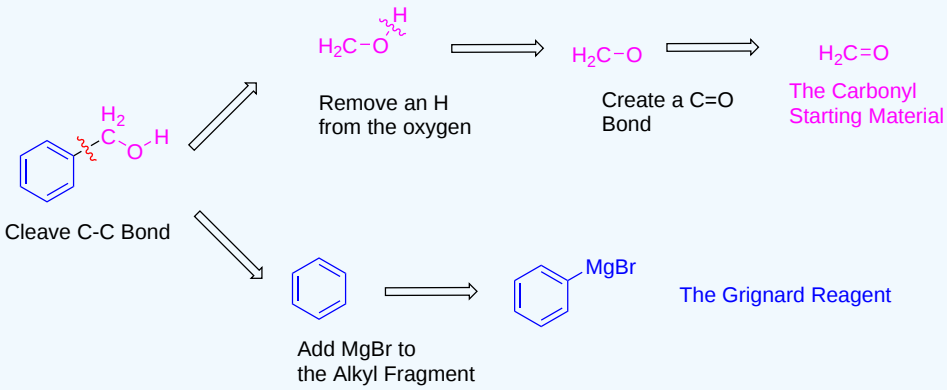
What reagents are required to make the following molecule using a Grignard Reaction?



Answer

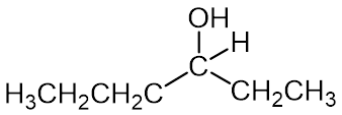
Analysis: Because the target molecule is a 1o alcohol there is only one C-C bond which can be cleaved to generate possible starting materials. The only possible reagents which would provide the target molecule would be formaldehyde and phenylmagnesium bromide.

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WORKED EXAMPLE 17.5.2

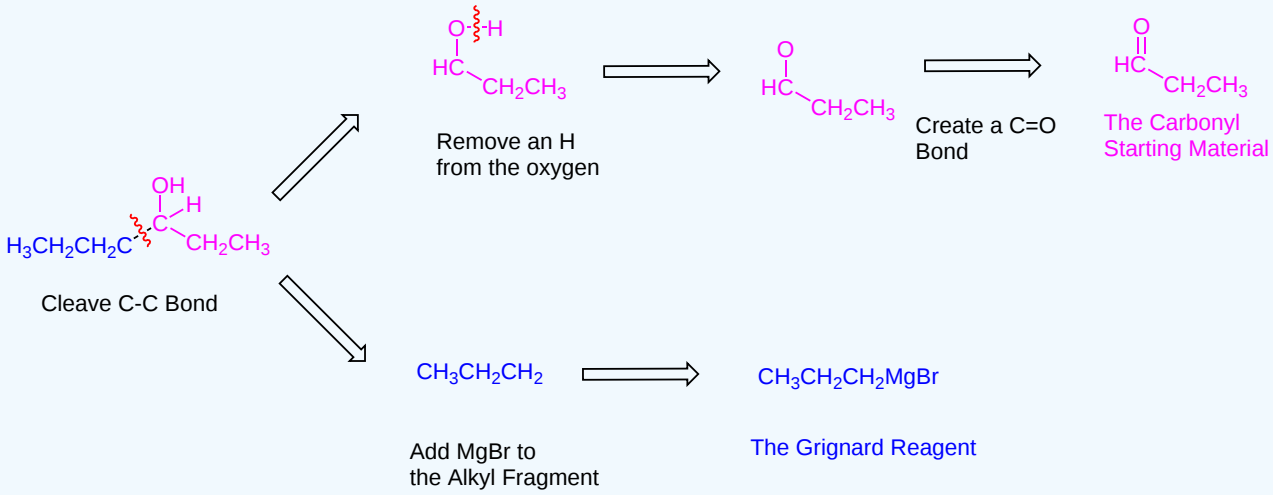
What reagents are required to make the following molecule using a Grignard Reaction?



Answer

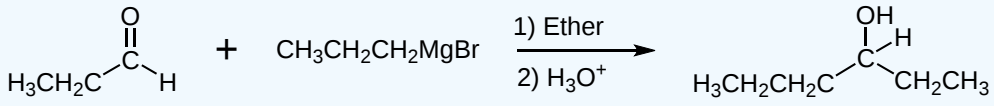
Analysis: Because the target molecule is an asymmetrical 2º alcohol there are two different C-C bond cleavage points. Each of these will provide a unique set of reagents which should be considered in terms of their reactivity and availability.

Pathway 1)



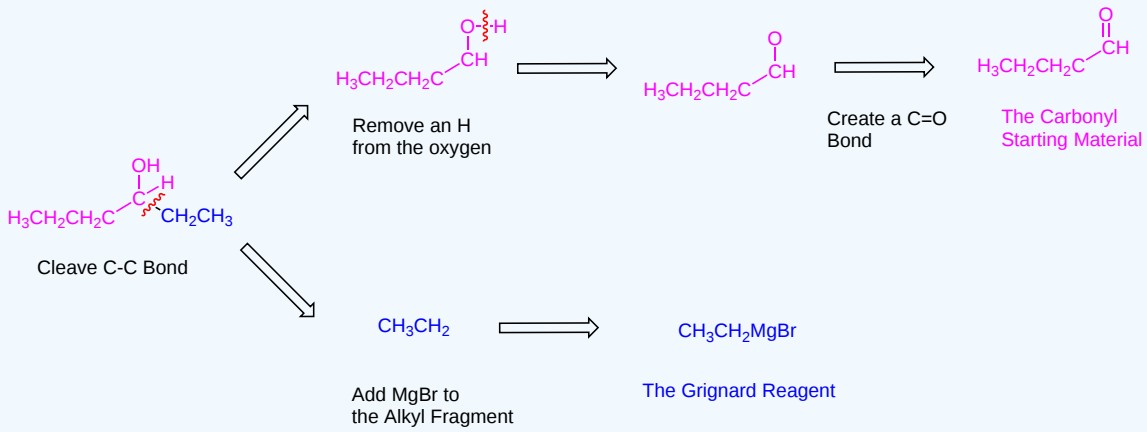
Pathway 1 synthesis)

Pathway 1 shows that propanal and propylmagnesium bromide can be reacted to create the target molecule.



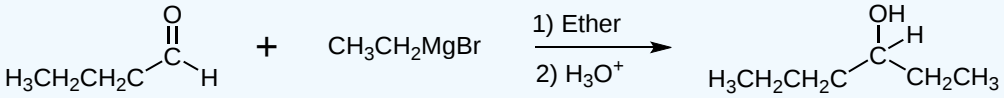
Pathway 2)

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Pathway 2 synthesis)

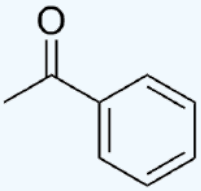
Pathway 2 shows that butanal and ethylmagnesium bromide can be reacted to create the target molecule.



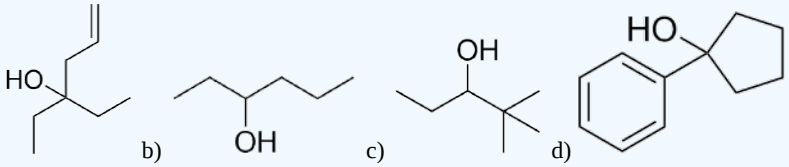
EXERCISES

EXERCISE 17.5.1

1) If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.



2) What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

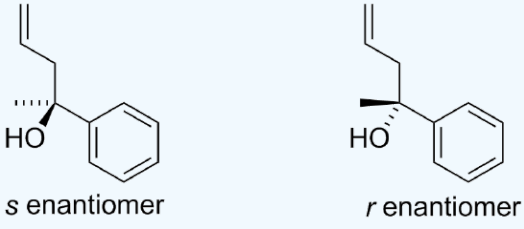


3) If the following compounds were reacted with methylmagnesium bromide what would be the products?

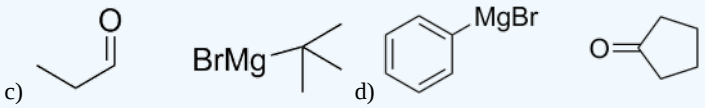
a) Cyclohexanone b) Acetophenone c) 2-Hexanone

Answer

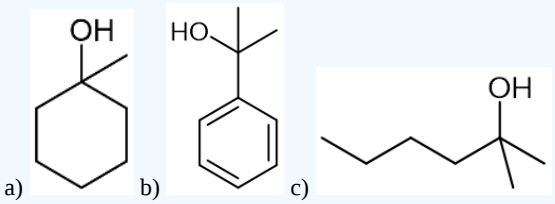
1) The result would be a racemic mixture of the following.



2)

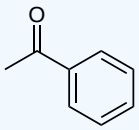


3)



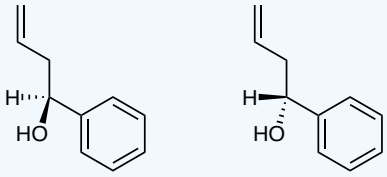
EXERCISE 17.5.2

If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.



Answer

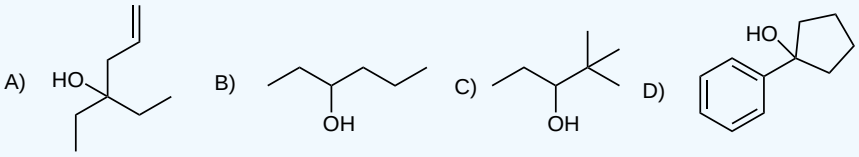
The result would be a racemic mixture of the following.



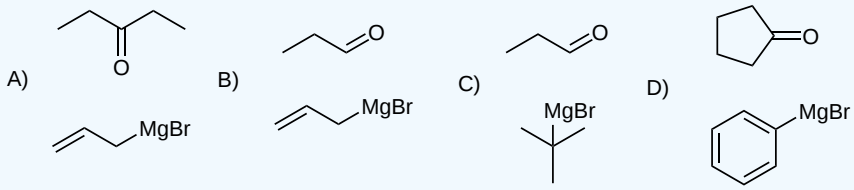
(*S*)-enantiomer (*R*)-enantiomer

EXERCISE 17.5.3

What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?



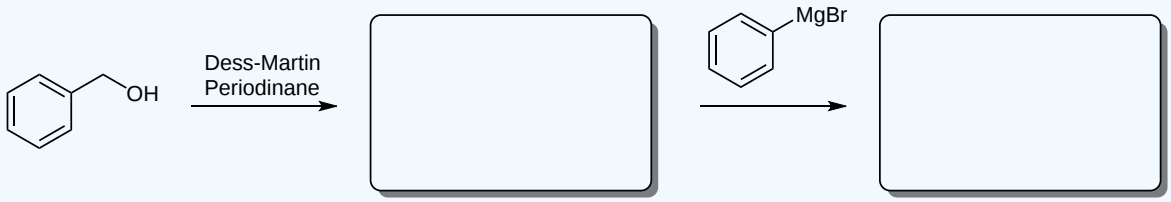
Answer



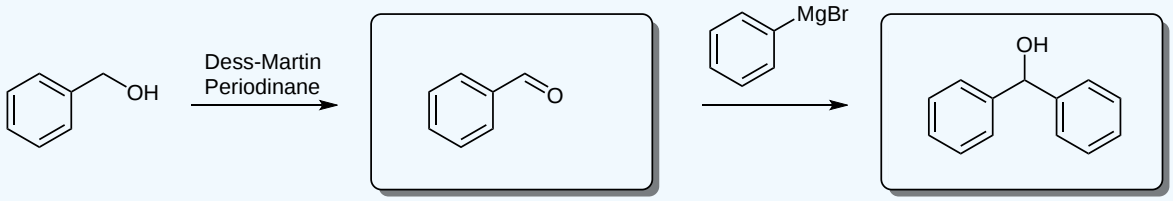
EXERCISE 17.5.4

Fill in the blanks of the following reaction scheme.

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Answer



This page titled 17.5: Alcohols from Carbonyl Compounds - Grignard Reagents is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, James Kabrhel, & James Kabrhel.

17.6: REACTIONS OF ALCOHOLS

OBJECTIVES

After completing this section, you should be able to

1. discuss the reactions of alcohols that have been introduced in previous units. These reactions include
   a. conversion of alcohols into alkyl halides.
   b. conversion of alcohols into tosylates.
   c. dehydration of alcohols to yield alkenes.
   d. conversion of alcohols into esters.

STUDY NOTES

As you read through Section 17.6 you should be prepared to turn back to those earlier sections in which some of the reactions of alcohols were discussed:

- dehydration to alkenes—Section 8.1.
- conversion to alkyl halides—Section 10.5.

You may also wish to review the discussion of acidity constants, which can be found in Section 2.8.

Remember that when an alcohol reacts with tosyl chloride to form a tosylate, it is the O-H bond of the alcohol that is broken, not the C-O bond. This means that the absolute configuration of the carbon atom attached to the hydroxyl group remains unchanged throughout the reaction. The reading illustrates how this fact can be exploited to control the stereochemistry in an organic synthesis.

Finally, the reading shows the production of an ester from an alcohol and and an acid chloride. In Section 21.3 we will discuss the Fischer esterification, a famous reaction that uses an alcohol and a carboxylic acid to form the ester.

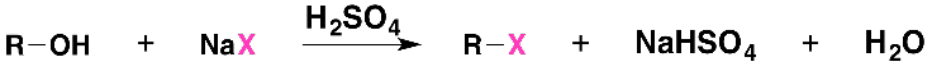
CONVERSION OF ALCOHOLS INTO ALKYL HALIDES

When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:



- The order of reactivity of alcohols is 3° > 2° > 1° methyl.
- The order of reactivity of the hydrogen halides is HI > HBr > HCl (HF is generally unreactive).

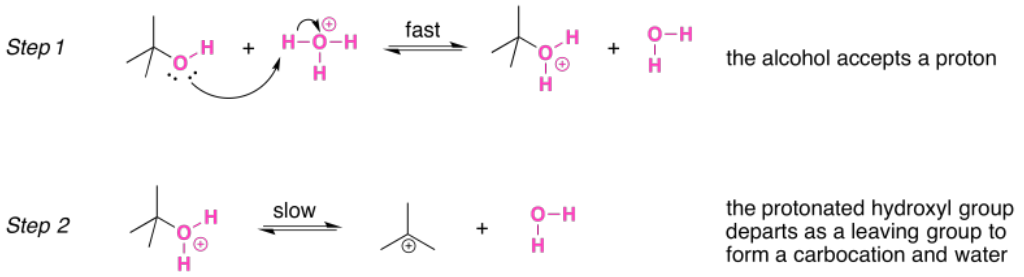
The reaction is acid catalyzed. Alcohols react with the strongly acidic hydrogen halides HCl, HBr, and HI, but they do not react with nonacidic NaCl, NaBr, or NaI. Primary and secondary alcohols can be converted to alkyl chlorides and bromides by allowing them to react with a mixture of a sodium halide and sulfuric acid:



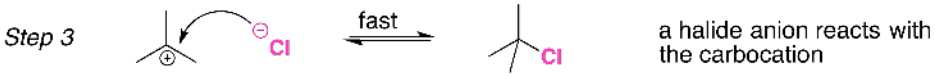
MECHANISMS OF THE REACTIONS OF ALCOHOLS WITH HX

Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as a leaving group.

The S_N1 mechanism is illustrated by the reaction of tert-butyl alcohol and aqueous hydrochloric acid (H_3O^+, Cl^-). The first two steps in this S_N1 substitution mechanism are protonation of the alcohol to form an oxonium ion. Although the oxonium ion is formed by protonation of the alcohol, it can also be viewed as a Lewis acid-base complex between the cation R^+ and H_2O. Protonation of the alcohol converts a poor leaving group (OH-) to a good leaving group H_2O, which makes the dissociation step of the S_N1 mechanism more favorable.

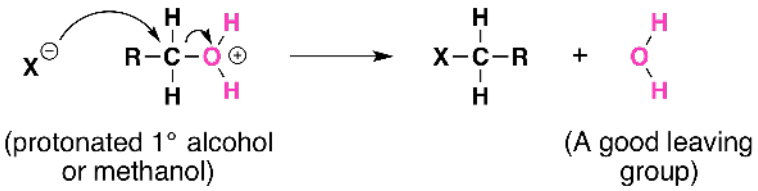


In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.

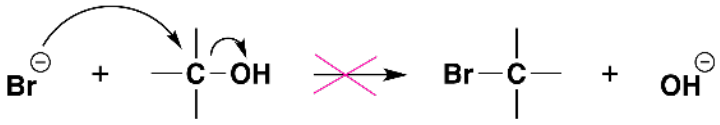


When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, most of the carbocations react with an electron pair of a halide ion to form a more stable species, the alkyl halide product. The overall result is an S_N1 reaction.

Not all acid-catalyzed conversions of alcohols to alkyl halides proceed through the formation of carbocations. Primary alcohols and methanol react to form alkyl halides under acidic conditions by an S_N2 mechanism. In these reactions the function of the acid is to produce a *protonated alcohol*. The halide ion then displaces a molecule of water (a good leaving group) from carbon; this produces an alkyl halide:



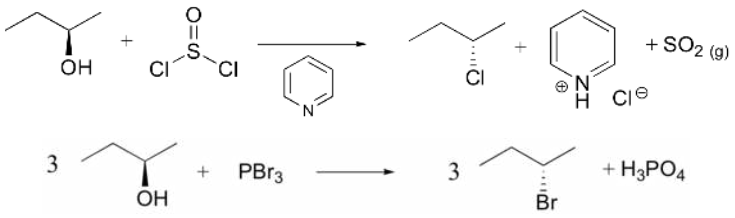
Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



CONVERSION OF ALCOHOLS INTO ALKYL HALIDES USING $SOCL_2$ OR PBR_3

The most common methods for converting 1º- and 2º-alcohols to the corresponding chloro and bromo alkanes (*i.e.* replacement of the hydroxyl group) are treatments with thionyl chloride and phosphorus tribromide, respectively. These reagents are generally preferred over the use of concentrated HX due to the harsh acidity of these hydrohalic acids and the carbocation rearrangements associated with their use.

Synthetic organic chemists, when they want to convert an alcohol into a better leaving group, have several methods to choose from. One common strategy is to convert the alcohol into an alkyl chloride or bromide, using thionyl chloride or phosphorus tribromide:



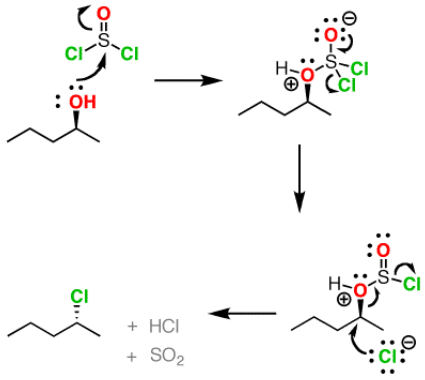
MECHANISMS

Both of these reagents form an alkyl halide through an S_N2 mechanism. The mechanism for both reactions start by making the alcohol's -OH a better leaving group through conversion to an intermediate. Thionyl chloride creates an intermediate chlorosulfite ($-OSOCl_2$) compound and phosphorus tribromide makes an intermediate dibromophosphite ($-OPBr_2$) compound. These intermediate compounds can

subsequently be eliminated as a leaving group during an S_N2 reaction with the corresponding nucleophilic halide ion. Since these reactions proceeds through a backside attack, there is inversion of configuration at the carbon.

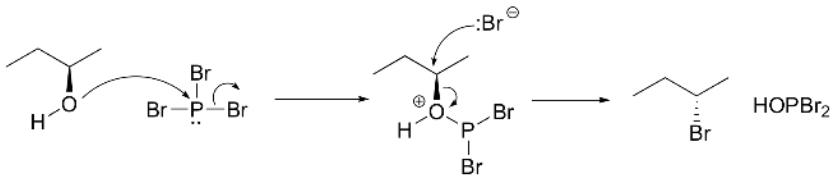
THIONYL CHLORIDE

Notice that during the reaction with thonyl chloride hydrochloric acid (HCl) and sulfurdioxide (SO_2) are produced as byproducts.



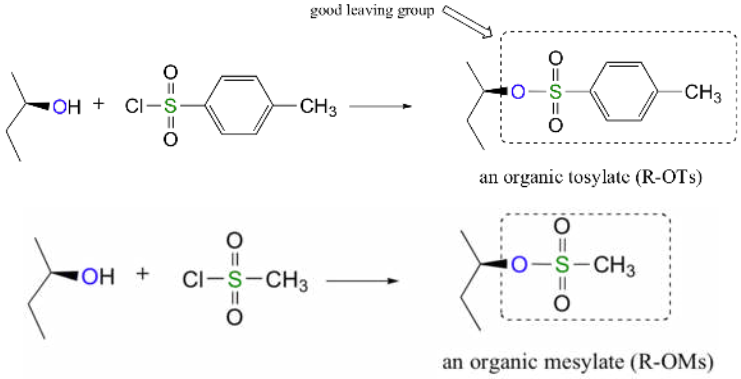
PHOSPHORUSTRIBROMIDE

During this reaction $HOPBr_2$ is made as biproducts.



CONVERSION OF ALCOHOLS INTO TOSYLATES

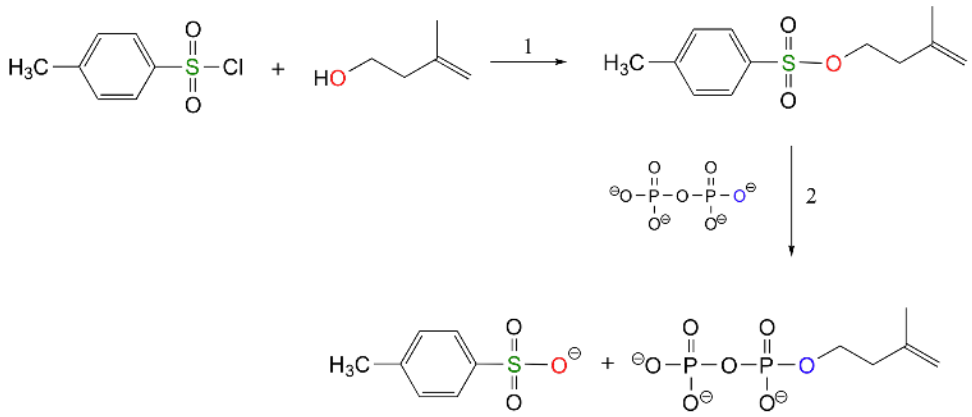
Alternatively, we can transform an alcohol group into sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate.** Notice that unlike the halogenation reactions above, the C-O bond of the alcohol is not broken during the conversion to a tosylate or mesylate so the reaction proceeds with retention of configuration at the electrophilic carbon.



Tosylate and mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen. They behave much line alkyl halides and can undergo S_N2 and S_N1 reaction depending on the conditions.



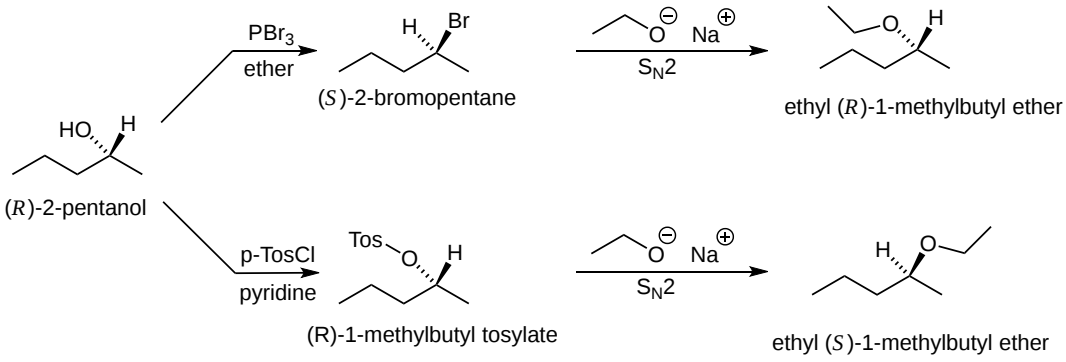
The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



USING SULFONATE ESTERS FOR STEREOCHEMICAL CONTROL

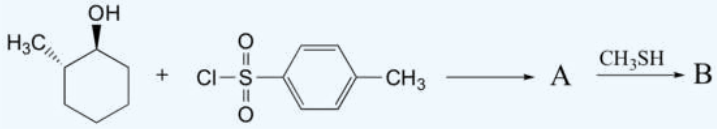
Tosylate and mesylate group's retention of conversion during formation makes them an important source of stereochemical control in organic synthesis. In the conversion of an alcohol to a halide for a subsequent S_N2 substitution there are two inversions of configuration. One during the conversion of the alcohol to a halide and the second during the S_N2 substitution reaction. Overall, these reaction steps produce a product with the same stereochemistry as the alcohol starting material.

When a tosylate or a mesylate are used for a similar conversion there is only one inversion of configuration. During the conversion of an alcohol to a tosylate the configuration of the alcohol strarting material is retained. This means that the tosylate will have the same stereochemical configuration as the alcohol starting material. The subsequent S_N2 reaction with the tosylate causes an inversion of configuration which provides a product of opposite stereochemistry as the alcohol starting material. The figure below outlines the relative stereochemistry of a series of reactions which summarize these points.

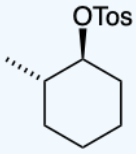


EXAMPLE 17.6.2

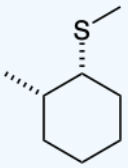
Predict the structures of A and B in the following reaction:



A. The tosylate is formed with retained stereochemistry.

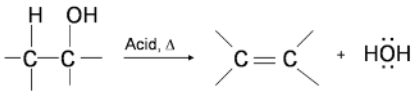


B. The thioether is formed with inverted stereochemistry.



DEHYDRATION OF ALCOHOLS TO YIELD ALKENES

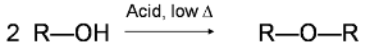
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 1° alcohols: 170° - 180°C
- 2° alcohols: 100°– 140 °C
- 3° alcohols: 25°– 80°C

If the reaction is not sufficiently heated, the alcohols do not dehydrate to form alkenes, but react with one another to form ethers (e.g., the Williamson Ether Synthesis).

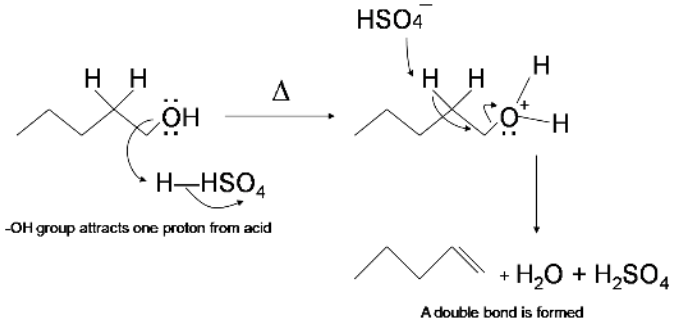


MECHANISM FOR THE DEHYDRATION OF ALCOHOL INTO ALKENE

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reaction is ranked as the following

Methanol < primary < secondary < tertiary

Primary alcohol dehydrates through the E2 mechanism. First, the hydoxyl oxygen becomes protonated by reagent acid (sulfuric acid H_2SO_4), forming an alkyloxonium ion leaving group. Next, in a concerted process, then the conjugate base of the reagent acid (HSO_4^-) removes an adjacent hydrogen, the alkyloxonium ion is removed as a leaving group, and alkene double bond is formed. Remember that this reaction follows Zaitsev's rule which states that the most stable alkene will be the major product. In this reaction there is only one possible alkene product.

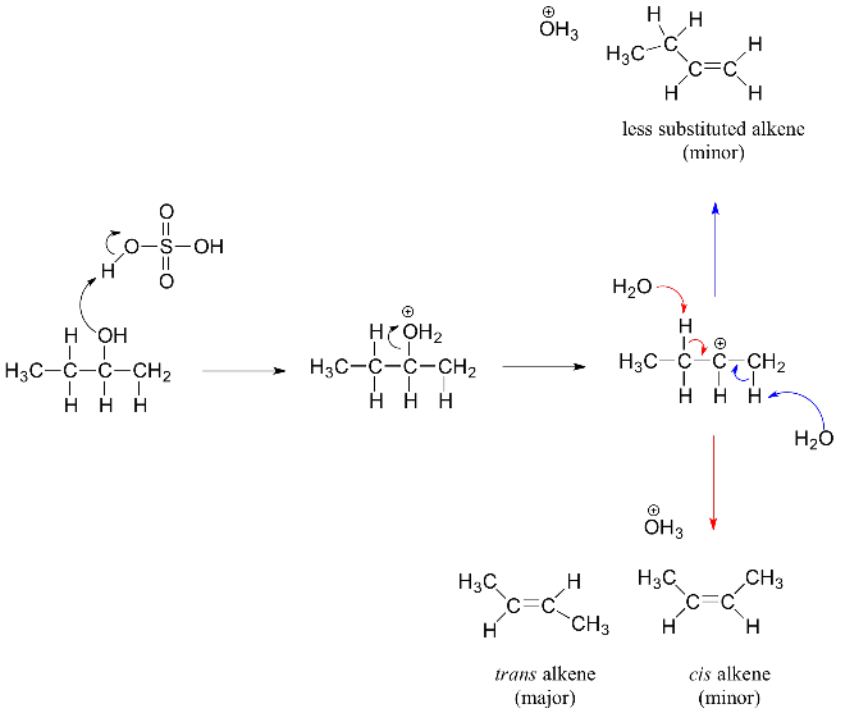


E1 MECHANISM FOR THE DEHYDRATION OF ALCOHOLS INTO ALKENES

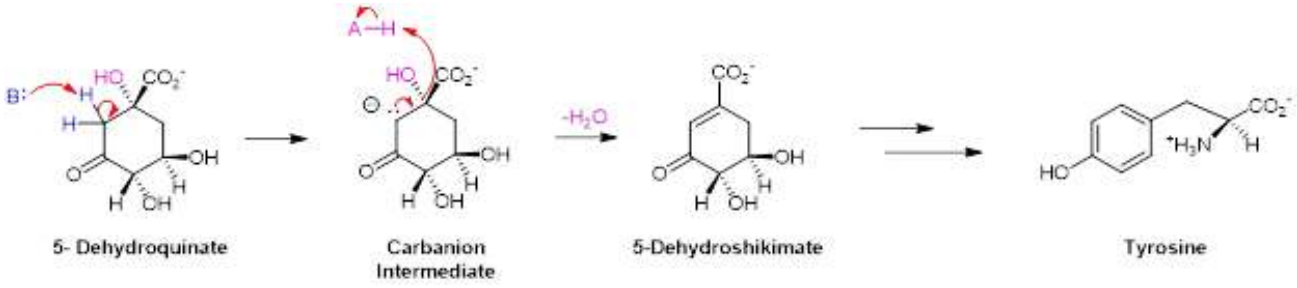
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first to form a carbocation a reaction intermediate. The eliminated water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond.

Notice in the mechanism below that the alkene formed depends on which adjacent proton is abstracted: the red arrows show formation of the more substituted 2-butene, while the blue arrows show formation of the less substituted 1-butene. This reaction also follows Zaitsev's rule which states that the most stable alkene will be the major product.

As a general rule that more substituted alkenes are more stable than less substituted alkenes. Also, *trans* alkenes are more stable than *cis* alkenes. Therefore, the *trans* isomer of the 2-butene product is expected to be the major product of this reaction.

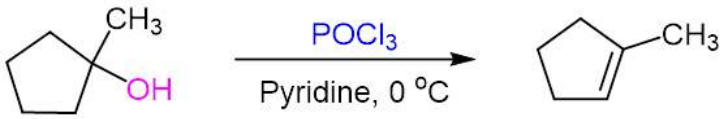


Similar biological dehydrations are fairly common. These reaction usually occur by an E1cB mechanism where the OH leaving group is two carbons away from a carbonyl group. An example is the dehydration of 5-dehydroquinate to form 5-dehydroshikimate as part of aromatic amino acid biosynthesis of tyrosine. Initially a biological deprotonates the carbon adjacent to the carbonyl group. The resulting carbanion intermediate forms a double bond by eliminating an OH group. This OH group is protonated by an acid and form water.



CONVERSION OF ALCOHOLS INTO ALKENES USING $POCl_3$

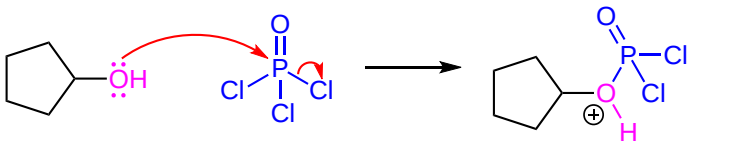
The E2 elimination of 2º and 3º-alcohols under mild, basic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. Pryidine is typically used as the reaction solvent and acts as the base which removes an adjacent proton in the E2 mechanism.



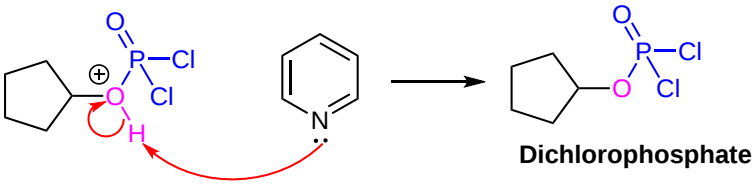
MECHANISM

The reaction starts with the reactant alcohol undergoing a substitution reaction with $POCl_3$ to form a dichlorophospate intermediate. Next pyridine removes an adjacent proton and the dichlorophospate group is eliminated as a leaving group to form a double bond by an E2 mechanism.

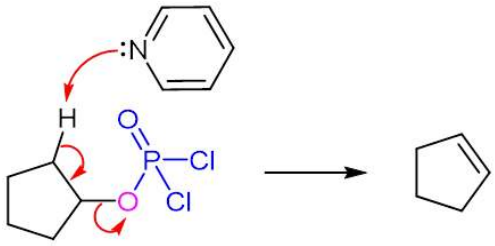
1) Formation of a dichlorphosphonium intermediate.



2) Deprotonation of the dichlorophosphonium intermediate to form a dichlorophosphate.

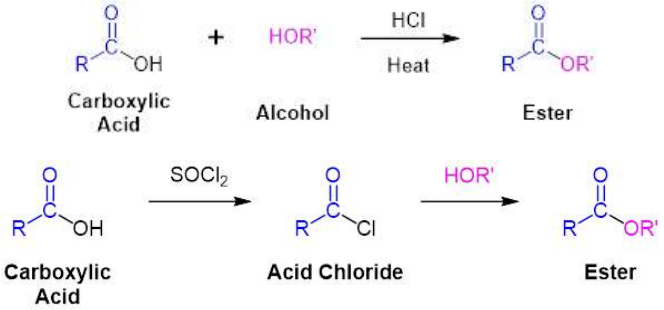


2) E2 elimination

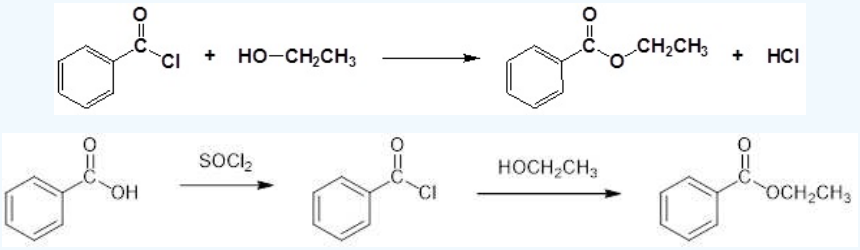


CONVERSION OF ALCOHOLS INTO ESTERS

Alcohols can be converted into esters through reaction with carboxylic acids using a strong acid as a catalyst. Often this transformation is performed by increasing the reactivity of the carboxylic acid by first converting it into a carboxylic acid chloride functional group by reacting with thionyl chloride ($SOCl_2$). The acid chloride can then be reacted with an alcohol to create an ester. These reactions will be discussed in greater detail in **Chapter 21**.

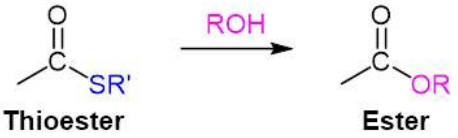


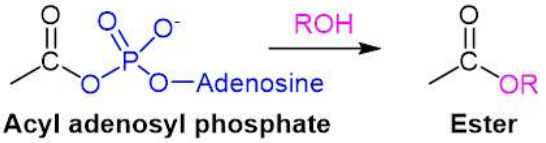
EXAMPLE 17.6.3



In biological systems, ester formation occurs through a similar process except thioester or acyl adenosyl phosphates are used instead of carboxylic acid chlorides. These reaction will be discussed in more detail in **Chapter 21**.

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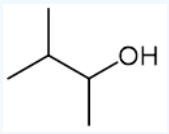
EXERCISES

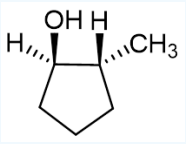
EXERCISE 17.6.1

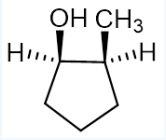
1) Draw the expected product of the reaction of cylohexanol with the following reagents.

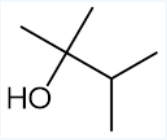
(a) $SOCl_2$ (b) PBr_3

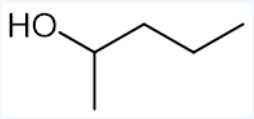
2) Draw the expected product of the treatment of the following compounds with $OPCl_3$ in pyridine.

a) 

b) 

c) 

d) 

e) 

Answer

1) a) Chlorocyclohexane b) Bromocyclohexane

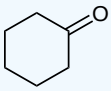
2) a) 2-Methyl-2-butene b) 3-Methylcyclopentene c) 1-Methylcyclopentene d) 2,3-Dimethyl-2-butene e) 2-Methyl-2-butene

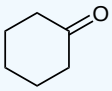
EXERCISE 17.6.2

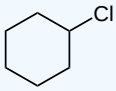
Draw the expected product of the reaction of cylohexanol with the following reagents.

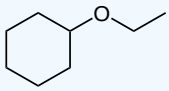
(A) CrO_3, H_2SO_4, H_2O (B) Dess-Martin Periodinane (C) $SOCl_2$ (D) NaH and 1-bromoethane (E) PBr_3

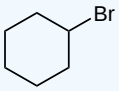
Answer

A) 

B) 

C) 

D) 

E) 

EXERCISE 17.6.3

Starting with cyclohexanol, describe how you would prepare the following?

(A) cyclohexyl acetate (B) 1-allylcyclohexan-1-ol (C) cyclohexene (D) ethoxycyclohexane

Answer

A) This can be seen as a transesterification, acid and some other ester would be needed to form cyclohexylacetate

B) First, oxidize the alcohol to a ketone, take for example Dess-Martin Periodinane, then use an allyl grignard to form 1-allylcyclohexan-1-ol

C) Alcohols can dehydrate to form alkenes under acidic conditions, so using anhydrous acid and heat would yield cyclohexene

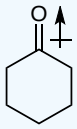
D) The alcohol can also be a nucleophile, perform a halogen substitution, using 1-X ethane, to yield ethoxycyclohexane

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EXERCISE 17.6.4

In cyclohexanone, a ketone, indicate the polarity of the bond between oxygen and carbon.

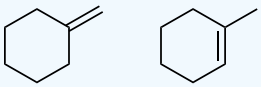
Answer



Oxygen is more electronegative than carbon creating the polar bond. This is the basis for the carbon's electrophilicity.

EXERCISE 17.6.5

In the dehydration of 1-methylcyclohexanol, which product is favored?

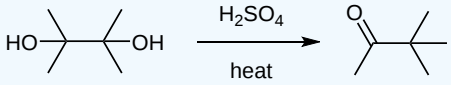


Answer

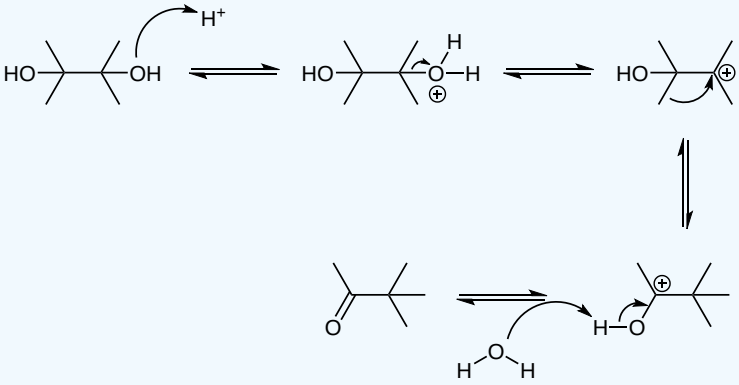
The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

EXERCISE 17.6.6

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint: a rearrangement occurs.)

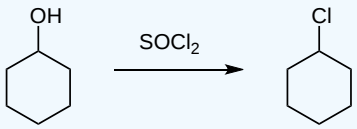


Answer



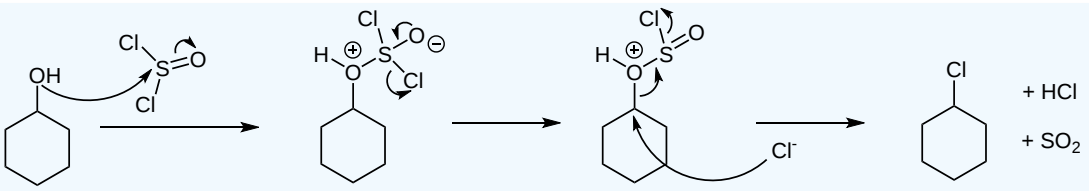
EXERCISE 17.6.7

Draw the mechanism of the reaction of thinoylchloride with cyclohexanol, given below.



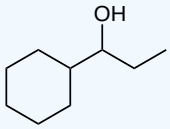
Answer

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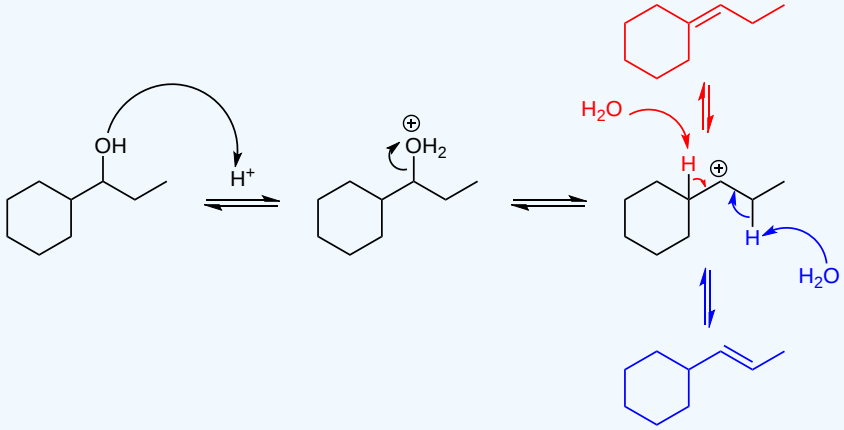
EXERCISE 17.6.8

Draw an arrow pushing mechanism for the acid catalyzed dehydration of the following alcohol, make sure to draw both potential mechanisms. Assume no rearrangement for the first two product mechanisms. Which of these two would likely be the major product? If there was a rearrangement, draw the expected major product.

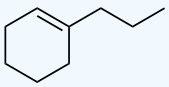


Answer

The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

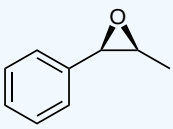


Note the secondary carbocation adjacent a tertiary carbon center, if there were a hydride transfer (rearrangement) to form a tertiary carbocation the following would be the major product. The minor product being the same product as the one formed from the red arrows.



EXERCISE 17.6.9

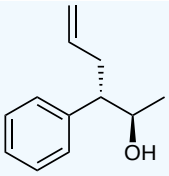
The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H_2O. Note the stereochemistry and also remember that benzyllic carbons are good S_N2 electrophiles.



Answer

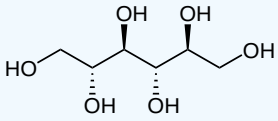
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EXERCISE 17.6.10

As seen in the previous example, there are many examples of chiral compounds containing alcohols. One common example of these are sugars, is the given the following sugar, allitol, also chiral?



Answer

This compound actually has a plane of symmetry, the plane parallel to the carbon chain/backbone. So, it is not chiral, also called a meso compound.

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17.7: OXIDATION OF ALCOHOLS

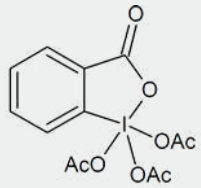
OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the oxidation of an alcohol.
2. identify the reagents that may be used to oxidize a given alcohol.
3. identify the specific reagent that is used to oxidize primary alcohols to aldehydes rather than to carboxylic acids.
4. identify the product formed from the oxidation of a given alcohol with a specified oxidizing agent.
5. identify the alcohol needed to prepare a given aldehyde, ketone or carboxylic acid by simple oxidation.
6. write a mechanism for the oxidation of an alcohol using a chromium(VI) reagent.

STUDY NOTES

The reading mentions that pyridinium chlorochromate (PCC) is a milder version of chromic acid that is suitable for converting a primary alcohol into an aldehyde without oxidizing it all the way to a carboxylic acid. This reagent is being replaced in laboratories by **Dess-Martin periodinane (DMP)**, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983.



Dess–Martin periodinane (DMP)

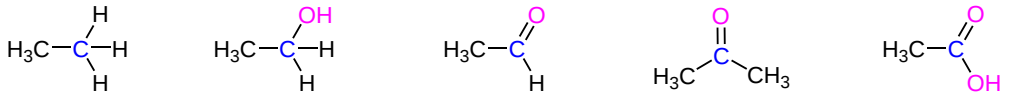
OXIDATION STATES OF CARBON

The general idea of oxidation and reduction reactions learned in general chemistry is that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. In order, to keep track of electrons in organic molecules a oxidation state formalism is used. Oxidation states to not represent the actual charge but it will allow the number of electrons being gained or lost by a particular atom during a reaction.

To calculate the oxidation state of a carbon atom the following rules are used:

1. A C-C bond does not affect the oxidation state of a carbon. So a carbon attached to 4 carbons has an oxidation state of zero.
2. Every C-H bond will **decrease** the oxidation state of the carbon by 1.
3. Each C-X bond will **increase** the oxidation state of the carbon by 1. Where X is an electronegative, such as nitrogen, oxygen, sulfur, or a halogen.

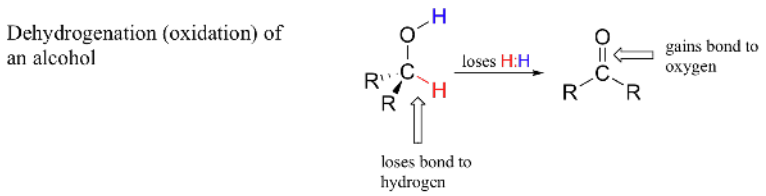
When looking at the oxidation states of carbon in the common functional groups shown below it can be said that carbon loses electron density as it becomes more oxidized.



	Ethane	Ethanol	Ethanal	Propanone	Ethanoic Acid
Oxidation State:	**3(-1) + O = -3**	**2(-1) +1 +0 = -1**	**2(+1) -1 +0 = +1**	**2(+1) + 2(0) = +2**	**3(+1) +0 = +3**

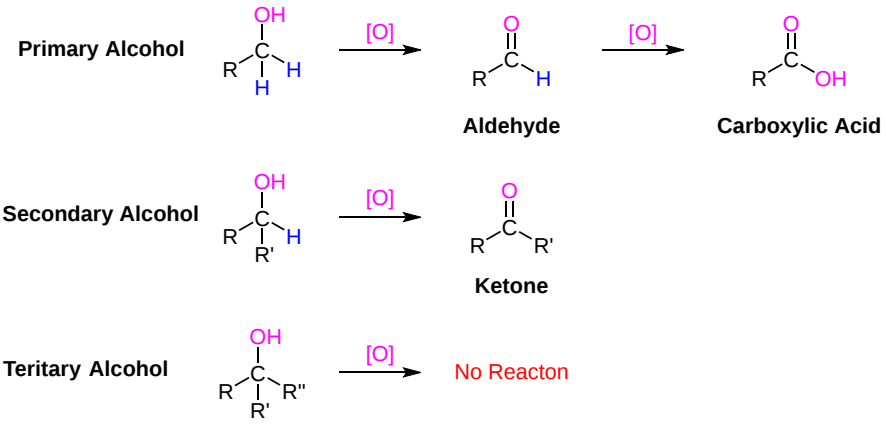
Most Reduced ⟹ **Most Oxidized**

For this section, a simpler way to consider this process is to say that when a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a oxygen it has been oxidized. A very commonly example is the oxidation of an alcohol to a ketone or aldehyde. Notice that during this process the carbon atom loses a hydrogen and gains a bond to oxygen.



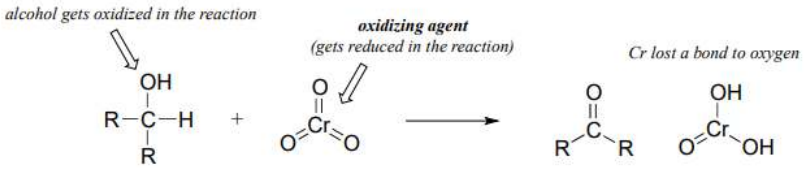
OXIDATION OF ALCOHOLS

On of the most important reactions of alcohols is their oxidation to carbonyl containing compounds such as aldehyde, ketones, and carboxylic acid. Typically primary alcohols, depending on the reagent used, produce aldehydes or carboxylic acids during oxidations. Secondary alcohols are oxidized to produce ketones, and tertiary alcohols are usually not affected by oxidations.



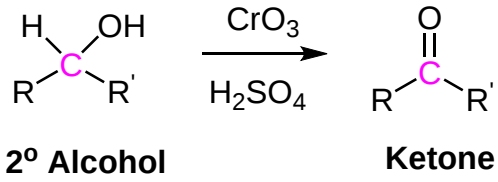
ALCOHOL OXIDIZING AGENTS

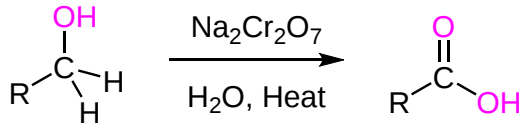
Oxidation and reduction reactions always occurs in tandem: when one compound is oxidized, another compound must be reduced. For an alcohol to be oxidized in a reaction there must also be a compound being reduced. This reduced compound is also called the oxidizing agent. For example, chromium trioxide (CrO_3) is a common oxidizing agent used by organic chemists to oxidize a secondary alcohol to a ketone. During this reaction CrO_3 is being reduced to form H_2CrO_3. A common method for oxidizing secondary alcohols to ketones uses **chromic acid** (**H_2CrO_4**) as the oxidizing agent. Chromic acid, also known as **Jones reagent**, is prepared by adding chromium trioxide (CrO_3) to aqueous sulfuric acid.



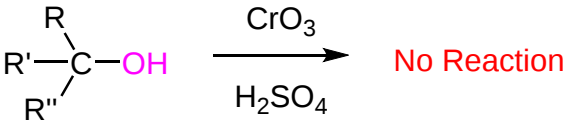
There is a wide selection of oxidizing agents available for use in the organic chemistry laboratory, each with its own particular properties and uses. In addition to CrO_3, other commonly used oxidizing agents include potassium permanganate ($KMnO_4$) and sodium dichromate ($Na_2Cr_2O_7$). Any of these reagents can be used to oxidize secondary alcohols to form ketones and primary alcohols to form carboxylic acids. Tertiary alcohols remain unreactive to oxidation.

GENERAL REACTIONS



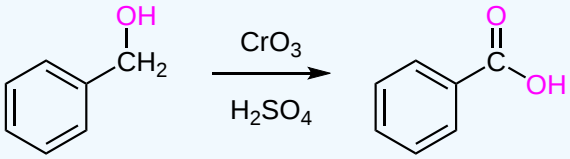


1º Alcohol **Carboylic Acid**

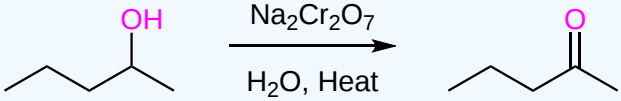


3º Alcohol

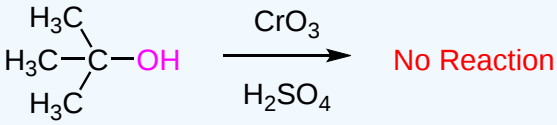
EXAMPLE 17.7.1



Oxidation of Benzyl Alcohol to Benzoic Acid

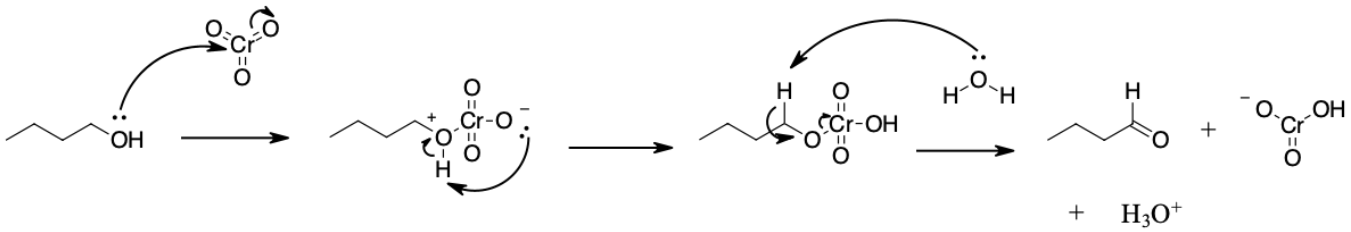


Oxidation of 2-Pentanol to 2-Pentanone



MECHANISM

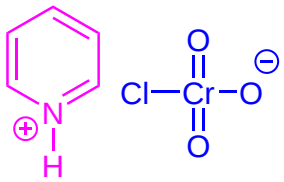
During this reaction mechanism the chromium atom is being reduced from Cr(VI) in the CrO_3 starting material to Cr(IV) in the H_2CrO_3 product. Also, notice the the C=O bond is formed in the third step of the mechanism through an E2 reaction. Although E2 reaction are generally know for forming C=C double bonds thought the elimination of a halide leaving group, in this case they are use to generate a C=O through the elimination of a reduced metal as a leaving group.



EXAMPLES

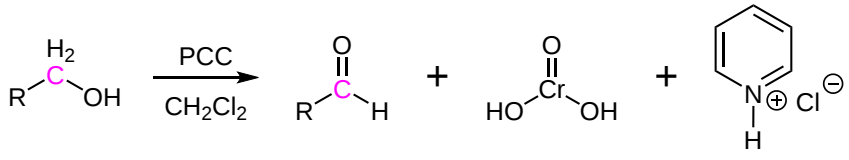
OXIDATION OF 1º ALCOHOLS WITH PCC TO FORM ALDEHYDES

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes 1º alcohols one rung up the oxidation ladder, turning primary alcohols into aldehydes and secondary alcohols into ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Cr(IV) as well as pyridinium chloride are produced as byproducts of this reaction.

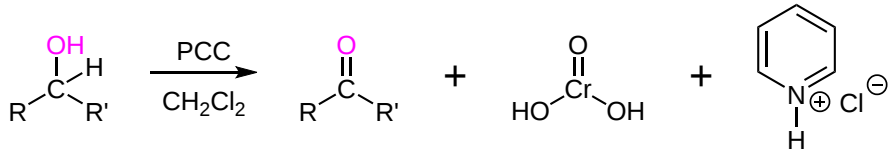


Pyridinium chlorochromate (PCC)

GENERAL REACTIONS

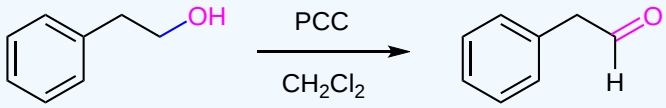


1° Alcohol **Aldehyde** **Cr(IV)** **Pyridinium Chloride**

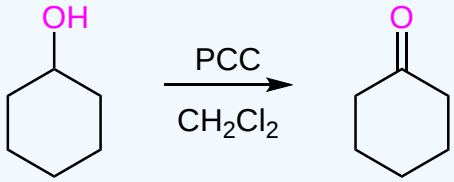


2° Alcohol **Ketone** **Cr(IV)** **Pyridinium Chloride**

? EXAMPLE 17.7.2



Oxidation of 2-Phenylethanol to Phenylacetaldehyde

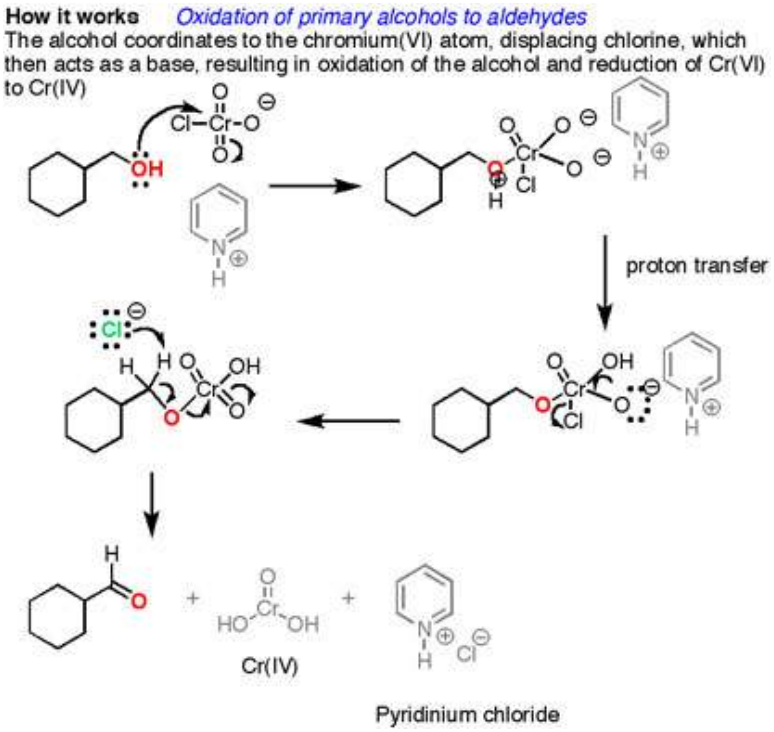


Oxidation of Cyclohexanol to Cyclohexanone

MECHANISM

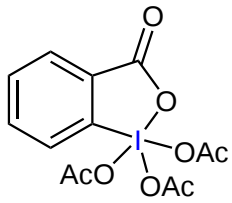
The first step of the mechanism is attack of alcohol oxygen on the chromium atom to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a reaction reminiscent of a 1,2 elimination reaction, to form what is known as a chromate ester.

The C-O double bond is formed when a base removes the proton on the carbon adjacent to the oxygen. It is also possible for pyridine to be used as the base here, although only very low concentrations of the deprotonated form will be present under these acidic conditions. In an E2 reaction, the electrons from the C-H bond move to form the C=O bond, and in the process break the O-Cr bond. During this step Cr(VI) gains two electrons to become Cr(IV) (drawn here as $O{=}Cr(OH)_2$).



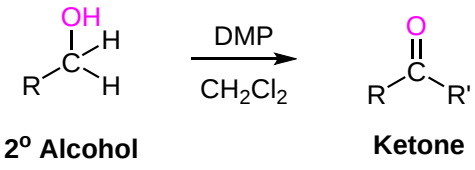
OXIDATION OF 1^{O} ALCOHOLS WITH DESS-MARTIN PERIODINANE (DMP) TO FORM ALDEHYDES

PCC is being replaced in laboratories by **Dess-Martin periodinane (DMP)** in dichloromethane solvent, which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous conditions (lower reaction temperature and a nonacidic medium). DMP is named after Daniel Dess and James Martin, who developed it in 1983.

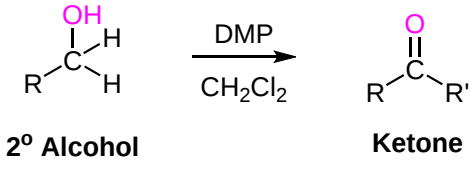


Dess-Martin periodinane (DMP)

GENERAL REACTIONS

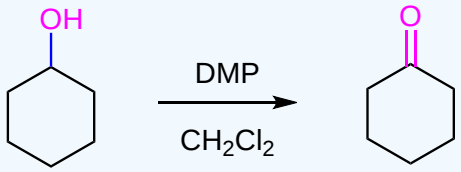


2° Alcohol **Ketone**

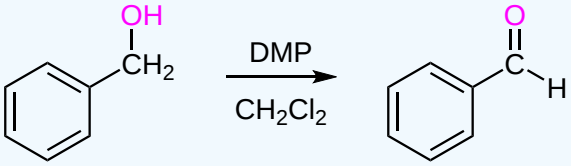


2° Alcohol **Ketone**

EXAMPLE 17.7.3



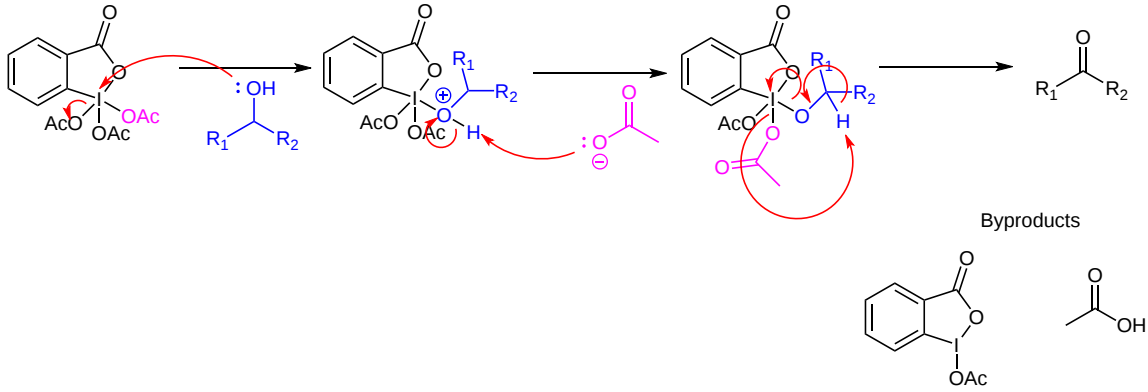
Oxidation of Cyclohexanol to Cyclohexanone



Oxidation of Benzyl Alcohol to Benzaldehyde

MECHANISM

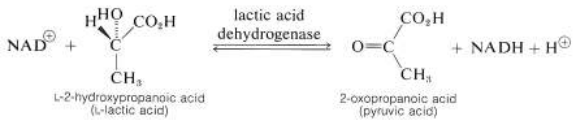
The first step of the mechanism involves the reactant alcohol attacking the Iodine (V) atom and eliminating an acetate (Ac^-) leaving group to form a periodinate intermediate. The next step is a concerted E2-like reaction where a hydrogen is removed from the alcohol, the C=O bond is formed, an acetate group is eliminated from the iodine atom, and the iodine (V) atom gains two electrons to be reduced to iodine (III).

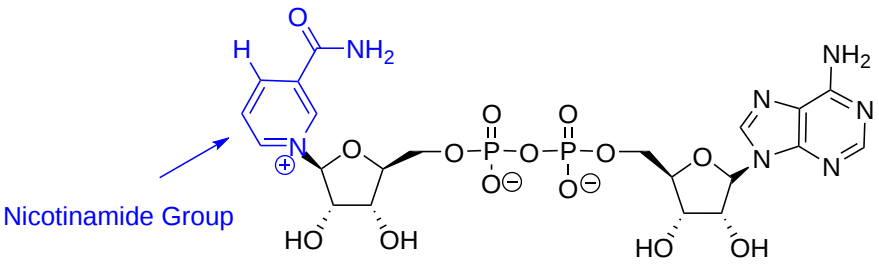


BIOLOGICAL ALCOHOL OXIDATIONS

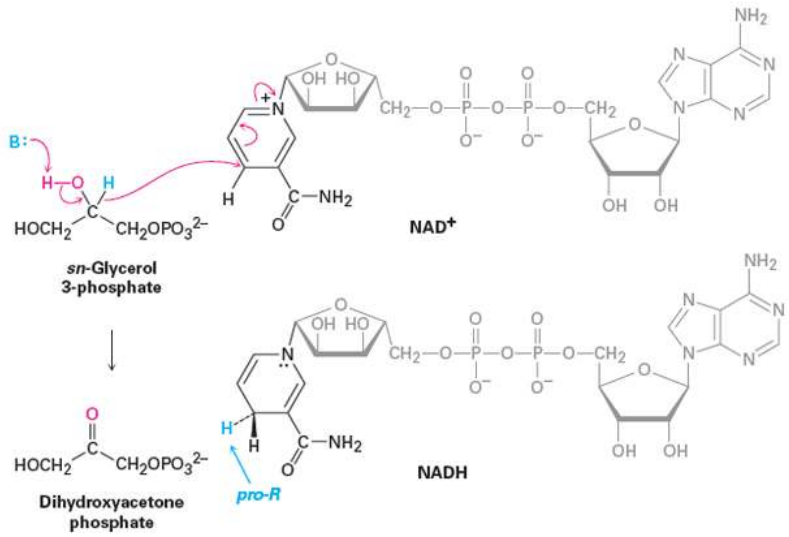
There are many biological oxidations that convert a primary or secondary alcohol to a carbonyl compound. These reactions cannot possibly involve the extreme pH conditions and vigorous inorganic oxidants used in typical laboratory oxidations. Rather, they occur at nearly neutral pH values and they all require enzymes as catalysts, which for these reactions usually are called *dehydrogenases*. An important group of biological oxidizing agents includes the pyridine nucleotides, of which nicotinamide adenine dinucleotide (NAD^+) is an example. This very complex molecule functions to accept hydride ($H:^-$) or the equivalent ($H^+ + 2e^-$) from the α carbon of an alcohol. The reduced form of NAD^+ is abbreviated as NADH and the $H:^-$ is added at the 4-position of the pyridine ring. It is important to note that the hydride adds exclusively to the *Re* face of the pyridine ring giving NADH a *pro*-R stereochemistry.

An example of the remarkable specificity of this kind of redox system. One of the last steps in the metabolic breakdown of glucose is the reduction of 2-oxopropanoic (pyruvic) acid to L-2-hydroxypropanoic (lactic) acid. The reverse process is oxidation of L-lactic acid. The enzyme *lactic acid dehydrogenase* catalyses this reaction, and it functions only with the L-enantiomer of lactic acid. During this reaction a base removes the alcohol hydrogen. The resulting alkoxide ion then forms the C=O bond causing a hydride ion to transfer to NAD^+.



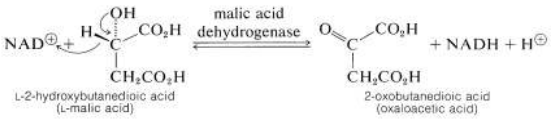


The Structure of NAD+



From an outside source. Convert mechanism to use lactic acid.

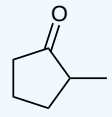
Another example is provided by one of the steps in metabolism by way of the Krebs citric acid cycle, is the oxidation of L-2-hydroxy-butanedioic (L-malic) acid to 2-oxobutanedioic (oxaloacetic) acid. This enzyme functions only with L-malic acid:

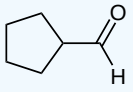


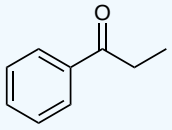
EXERCISES

? EXERCISE 17.7.1

Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

a) 

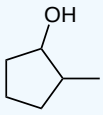
b) 

c) 

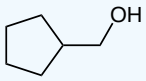
Answer

1)

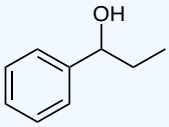
a) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



b) Since this is a primary alcohol, there are some precautions necessary to avoid formation of the carboxyllic acid. Milder oxidants such as the Dess-Martin periodinane, and also PCC (there is no water to form the carboxyllic acid) would work



c) Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.



EXERCISE 17.7.2

Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

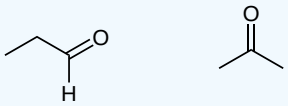
Answer



EXERCISE 17.7.3

Show the products of the oxidation of 1-propanol and 2-propanol with Dess-Martin periodinane.

Answer



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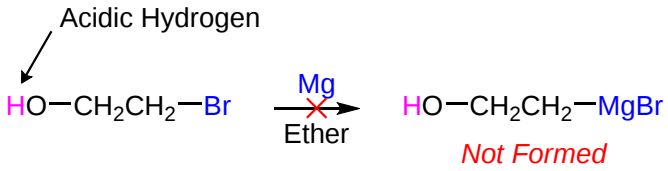
17.8: PROTECTION OF ALCOHOLS

OBJECTIVES

After completing this section, you should be able to

1. explain what is meant by “protecting” a functional group during an organic synthesis.
2. describe one common method for protecting the hydroxy group of an alcohol, and give an example of its use (e.g., in the preparation of a Grignard reagent).

Often during the synthesis of complex molecules one functional group in a molecule interferes with an intended reaction on a second functional group on the same molecule. An excellent example is the fact that a Grignard reagent can't be prepared from halo alcohol because the C-Mg bond is not compatible with the acidic -OH group.



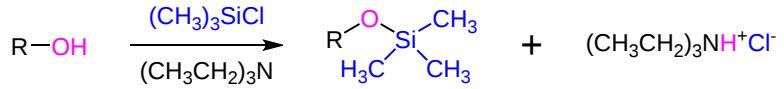
When situations like this occurs chemists circumvent the problem by changing the interfering functional group into one that does not interfere with the intended reaction. Chemists call this process protection of a functional group. Functional group protection involves three steps:

1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

PROTECTING ALCOHOLS THROUGH THE FORMATION OF TRIALKYLSILYL ETHERS

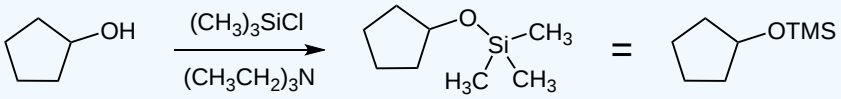
There are several methods for protecting an alcohol, however, the most common is the reaction with a chlorotrialkylsilane, Cl-SiR_3 This reactions forms a trialkylsilyl ether, R'O-SiR_3. One of the most common reagents is chlorotrimethylsilane [$(CH_3)_3SiCl$] which is often used in conjunction with a base, such as triethylamine. The base helps to form the alkoxide anion and remove the HCl produced by the reaction. The produced trimethylsilyl ether is commonly abbreviated -OTMS. This silyl ether no longer has the fairly acidic OH proton as the alcohol group has been changed (protected).

GENERAL REACTION

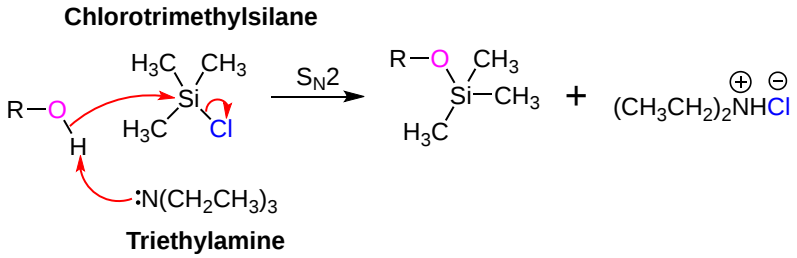


Alcohol **Trimethylsilyl ether (TMS)**

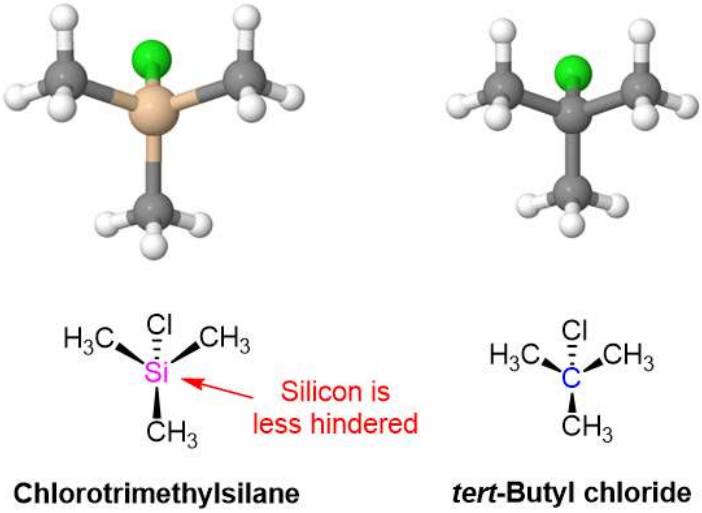
EXAMPLE 17.8.1



MECHANISM

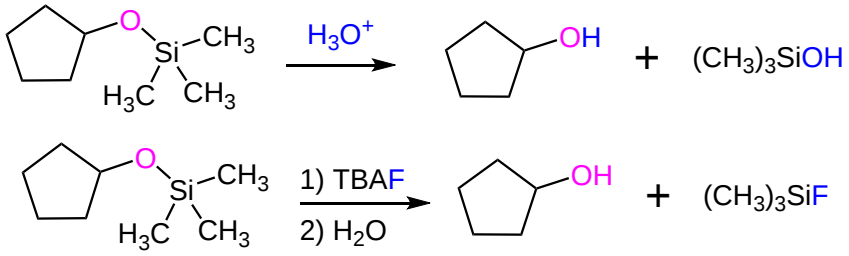


Notice this reaction occurs through an S_N2-like mechanism with the alcohol attacking a trialkyl-substitued silicon atom. Normally, an S_N2 reaction would not be viable for the analogous *tert*-butyl chloride due to the steric hindrance of the tertiary electrophilic carbon. Being a third-row atom, silicon is larger and forms longer bonds that carbon. The Si-C bonds of chlorotrimethylsilane are 195 pm compared to the 154 pm C-C bonds or *tert*-butylchloride. The three methyl groups attached to silicon are more spread out and offer less steric hindrance so the S_N2-like reaction can occur.



DEPROTECTION

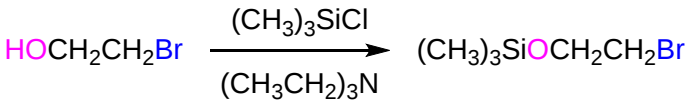
Trimethylsilyl ethers, like most other ethers, are relatively unreactive towards many reagents such as oxidizing agents, reducing agents, or Grignard reagents. However, the TMS ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion (F^-) to regenerate the alcohol. Common sources of the fluoride ion are lithium fluoride (LiF) and tetrabutylammoniumfluoride (TBAF) [$(CH_3CH_2CH_2CH_2)_4NF$]. This step is commonly referred to as a **deprotection**.



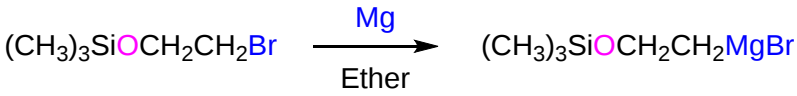
UTILIZING A PROTECTING GROUP FOR A GRIGNARD REACTION

The problem posed at the beginning of this section can be solved through the use of a TMS protecting group. Once the alcohol is converted into a TMS ether the acidic hydrogen will no longer be present and a Grignard reagent can be formed.

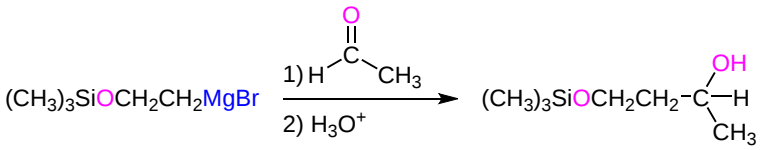
1) Protection of the Alcohol



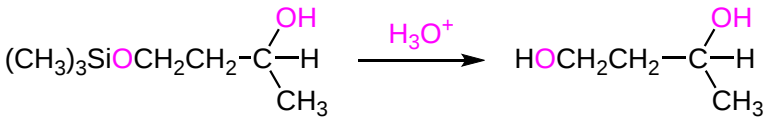
2) Form the Grignard Reagent



3) Perform the Grignard Reaction



4) Deprotection

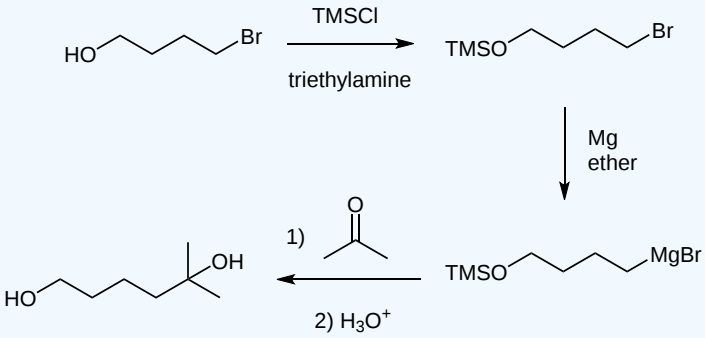


EXERCISES

? EXERCISE 17.8.1

Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 2-methylhexane-2,6-diol.

Answer



CONTRIBUTORS AND ATTRIBUTIONS

-
- Layne Morsch (University of Illinois Springfield)
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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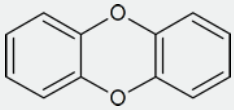
17.9: PHENOLS AND THEIR USES

OBJECTIVES

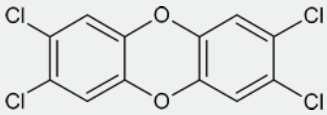
After completing this section, you should be able to describe two methods that can be used to obtain phenol on an industrial scale.

STUDY NOTES

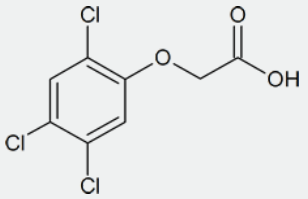
One substance that has become symbolic of the struggle between industrial development and environmental protection is dioxin. The name dioxin is used to refer to a family of compounds having a basic structure in which two benzene rings are joined by two oxygen atoms:

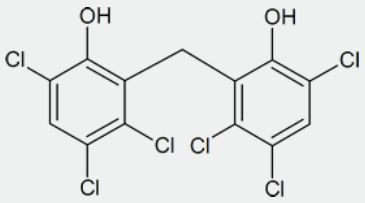


However, media references to dioxin are usually in connection with 2,3,7,8-tetrachlorodibenzo- *p*-dioxin, or TCDD:

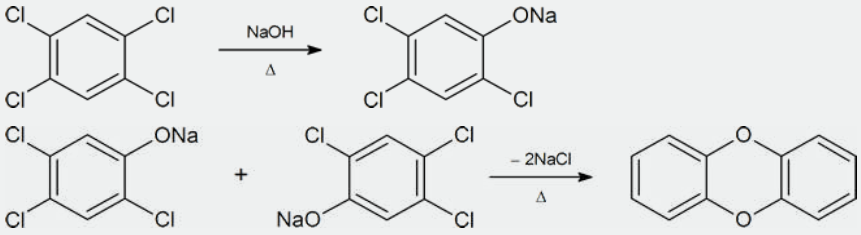


TCDD is a by-product formed in the manufacture of trichlorophenol, an intermediate in the production of the herbicide 2,4,5-T (one of the ingredients of the infamous Agent Orange), in the manufacture of hexachlorophene, by pulp and paper mills that use chlorine to produce white paper, and as a result of the incineration of municipal refuse.





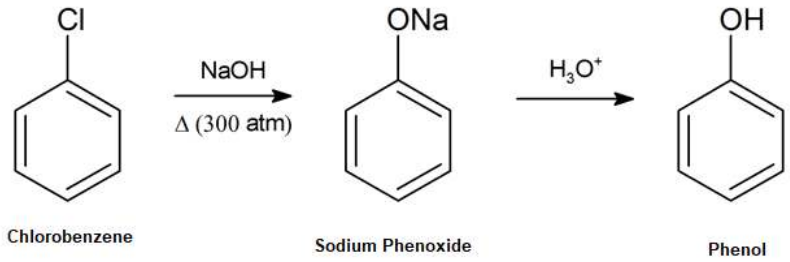
The equation given below shows how 2,3,7,8-tetrachlorodibenzo- *p*-dioxin is formed during the manufacture of 2,4,5-trichlorophenol, an intermediate produced in the synthesis of 2,4,5-T. The process involves the reaction of 1,2,4,5-tetrachlorobenzene with base at a temperature of about 160°C.



The possible hazards presented by dioxin first became apparent in 1957, when some German workers involved in the manufacture of 2,4,5-T developed chloracne—a skin condition resembling acne. The precise toxicological effects of dioxin on humans is open to debate, but as little as 0.6 mg per kg of body weight will kill 50% of guinea pigs injected with TCDD within a specified time.

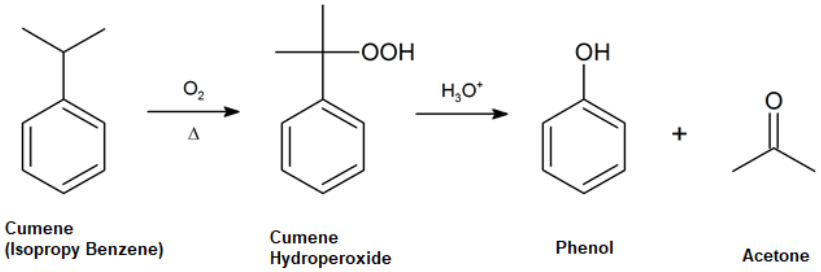
DOW'S PROCESS

An early commercial preparation of phenol in the late 19th and early 20th century was by the hydrolysis of chlorobenzene with strong base to produce a sodium phenoxide intermediate, which affords phenol upon acidification.



CUMENE PROCESS

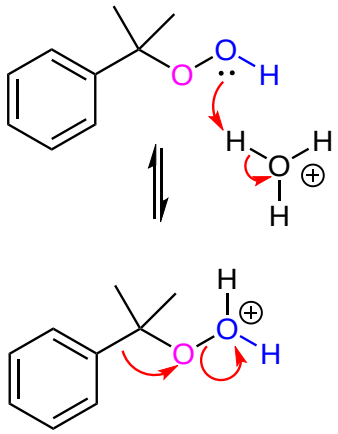
Developed in the 1940s and currently responsible for most industrial phenol production this process involves isopropylbenzene—commonly known as cumene. Treatment of cumene with oxygen in air generates 2-hydroperoxypropan-2-ylbenzene (cumene hydroperoxide) through a radical pathway. When hydrolyzed in acidic medium the peroxide intermediate produces phenol and acetone, which are both valuable chemical products.



MECHANISM

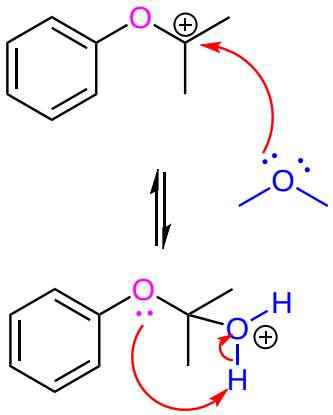
PROTONATION AND WATER LOSS

Initially cumene react with oxygen (O_2) to form cumene hydroperoxide. The -OH oxygen of the peroxide is protonated creating a good leaving group. This is following by a rearrangement where the phenyl group shifts form a carbon to an oxygen with the simultaneous loss of water.



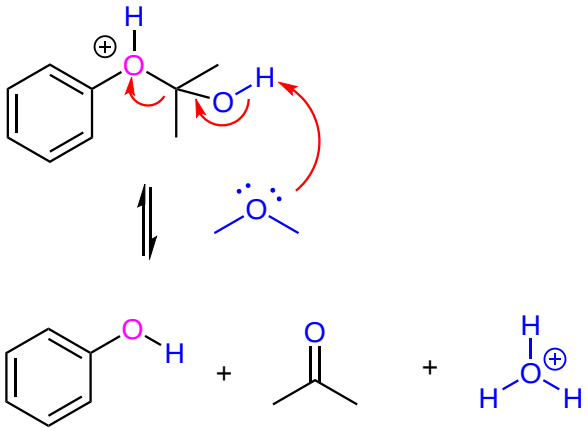
ADDITION OF WATER AND PROTON TRANSFER

The resulting carbocation intermediate is attacked by a nucleophilic water to form a protonated hemiacetal. A hemiacetal is a compound with an ether group (-OR) and a hydroxide group (-OH) bonded to the same carbon atom. A proton transfer occurs with the oxygen near the ring taking the extra hydrogen.



ELIMINATION

An E2 reaction occurs which forms the C=O bond in the product acetone, and eliminating phenol as the other product.



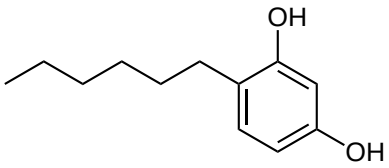
TO YOUR HEALTH: PHENOLS AND US

Phenols are widely used as antiseptics (substances that kill microorganisms on living tissue) and as disinfectants (substances intended to kill microorganisms on inanimate objects such as furniture or floors). The first widely used antiseptic was phenol. Joseph Lister used it for antiseptic surgery in 1867. Phenol is toxic to humans, however, and can cause severe burns when applied to the skin. In the bloodstream, it is a systemic poison—that is, one that is carried to and affects all parts of the body. Its severe side effects led to searches for safer antiseptics, a number of which have been found.



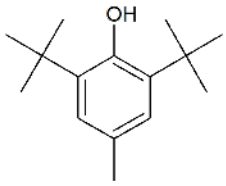
An operation in 1753, painted by Gaspare Traversi, of a surgery before antiseptics were used.

One safer phenolic antiseptic is 4-hexylresorcinol (4-hexyl-1,3-dihydroxybenzene; resorcinol is the common name for 1,3-dihydroxybenzene, and 4-hexylresorcinol has a hexyl group on the fourth carbon atom of the resorcinol ring). It is much more powerful than phenol as a germicide and has fewer undesirable side effects. Indeed, it is safe enough to be used as the active ingredient in some mouthwashes and throat lozenges.

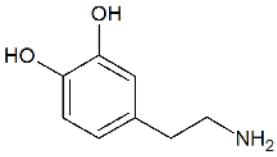


The compound 4-hexylresorcinol is mild enough to be used as the active ingredient in antiseptic preparations for use on the skin.

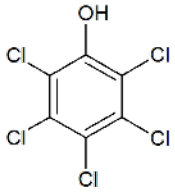
In addition to acting as an antiseptic, phenol is also a useful precursor in many chemical syntheses to produce pharmaceuticals, food preservatives, polymers, resins and adhesives. Phenolics are also present in a number of biological systems and natural products such as neurotransmitters, flavoring agents, and vitamins to name a few.



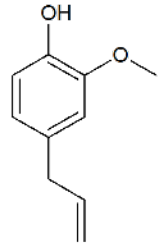
butylated hydroxytoluene
BHT (food preservative)



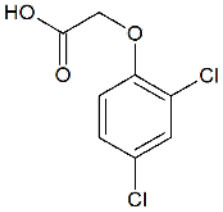
dopamine (neurotransmitter)



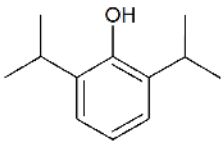
pentachlorophenol (wood preservative)



eugenal (perfume)



2,4-dichlorophenoxyacetic acid
2,4-D (herbicide)



propofol (pharmaceutical)

BISPHENOL A

In the United States, single-serve bottled water is the fastest growing beverage of choice. However, drinking tap water creates less pollution and uses less energy and natural resources than transporting and manufacturing plastic water bottles. Unlike soda and other carbonated beverages, there is no deposit on water bottles and therefore fewer are recycled by consumers. Nationally, only 10% of plastic water bottles are recycled creating large quantities of waste. Many water bottles consist of a polycarbonate plastic made with Bisphenol A (BPA).

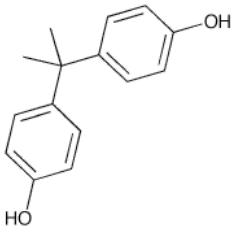


Figure 1: *Bisphenol A*

BPA was first synthesized by Thomas Zincke of the University of Marburg, Germany in 1905. Zincke did not propose uses for BPA however scientists discovered the many uses of BPA in 1953. Polycarbonate plastics became a commonly used commercial product in the 1950's.

BPA was created from a condensation reaction of phenol and acetone with hydrogen chloride, an acid catalyst, and a promoter such as methyl mercaptan. Once formed by this reaction, BPA is washed with water, neutralized with calcium hydroxide and distilled under vacuum. BPA can also be purified further by distillation and extractive crystallisation. Higher purity BPA is used to make polycarbonate plastics while the lower purity BPA is used to make Epoxy Resin. BPA's IUPAC name is 4,4'-dihydroxy-2,2,-diphenylpropane. It's chemical formula is $C_{15}H_{16}O_2$. The production of BPA produces H_2O (see image below) and therefore requires a condensation reaction for production.

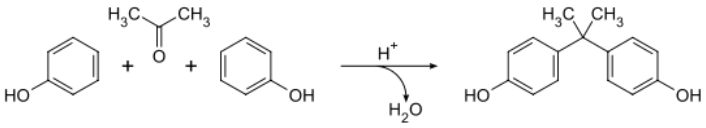


Figure 2 *The production of BPA*

A concern with the use of BPA in water bottles is the potential for leaching into the water which is then consumed. When BPA is present in the human body, it mimics the hormone estrogen and is capable of binding to estrogen receptors. In doing so, it changes the genes in the body that are expressed which triggers changes in hormone concentration, enzyme function and protein synthesis.

Using plastic water bottles that contain BPA is damaging both to the environment and human health. A greener alternative to the use of plastic water bottles is filtered tap water carried in refillable stainless steel containers.

CONTRIBUTORS AND ATTRIBUTIONS

-
-
- Ed Vitz (Kutztown University), John W. Moore (UW-Madison), Justin Shorb (Hope College), Xavier Prat-Resina (University of Minnesota Rochester), Tim Wendorff, and Adam Hahn.
- Layne Morsch (University of Illinois Springfield)

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17.10: REACTIONS OF PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. explain why phenols and phenoxide ions are very reactive towards electrophilic aromatic substitution (see Section 16.4 of the textbook).
2. write an equation to illustrate the oxidation of a phenol or an arylamine to a quinone, and identify the reagents used to oxidize phenols.
3. write an equation to illustrate the reduction of a quinone to a hydroquinone, and identify the reagents used to reduce quinones.
4. describe, briefly, the biological importance of the redox properties of quinones.

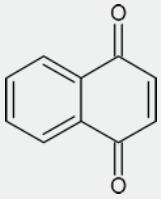
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

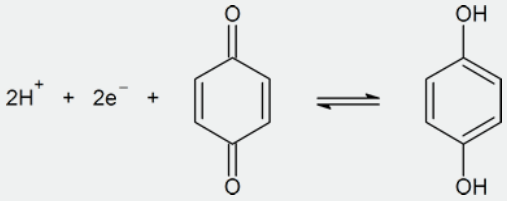
- hydroquinone
- quinone
- ubiquinone

STUDY NOTES

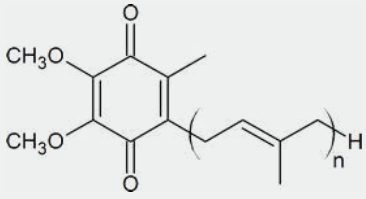
"Quinone" is a term used to describe cyclohexadiendiones in general, and *p*-benzoquinone in particular. In addition to benzene, other aromatic systems also give rise to quinones; for example, 1,4-naphthoquinone



"Hydroquinones" are produced by the reduction of quinones according to the following half-reaction:

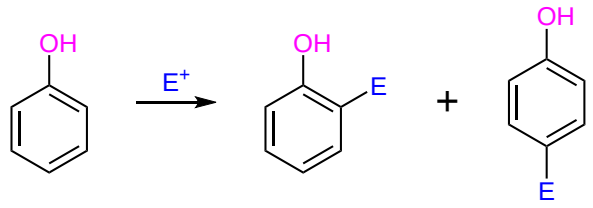


"Ubiquinones" are naturally occurring quinones whose role is to transfer a pair of electrons from one substance to another in enzyme-catalyzed reactions. Ubiquinones are also called coenzymes Q.



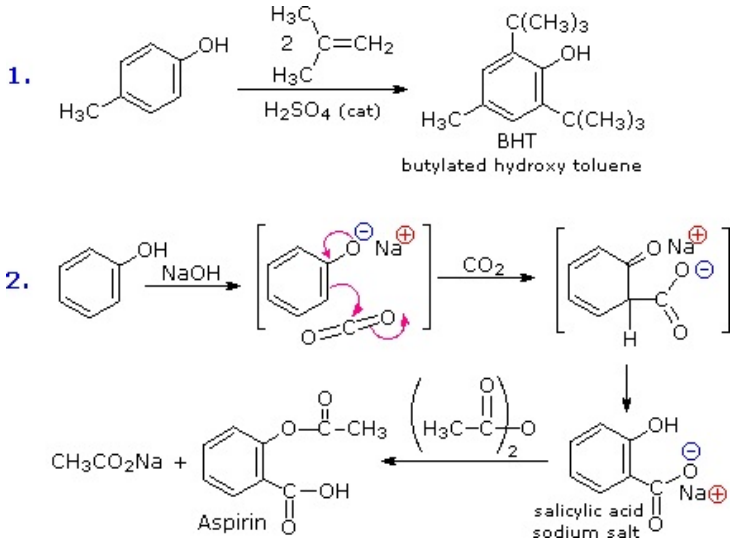
ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS

The hydroxyl subsistent of phenol is *ortho* and *para* directing and makes the aromatic ring strongly activated towards electrophilic aromatic substitution reaction (Section 16-4). In fact, phenols are strongly activating that often times electrophilic addition is difficult to limit to a single addition.



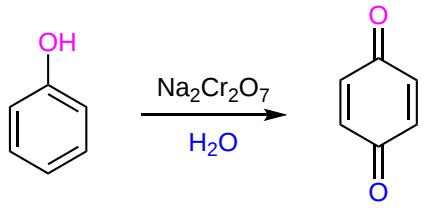
The ease with which the aromatic ring of phenols and phenol ethers undergoes electrophilic substitution is shown in the two examples in the diagram below. The first shows the Friedel-Crafts synthesis of the food preservative BHT from *para*-cresol. In this example, an electrophilic is added to both of the *ortho* positions to the alcohol of *para*-cresol.

The second example is interesting in that it further demonstrates the delocalization of charge that occurs in the phenolate anion. Carbon dioxide is a weak electrophile and normally does not react with aromatic compounds; however, the negative charge concentration on the phenolate ring enables the carboxylation reaction shown in the second step. The sodium salt of salicylic acid is the major product, and the preference for *ortho* substitution may reflect the influence of the sodium cation. This is called the **Kolbe-Schmidt reaction**, and it has served in the preparation of aspirin, as the last step illustrates.



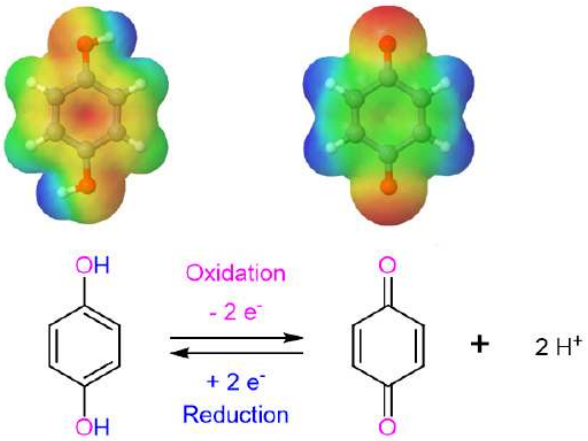
OXIDATION OF PHENOLS: QUINONES

Phenols are rather easily oxidized despite the absence of a hydrogen atom on the hydroxyl bearing carbon. Among the colored products from the oxidation of phenol by chromic acid is the dicarbonyl compound **para-benzoquinone** (also known as 1,4-benzoquinone).



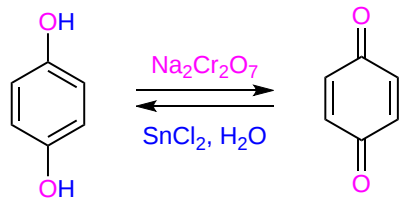
Phenol **para-Benzoquinone**

Quinones are an important class of compounds because of their redox equilibrium with their dihydroxybenzene analogs. The difference in electron density is seen in the electron potential map of hydroquinone and *para*-benzoquinone. The reduced compound, hyrodoquinone, has a greater electron density in the ring seen as a yellow/red color. The oxidized compound, *para*-benzoquinone, has significantly less electron density around the ring shown by the presence of green and blue colors.

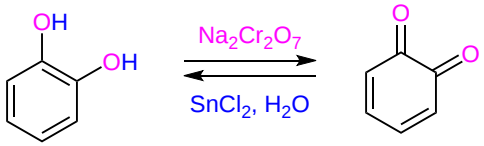


Hydroquinone (Reduced Form) **_para_-Benzoquinone (Oxidized Form)**

Dihydroxybenzenes can easily be oxidzed to the corresponding quinones by a wide variety of oxidizing agents including: sodium dichromate ($Na_2Cr_2O_7$), chromium trioxide (CrO_3), and potassium nitrosodisulfonate [$(KSO_3)_2NO$] called **Fremy's salt**. Likewise, quinone can be easily reduced back to hydroquinones using reagents such as stannous chloride ($SnCl_2$) or sodium borohydride ($NaBH_4$).



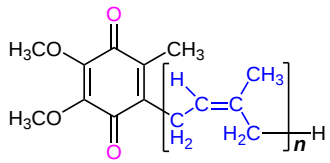
Hydroquinone (1,4-Dihydroxybenzene) **_para_-Benzoquinone**



Catechol (1,2-Dihydroxybenzene) **_ortho_-Benzoquinone**

UBIQUINONES

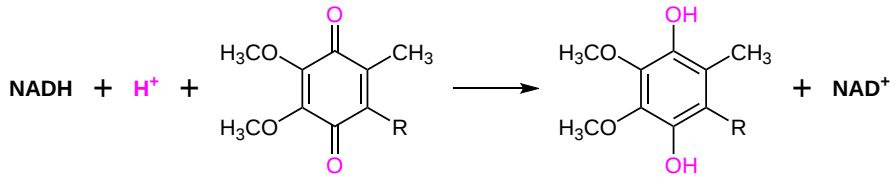
The redox abilities of quinones are utilized as biological oxidizing agents in the mitochondria of cells of aerobic organism. These quinone containing compounds called ubiquinones or coenzymes Q are a coenzyme family that is ubiquitous in all animals and bacteria which is the source of their name.



Ubiquinones (n = 1-10)

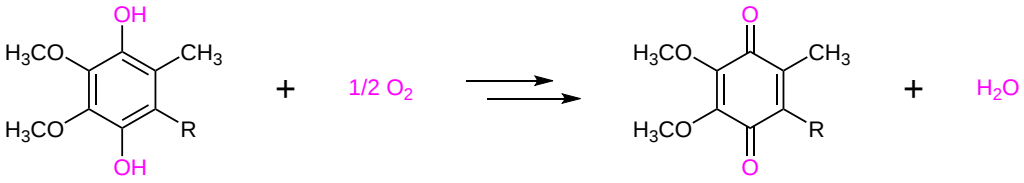
During the production of energy in cells, the redox capabilities of ubiquinones is utilized to mediate the electron-transfer process in which electrons are transferred from the biological reducing agent NADH to molecular oxygen. This process occurs in a series of steps. Initially, a ubiquinone reduced to its corresponding dihydroxy benzene in order to oxidize NADH to NAD^+. Later, the dihydroxy benzene is oxidized back to its ubiquinone form allowing for oxygen (O_2) to be reduced to water. When looking at the overall process NADH is oxidized to NAD^+ and oxygen is reduced to water. The ubiquinone only acts as an intermediate and is unchanged during this process.

STEP 1



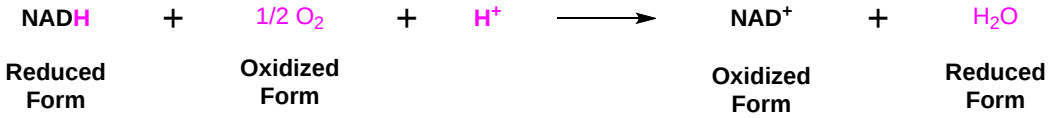
Reduced Form | Oxidized Form | Reduced Form | Oxidized Form

STEP 2



Reduced Form | Oxidized Form | Oxidized Form | Reduced Form

OVERALL PROCESS

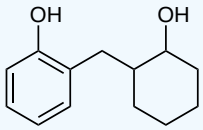


Reduced Form | Oxidized Form | Oxidized Form | Reduced Form

EXERCISES

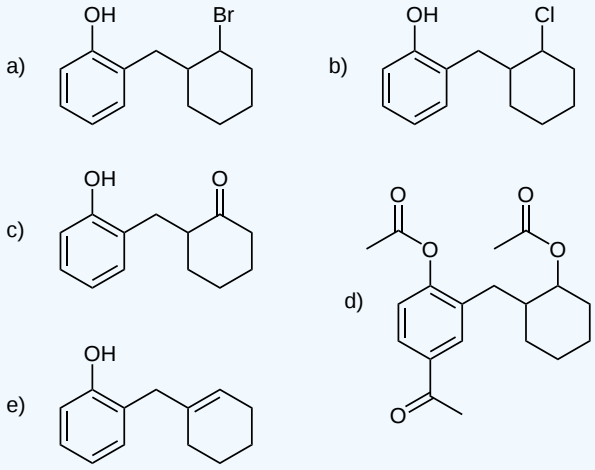
? EXERCISE 17.10.1

Predict the major product if the following reagents/reagents were used. No reaction is also a possible answer.



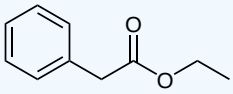
a. 1 equivalent of PBr_3
b. 1 equivalent of $SOCl_2$
c. Dess–Martin periodinane
d. 3 equivalents of acetyl chloride and $AlCl_3$ as a catalyst
e. Heat and H_2SO_4 (assume the phenol does not act as a nucleophile in this case)

Answer



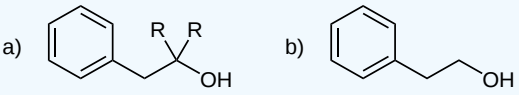
EXERCISE 17.10.2

Predict the major product if the following reagents/conditions were used. No reaction is also a possible answer.



a. 2 equivalents of RMgBr and H_3O^+ work-up
b. $LiAlH_4$ and H_3O^+ work-up
c. $NaBH_4$ and H_3O^+ work-up

Answer



CONTRIBUTORS AND ATTRIBUTIONS

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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17.11: SPECTROSCOPY OF ALCOHOLS AND PHENOLS

OBJECTIVES

After completing this section, you should be able to

1. identify the two most prominent absorptions seen in the infrared spectra of alcohols and phenols.
2. describe the characteristic feature of the proton NMR spectra of alcohols and phenols.
    a. explain how deuterium oxide (D_2O) can be used to assist in the identification of the signal caused by the presence of the O-H proton in the ^1H NMR spectrum of an alcohol.
    b. predict the general form (i.e., number of peaks, approximate chemical shifts, and splitting pattern) of the proton NMR of a given alcohol or phenol.
3. describe the two most common initial fragmentations in the mass spectra of alcohols.
4. use spectral data (infrared, NMR, mass spectroscopy) to assist in the identification of an unknown alcohol or phenols. You may use tables of characteristic absorptions as an aid to accomplishing this objective.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha cleavage
- dehydration

STUDY NOTES

The ^1H NMR chemical shifts for phenols are not particularly distinctive. However, one expects the **–OH** signal to be in the 4–7 ppm range, while the aromatic protons (see Section 15.7) are expected to be found at 7–8 ppm.

In a mass spectrometer, alcohols fragment in two characteristic ways: alpha cleavage and dehydration. From the equation showing H-Y elimination, you can see that the dehydration of an alcohol in a mass spectrometer is essentially the same as the dehydration of an alcohol in a normal chemical reaction. “Alpha cleavage” refers to the breaking of the bond between the oxygen-bearing carbon atom and one of the neighboring carbons.

INFRARED SPECTROSCOPY

The IR spectrum of aliphatic alcohols have a distinctive O-H stretch in the range of 3300 to 3400 cm^{-1}. This peak tends to be very strong and very broad. This exact position of the peak is dependent on the amount of hydrogen bonding in the alcohol. In addition alcohol have a strong C-O stretch near 1000 cm^{-1}. In the IR spectra of 1-butanol, show below, the O-H stretch appears at 3300 cm^{-1} and the C-O stretch appears at 1073 cm^{-1}.

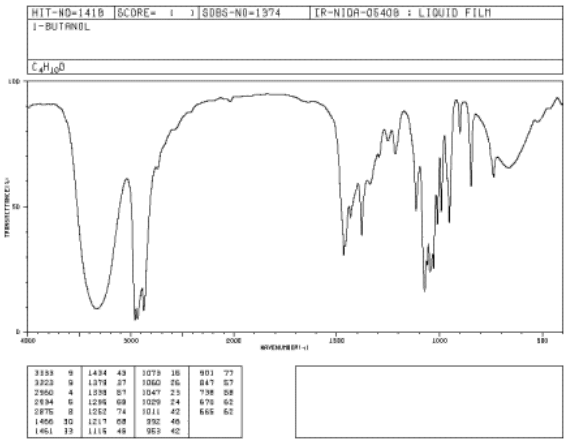
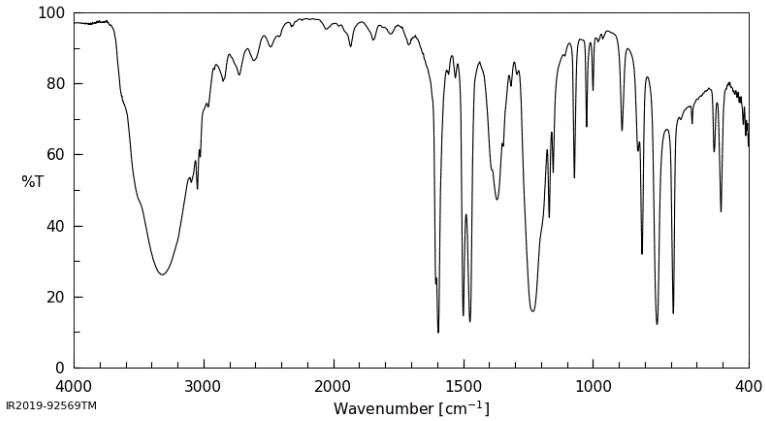


Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

Peak shapes are sometimes very useful in recognizing what kind of bond is present. The rounded shape of most O-H stretching modes occurs because of hydrogen bonding between different hydroxy groups. Because protons are shared to varying extent with neighboring oxygens, the covalent O-H bonds in a sample of alcohol all vibrate at slightly different frequencies and show up at slightly different positions in the IR spectrum. Instead of seeing one sharp peak, you see a broad set of multiple overlapping peaks. The broadness of the O-H peak makes it very easy to distinguish in an IR spectrum.

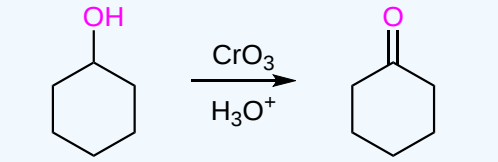
The IR spectrum of phenols the O-H stretch appears at roughly 3500 cm^{-1}. In addition, the IR spectra will show the bands typical for aromatic compounds in the region of 1500-1600 cm^{-1}.



The IR Spectrum of Phenol

? EXERCISE 17.11.1

Assume that you have just converted cyclohexanol into cyclohexanone. How would you use IR spectroscopy to tell if the conversion was successful? What changes would you expect to see between the starting material and the product?



Cyclohexanol **Cyclohexanone**

Answer

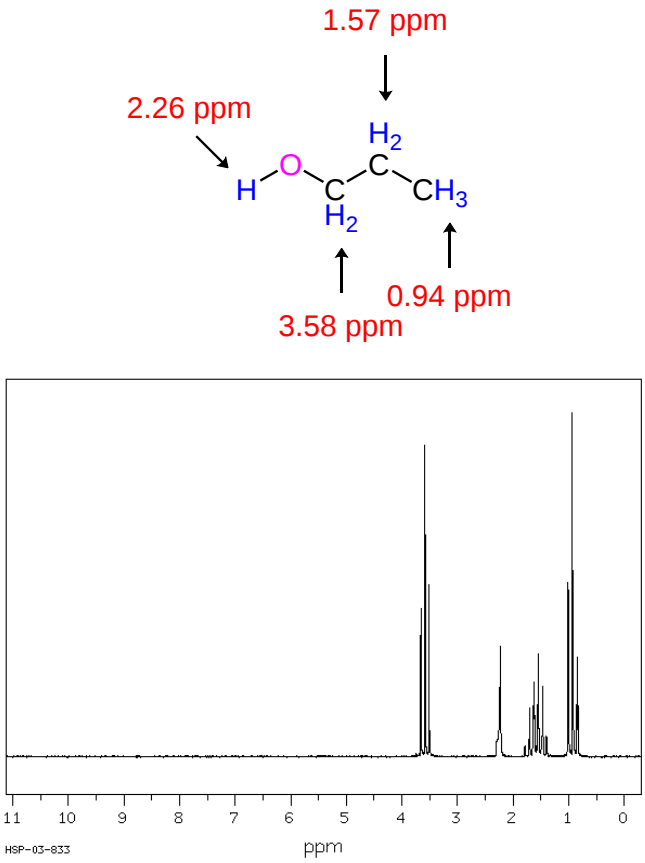
The cyclohexanol starting material would have a distinctive O-H stretch between 3300 and 3400 cm^{-1}. If the conversion were successful this peak would not be present in the product. Also, the IR spectrum of the product would have a strong C=O stretch between 1700 and 1800 cm^{-1}.

^{1}H NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ALCOHOLS

- Protons on carbon adjacent to the alcohol oxygen show up in the region of 3.4-4.5 ppm. The electronegativity of the alcohol oxygen de-shields these protons causing them to appear downfield when compared to alkane protons.
- Protons directly attached to the alcohol oxygen often appear in the region of 2.0 to 2.5 ppm. These peaks tend to appear as short, broad singlets. The position of the -OH peak can vary depending on the conditions, such as the NMR solvent used, the concentration of the alcohol, the purity of the alcohol, temperature, and if any water is present in the sample.

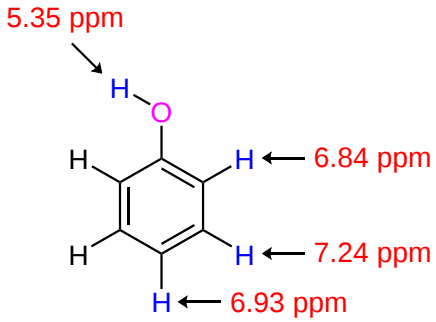
Notice that the alcohol proton is not involved in spin-spin splitting. This is usually true unless the alcohol is exceptionally pure. Most samples of alcohols contain minute amounts of acidic impurities which catalyze the exchange of protons causing the splitting effects to be removed. This is why alcohol protons typically appears as a singlet in NMR spectrum. The ^{1}H NMR spectrum of propanol shows the -CH_2- attached to the alcohol as a triplet at 3.58 ppm. This shows that the signal is being split by the adjacent -CH_2- group and not the alcohol -OH. The signal for the proton attached to the oxygen appears as a singlet at 2.26 ppm. If this signal was involved in spin-spin splitting with the adjacent -CH_2- group it would appear as a triplet.

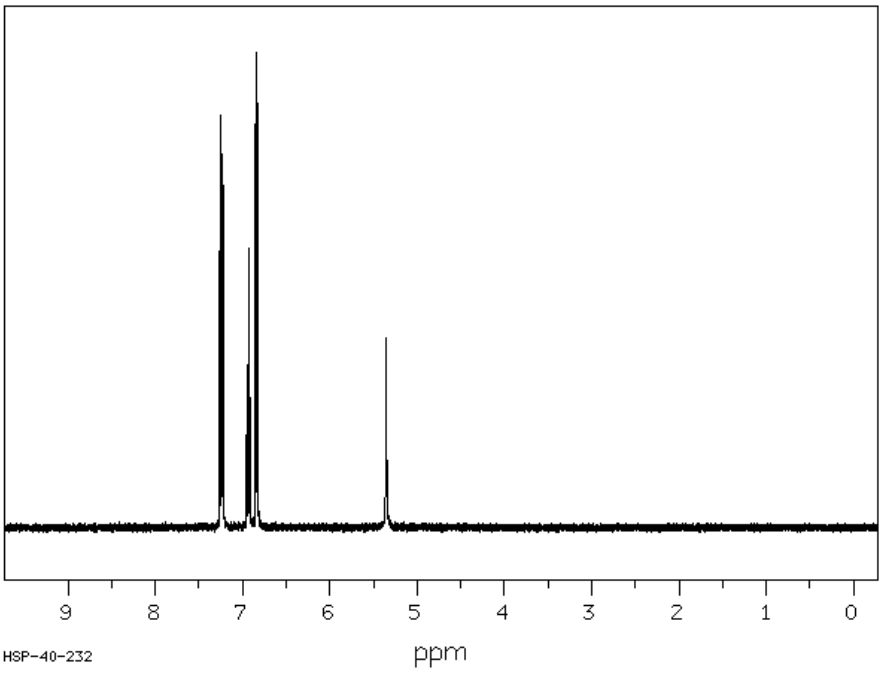


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017

PHENOL

- Protons attached to the aromatic ring in phenols show up near the aromatic region of an NMR spectrum (7-8 ppm). These peaks will have splitting typical for aromatic protons.
- The protons directly attached to the alcohol oxygen of phenols appear in the region of 3 to 8 ppm. These peaks tend to appear as short, broad singlets similarly to other alcohols.

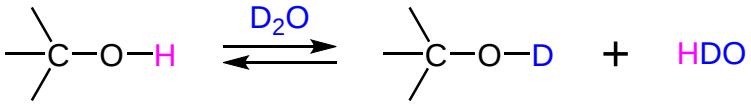




DETERMINING THE POSITION OF AN -OH PEAK IN ^{1}H NMR

The position of the -OH absorption for alcohols and phenols can be easily determined through the addition a few drops of deuterium oxide, D_2O to the NMR sample tube.

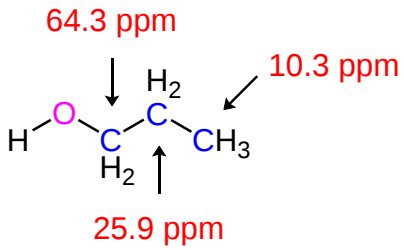
After addition, the OH proton will be rapidly exchanged for a deuterium. Because deuterium atoms do not produce peaks in a typical NMR spectrum the original -OH peak will disappear. This technique is sometimes called a **"D_2O shake"** due to the mixing required after D_2O has been added to the NMR sample tube.

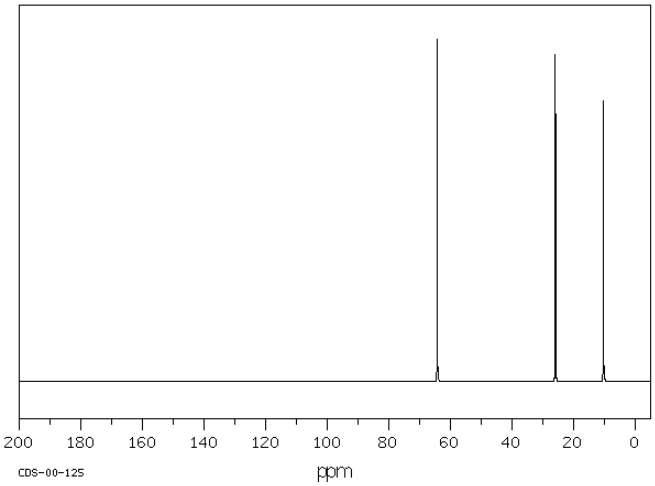


^{13}C NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

ALCOHOLS

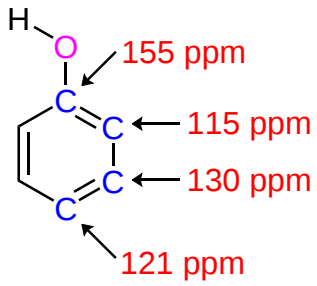
- Carbons adjacent to the alcohol oxygen show up in the distinctive region of 50-65 ppm in ^{13}C NMR spectrum.

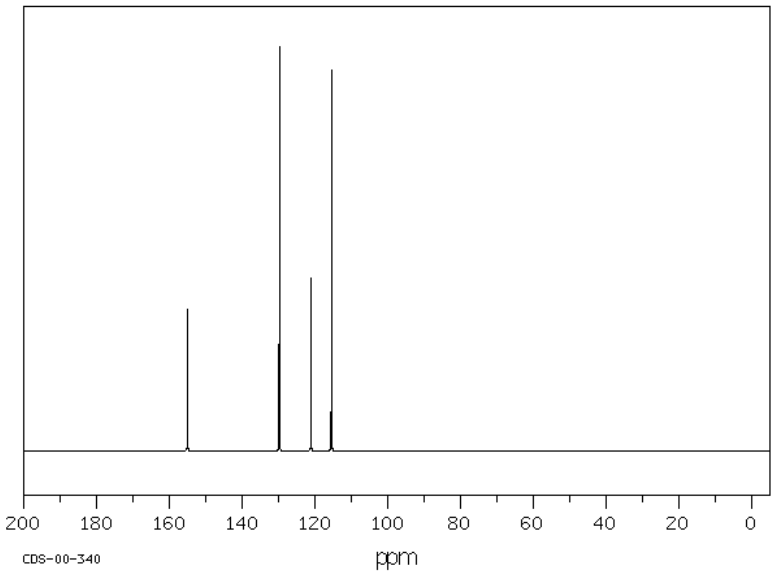




PHENOLS

- Due to the electronegative oxygen, the aromatic carbon attached to the -OH group is shifted downfield to 155 ppm.
- The other carbons in the phenol ring appear in the region typical for aromatic carbons of 125-150 ppm.





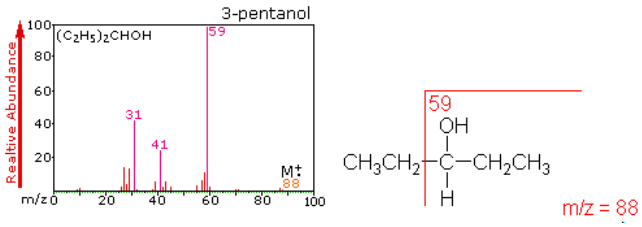
MASS SPECTRA

ALCOHOLS

An alcohol's molecular ion is small or non-existent. Alpha-cleavage of the C-C bond next to the oxygen usually occurs. A loss of H_2O may occur as in the spectra below.

3-Pentanol ($C_5H_{12}O$) with MW = 88.15

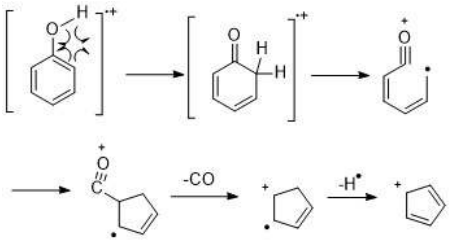
3-Pentanol shows three significant fragment ions. Alpha-fragmentation (loss of an ethyl radical) forms the m/z=59 base peak. Loss of water from this gives a m/z=41 fragment, and loss of ethene from m/z=59 gives a m/z=31 fragment.



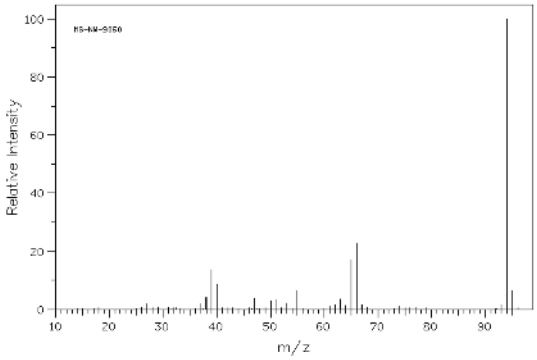
PHENOL

Phenol (C_6H_6O) with MW = 94.11

Phenol exhibit a strong molecular ion peak. The presence of an aromatic ring and an OH gives phenol a unique fragmentation pattern. In particular loss of CO (M – 28) and loss of a formyl radical (HCO·, M – 29) are common observed.

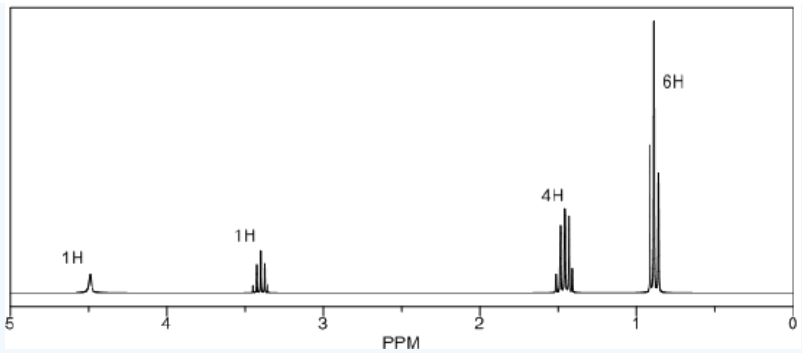


From an outside source



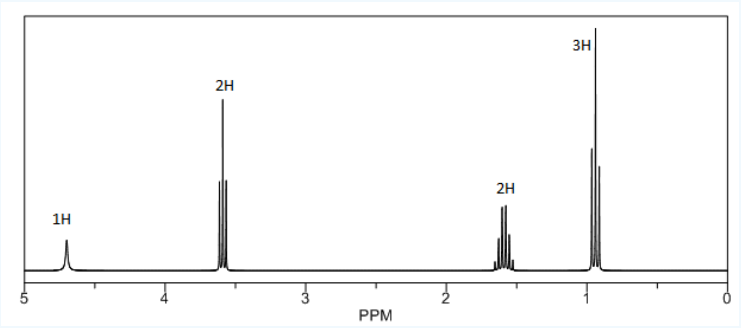
EXERCISE 17.11.1

1) From mass spectroscopy analysis it was determined that a compound has the general formula $C_5H_{12}O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



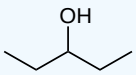
2) How would you expect the NMR spectrum show in question one to change if D_2O was added to the NMR sample tube.

3) From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1) 3-Pentanol



EXERCISE 17.11.2

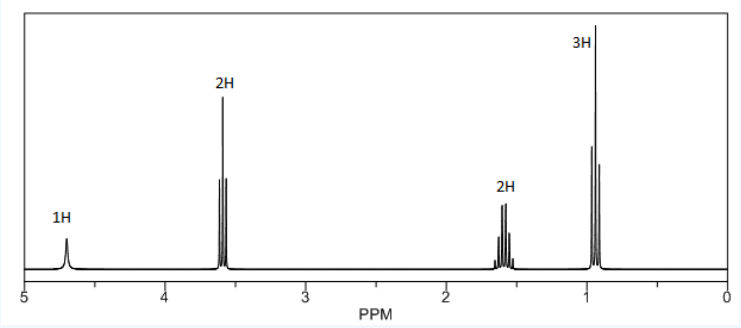
How would you expect the NMR spectrum shown in Exercise 1 to change if D_2O was added to the NMR sample tube.

Answer

The -OH peak at 4.5 ppm would dissappear due to dueterium exchange.

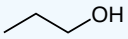
EXERCISE 17.11.3

From mass spectroscopy analysis it was determined that a compound has the general formula $C3H_8O$. Given the following ^1H NMR spectrum, draw the structure. The integration values of each group of signals is given on the spectrum.



Answer

1-Propanol



CONTRIBUTORS AND ATTRIBUTIONS

-
-
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- James Kabrhel (University of Wisconsin - Green Bay, Sheboygan Campus)

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17.S: ALCOHOLS AND PHENOLS (SUMMARY)

CONCEPTS & VOCABULARY

17.0 Introduction

- Alcohols have hydroxide groups (OH) bonded to an sp^3 carbon.
- Enols have a hydroxide bonded to an sp^2 carbon that is not part of an aromatic ring, a vinyl carbon.
- Phenols have a hydroxide bonded to an sp^2 carbon that is part of an aromatic ring, an aryl carbon.

17.1 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

17.2 Properties of Alcohols and Phenols

- Alcohols, enols and phenols all have significantly higher boiling points than alkanes, due to hydrogen bonding.
- Small alcohols are soluble in water.
- Alcohols are amphoteric, they act as an acid when reacting with bases and as a base when reacting with acids.
- Phenols are more acidic than alcohols due to resonance delocalization of the negative charge in the phenoxide conjugate base.
- Substituent groups on an aromatic ring that withdraw electron density increase the acidity of phenols, while substituent groups that donate electron density decrease acidity of phenols.

17.3 Preparation of Alcohols: A Review

- Alcohols can be prepared from alkyl halides by reacting with hydroxide.
- Alcohols can be prepared from alkenes by reaction with acid/water or oxymercuration to form the more substituted alcohol.
- Alcohols can be prepared from alkenes by hydroboration/oxidation to form the less substituted alcohol.
- Diols can be prepared from alkenes by first forming an epoxide, then ring opening the epoxide to form an anti-diol.
- Diols can be prepared from alkenes by reacting with osmium tetraoxide, then reducing off the osmium to form syn-diols.

17.4 Alcohols from Carbonyl Compounds: Reduction

- Organic reduction can be defined by increasing the number of bonds to hydrogen.
- Aldehydes and ketones can be reduced to alcohols with several different hydride donor reagents.
- NADH is an example of a biological reducing agent, which donates a hydride to carbonyl groups, reducing them to an alcohol.
- Carboxylic acids and esters can be reduced to alcohols with a strong reducing agent such as lithium aluminum hydride $LiAlH_4$.

17.5 Alcohols from Carbonyl Compounds: Grignard Reaction

- One of the most important organometallic groups of molecules are Grignard reagents, which are alkyl magnesium halides.
- Grignard reagents, like other organometallic compounds, include a nucleophilic alkyl group that can react with many different electrophiles.
- Grignard reagents will add to aldehydes and ketones forming alcohol products.
- Grignard reagents will add twice to ester molecules, forming alcohol products.
- Grignard reagents are strong bases, therefore the will not undergo nucleophilic addition reactions with molecules that have protons that are even slightly acidic such as: alcohols, carboxylic acids, alkynes, and amines or amides that have an N-H bond.

17.6 Reactions of Alcohols

- Alcohols can be converted into alkyl halides directly by reaction with strong hydrogen halides. This works best for 3° alcohols.
- Conversion of 1° and 2° alcohols into alkyl halides commonly use thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3).
- To activate an alcohol in order to make the hydroxide a good leaving group, tosylates (toluenesulfonates) and mesylates (methanesulfonates) can be formed.
- Alcohols can be dehydrated by heating in strong acid solution to form an alkene.
- Alcohols react with acid chlorides to form esters.

17.7 Oxidation of Alcohols

- Primary and secondary alcohols can be oxidized with various chromium reagents, while tertiary alcohols are not.
- Secondary alcohols are oxidized to ketones.
- Primary alcohols are oxidized to carboxylic acids using chromium trioxide or dichromate compounds.

- Primary alcohols can be stopped in their oxidation at aldehydes by reacting with pyridinium chlorochromate or Dess-Martin periodinane.

17.8 Protection of Alcohols

- Protection of a functional group is useful when that functional group may interfere with an intended reaction.
- Protection converts a functional group into a non-interfering derivative molecule through a reaction that can be easily reversed to remove the protecting group.
- Protection consists of a series of reactions that include protect, perform intended reactions, and deprotect.
- Alcohols can be protected as silyl ethers by reacting with chlorotrialkyl silanes.

17.9 Phenols and Their Uses

- Phenols can be prepared from chlorobenzene or isopropylbenzene.
- Phenol and phenol derivatives (such as resorcinol) are used as germicides and antiseptics.
- Bisphenol A (BPA) has controversially been used to create polycarbonate plastics such as water bottles.

17.10 Reactions of Phenols

- Phenols can react with strong electrophiles (such as in Friedel-Crafts reactions).
- Phenols react with strong oxidizing agents including Jones reagent or silver oxide to form quinones.

17.11 Spectroscopy of Alcohols and Phenols

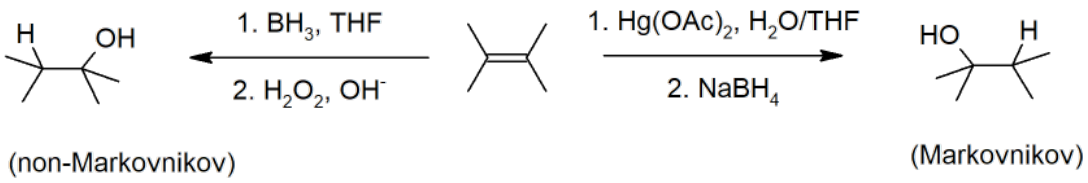
- Alcohols are among the most identifiable functional groups in infrared spectroscopy due to the strong, wide absorbance around 3400 cm^{-1}.
- Alcohol peaks are much more difficult to recognize in ^1H NMR, since OH hydrogens are relatively reactive and can exchange with hydrogens from the solvent, they are often weak absorptions without strong, sharp peaks.
- Hydroxide protons are not split in ^1H NMR.
- Loss of hydroxide in mass spectroscopy can lead to loss of a fragment with 17 m/z.

SKILLS TO MASTER

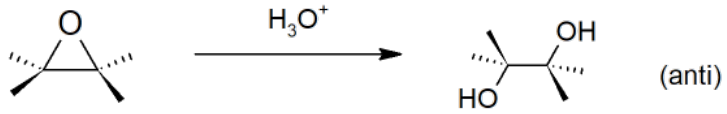
- Skill 17.1 Identify types of alcohols.
- Skill 17.2 Name molecules with hydroxide groups using IUPAC rules.
- Skill 17.3 Describe properties related to intermolecular forces (including hydrogen bonding).
- Skill 17.4 Explain acid-base properties of alcohols and phenols.
- Skill 17.5 Describe how additional functional groups affect the acidity of phenols.
- Skill 17.6 Draw mechanisms to form alcohols from alkyl halides.
- Skill 17.7 Draw mechanisms to form alcohols from alkenes.
- Skill 17.8 Draw mechanisms to form alcohols by reduction reactions.
- Skill 17.9 Draw mechanisms to form alcohols by reaction of carbonyl compounds with Grignard reagents (and other organometallics).
- Skill 17.10 Draw mechanisms for conversion of alcohols to alkyl halides.
- Skill 17.11 Draw mechanisms for conversion of alcohols to tosylates.
- Skill 17.12 Draw mechanisms for dehydration of alcohols to alkenes.
- Skill 17.13 Draw mechanisms for conversion of alcohols to esters.
- Skill 17.14 Draw mechanisms for oxidation of alcohols to aldehydes, ketones, and carboxylic acids.
- Skill 17.15 Write out syntheses that incorporate protection and deprotection of alcohols.
- Skill 17.16 Identify presence of alcohols by IR, NMR and MS.

SUMMARY OF REACTIONS

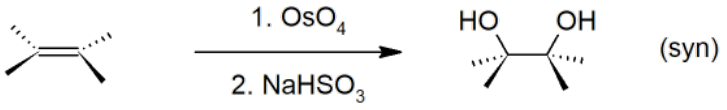
ALCOHOL PREPARATION (HYDROLYSIS)



(non-Markovnikov) (Markovnikov)

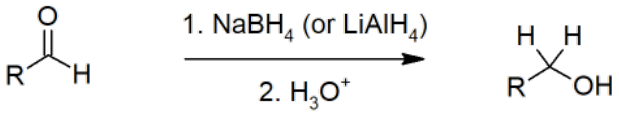


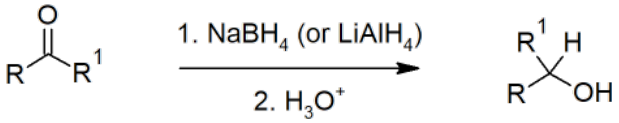
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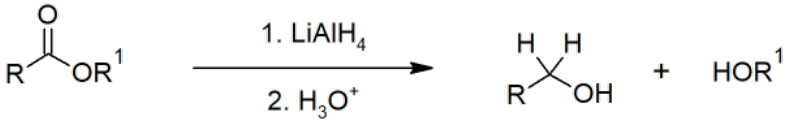


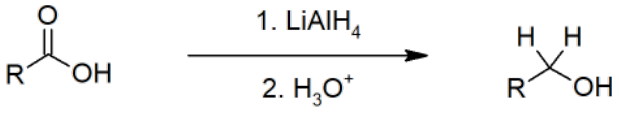
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ALCOHOL PREPARATION (REDUCING THE CARBONYL)



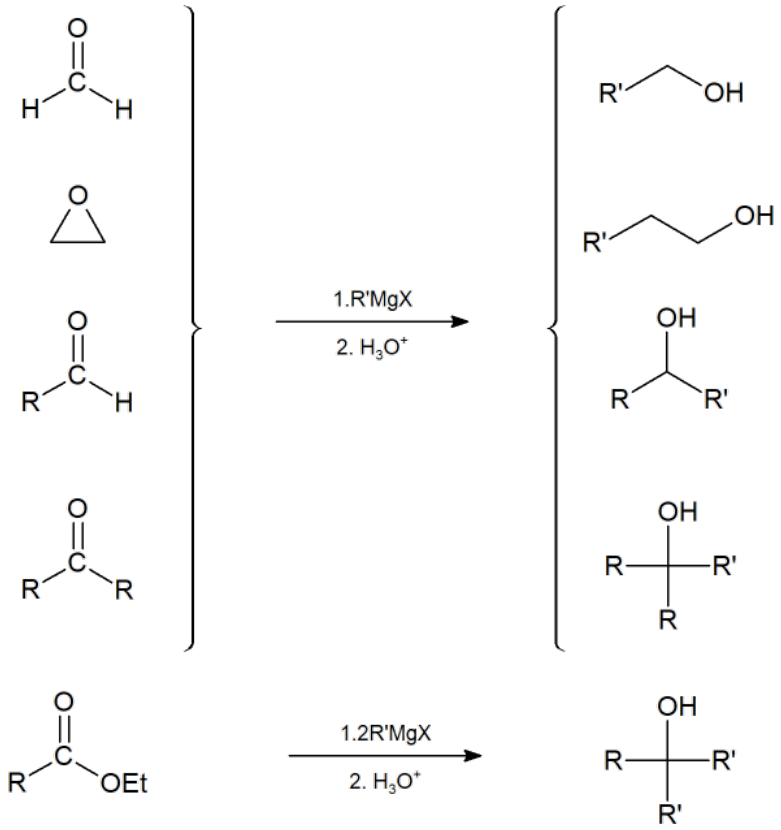




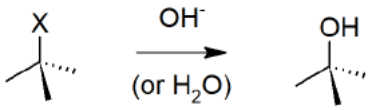


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ALCOHOL PREPARATION (GRIGNARD ADDITIONS)

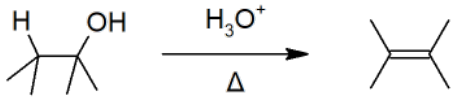


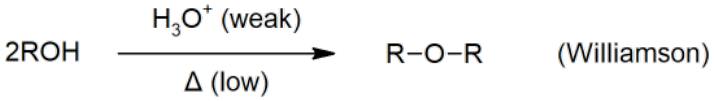
ALCOHOL PREPARATION (FROM ORGANOHALIDE)

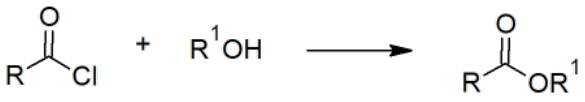


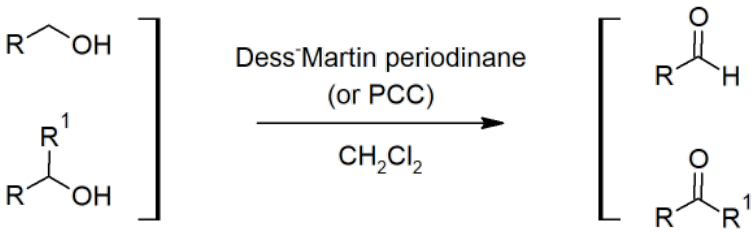
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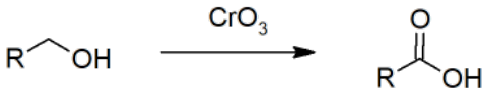
ALCOHOL REACTIONS



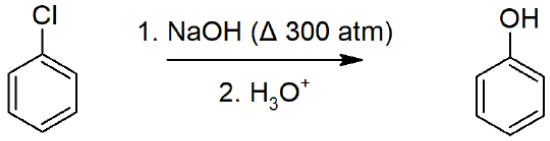


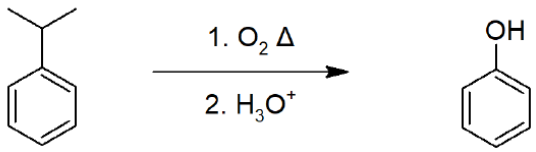






PHENOL PREPARATION





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CHAPTER OVERVIEW

18: ETHERS AND EPOXIDES; THIOLS AND SULFIDES

We shall begin in a very traditional manner, with a discussion of the nomenclature of ethers. We will then describe how ethers may be prepared in the laboratory, and discuss the relative inertness of these compounds. A discussion of the chemistry of cyclic ethers follows, with particular emphasis on the preparation and reactions of epoxides (cyclic ethers containing a three-membered ring). We will then introduce crown ethers—compounds that consist of large rings containing several oxygen atoms and the spectroscopic properties of ethers. The unit will close with a description of the chemistry of thiols and sulfides, the sulfur-containing analogues of alcohols and ethers.

18.0: Introduction
18.1: Names and Properties of Ethers
18.2: Preparing Ethers
18.3: Reactions of Ethers - Acidic Cleavage
18.4: Reactions of Ethers - Claisen Rearrangement
18.5: Cyclic Ethers - Epoxides
18.6: Reactions of Epoxides - Ring-opening
18.7: Crown Ethers
18.8: Thiols and Sulfides
18.9: Spectroscopy of Ethers
18.10: Interchapter - A Preview of Carbonyl Chemistry
18.S: Ethers and Epoxides; Thiols and Sulfides (Summary)

LEARNING OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis using one or more of the reactions introduced in this chapter, along with any number of the reactions you have studied to date.
- solve “road-map” problems that may require a knowledge of the chemistry of ethers, epoxides, thiols and sulfides, in addition to any of the material you have studied up to this point in organic chemistry.
- define, and use in context, the key terms introduced in this chapter.

CONTRIBUTORS AND ATTRIBUTIONS

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18.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to use the terms “ether,” “diethyl ether ” and “ethyl ether ” appropriately in context.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

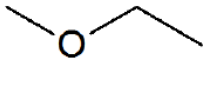
- ether (**R–O–R′**)
- sulfide (**R–S–R′**)
- thiol (**R–S–H**)

STUDY NOTES

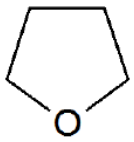
As defined in the textbook, an “ether” is a substance with the general formula (**R–O–R′**) where **R** and **R′** are alkyl, aryl, vinyl or allyl groups. However, the word “ether” is also commonly used to refer to the specific compound, **CH_3–CH_2–O–CH_2–CH_3**, which is correctly called “diethyl ether.” Further confusion can arise because some chemists refer to “diethyl ether ” as “ethyl ether.” In this course, “ether ” will be used to refer to the class of compounds with the structure (**R–O–R′**); diethyl ether will refer to the compound, **CH_3–CH_2–O–CH_2–CH_3**; and “ethyl ether ” will not be used.

ETHERS AND EPOXIDES

While the general formula for ethers is R-O-R′, keep in mind that there also cyclic ethers like tetrahydrofuran (a common organic solvent) or even epoxides which you first encounter in Section 8.7 in synthesizing diols from alkenes.



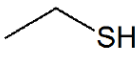
ethyl methyl ether



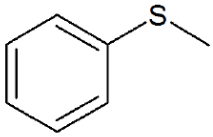
tetrahydrofuran

THIOLS AND SULFIDES

Thiols (thio alcohols or mercaptans) and sulfides (thioethers) are the sulfur analogues of alcohols and ethers and have the general formulas of R-S-H and R-S-R′, respectively.



ethanethiol



methyl phenyl sulfide

CONTRIBUTORS AND ATTRIBUTIONS

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18.1: NAMES AND PROPERTIES OF ETHERS

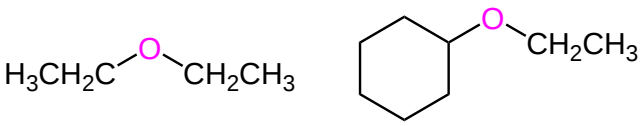
OBJECTIVES

After completing this section, you should be able to

1. write two acceptable names for a simple dialkyl ether, given its Kekulé, shorthand or condensed structure.
2. name a complicated ether by the IUPAC system, given its Kekulé, shorthand or condensed structure.
3. draw the Kekulé, condensed or shorthand structure of an ether, given an acceptable name.
4. explain why the boiling point of an ether is generally higher than that of an alkane of similar molecular mass.

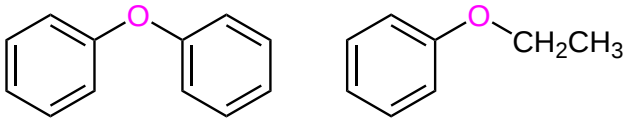
STRUCTURE OF ETHERS

Ethers are a class of organic compounds that contain an sp^3 hybridized oxygen between two alkyl groups and have the formula R-O-R'. These compounds are used in dyes, perfumes, oils, waxes and other industrial uses. Aliphatic ethers have no aryl groups directly attached to the ether oxygen.



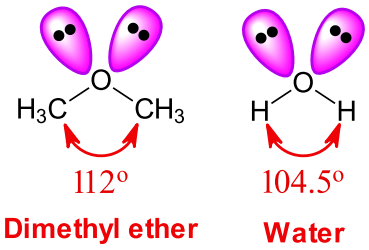
Examples of Aliphatic Ethers

Aromatic ethers have at least one aryl ring directly attached to the ether oxygen. In aryl ethers, the lone pair electrons on oxygen are conjugated with the aromatic ring which significantly changes the properties of the ether.

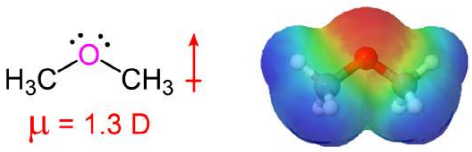


Example of Aromatic Ethers

The sp^3 hybridization of oxygen gives ethers roughly the same geometry as alcohols and water. The R-O-R' bond angle is close to what is expected in a tetrahedral geometry. The bond angle of dimethyl ether is 112° which is larger than the H-O-H bond angle in water (104.5°) due to the steric repulsion of the methyl groups.



The presence of an electronegative oxygen atom gives ethers a small dipole moment with the electron density primarily on oxygen (red and orange in the electrostatic potential map).



COMPARISONS OF PHYSICAL PROPERTIES OF ALCOHOLS AND ETHERS

Ethers, unlike alcohols, have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore, there is no intermolecular hydrogen bonding between ether molecules, which makes their boiling points much lower than an alcohol with similar mass. Despite the presence of a

small dipole moment, ethers have boiling points that are about the same as alkanes of comparable molar mass. (Table 18.1.1).

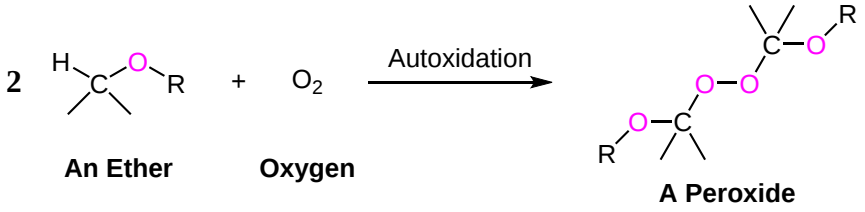
Table 18.1.1 : Comparison of Boiling Points of Alkanes, Alcohols, and Ethers

Condensed Structural Formula	Name	Molar Mass	Boiling Point (°C)	Intermolecular Hydrogen Bonding in Pure Liquid?
$CH_3CH_2CH_3$	propane	44	–42	no
CH_3OCH_3	dimethyl ether	46	–25	no
CH_3CH_2OH	ethyl alcohol	46	78	yes
$CH_3CH_2CH_2CH_2CH_3$	pentane	72	36	no
$CH_3CH_2OCH_2CH_3$	diethyl ether	74	35	no
$CH_3CH_2CH_2CH_2OH$	butyl alcohol	74	117	yes

Ether molecules do have an oxygen atom, however, and engage in hydrogen bonding with water molecules. Consequently, an ether has about the same solubility in water as the alcohol that is isomeric with it. For example, dimethyl ether and ethanol (both having the molecular formula C_2H_6O) are completely soluble in water, whereas diethyl ether and 1-butanol (both $C_4H_{10}O$) are barely soluble in water (8 g/100 mL of water).

PEROXIDE FORMATION

Many ethers can react with oxygen to form explosive peroxide compounds n a free radical process called autoxidation. For this reason ethers should not be stored for long periods of time and should not be stored in glass bottles. The danger is particularly acute when ether solutions are distilled to near dryness. The hydroperoxides can become more concentrated during a distillation because they tend to have a slightly higher boiling point than the corresponding ether. Before performing an ether distillation great care should be taken to test for the presence of peroxides.

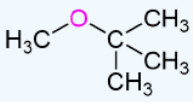


An Ether **Oxygen** **A Peroxide**

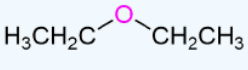
NAMING ETHERS

When no other functional group is present, simple ethers are often given common functional class names. Both alkyl groups attached to the oxygen atom are named as substituents (in alphabetical order) and then the word *ether* is added. The common names for alkyl substituents discussed in **Section 3.3** are often used.

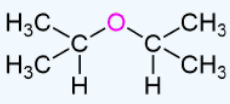
EXAMPLE 18.1.1



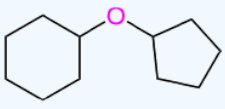
Methyl *tert*-butyl ether



Diethyl ether



Diisopropyl ether



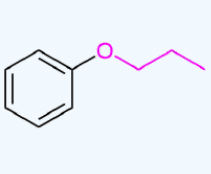
Cyclohexyl cyclopentyl ether

IUPAC nomenclature for ethers should be used for complicated ethers, compounds with more than one ether linkage, and compounds where other functional groups are present with an ether. In these cases, an RO group of the ether is named as an alkoxy substituent. Common alkoxy substituents are given names derived from their alkyl component. The suffix *-yl* is replaced with *-oxy*. (Table 18.1.2):

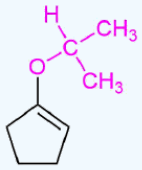
Table 18.1.2 : Common Alkyl and Alkoxy Groups

Alkyl Group	Name	Alkoxy Group	Name
CH_3–	Methyl	CH_3O–	Methoxy
CH_3CH_2–	Ethyl	CH_3CH_2O–	Ethoxy
$(CH_3)_2CH$–	Isopropyl	$(CH_3)_2CHO$–	Isopropoxy
$(CH_3)_3C$–	tert-Butyl	$(CH_3)_3CO$–	tert-Butoxy
C_6H_5–	Phenyl	C_6H_5O–	Phenoxy

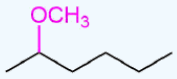
EXAMPLE 18.1.2



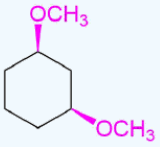
Propoxybenzene



1-Isopropoxycyclopentene



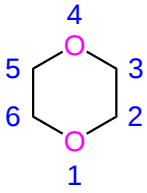
2-Methoxyhexane



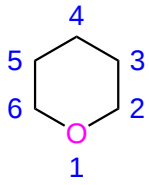
Cis-1,3-Dimethoxycyclohexane

CYCLIC ETHERS

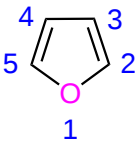
Cyclic ethers are a type of heterocycle with one or more oxygens located in the ring. Many cyclic ethers have common names and are often used as solvents due to their inert nature. These ring structures are also found in many biological molecules such as sugars and DNA. The rings are numbered so that an oxygen gets position 1.



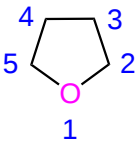
Dioxane



Tetrahydropyran

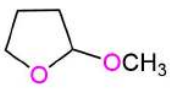


Furan

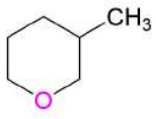


Tetrahydrofuran

EXAMPLE 18.1.3



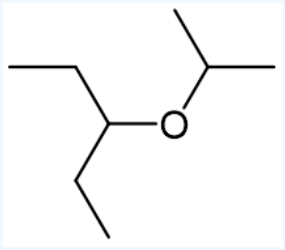
2-Methoxytetrahydrofuran



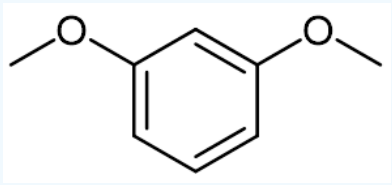
3-Methyltetrahydropyran

EXERCISE 18.1.1

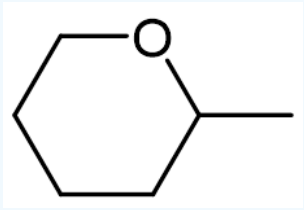
Name the following ethers:



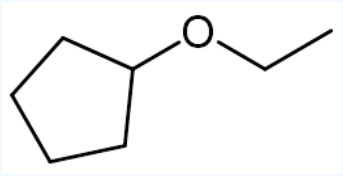
b)



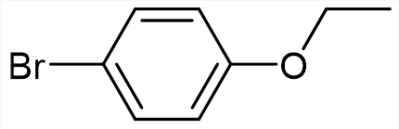
c)



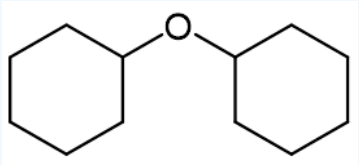
d)



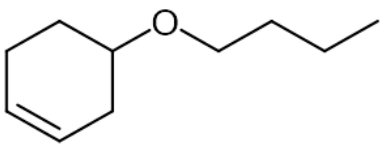
e)



f)



g)



Answers

a) 3-Isopropoxypentane

b) 1,3-Dimethoxybenzene

c) 2-Methyltetrahydropyran

d) Cyclopentyl ethyl ether

e) 4-Bromo-1-ethoxybenzene

f) Dicyclohexyl ether

g) 4-Butoxycyclohexene

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18.2: PREPARING ETHERS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the industrial preparation of simple symmetrical ethers.
2. write an equation to illustrate the Williamson synthesis of ethers.
   a. identify the ether obtained from the reaction of a given alkyl halide with a given alkoxide ion.
   b. identify the reagents needed to prepare a given ether through a Williamson synthesis.
   c. identify the limitations of the Williamson synthesis, and make the appropriate choices when deciding how best to synthesize a given ether.
   d. write an equation to describe the formation of an alkoxide from an alcohol.
   e. identify silver(I) oxide as a reagent which can be used in a Williamson synthesis.
3. write an equation to show how an ether can be prepared by the alkoxymercuration-demercuration of an alkene.
   a. identify the product formed from the alkoxymercuration-demercuration of a given alkene.
   b. identify the alkene, the reagents, or both, needed to prepare a given ether by the alkoxymercuration-demercuration process.
   c. write the detailed mechanism of the reaction between an alkene, an alcohol and mercury(II) trifluoroacetate.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alkoxymercuration
- oxymercuration
- Williamson ether synthesis

STUDY NOTES

We studied oxymercuration as a method of converting an alkene to an alcohol in Section 8.5. “Alkoxymercuration” is a very similar process, except that we are now converting an alkene into an ether. The two processes are compared below.

Description	oxymercuration	alkoxymercuration
we react an	alkene	alkene
with	water	an alcohol
in the presence of	$Hg(O_2CCH_3)_2$	$Hg(O_2CCF_3)_2$
followed by treatment with	$NaBH_4$	$NaBH_4$
to produce an	alcohol	ether

Review the mechanism of the oxymercuration reaction in Section 8.5, paying particular attention to the regiochemistry and the stereochemistry of the reaction. The mechanism is identical to alkoxymercuration.

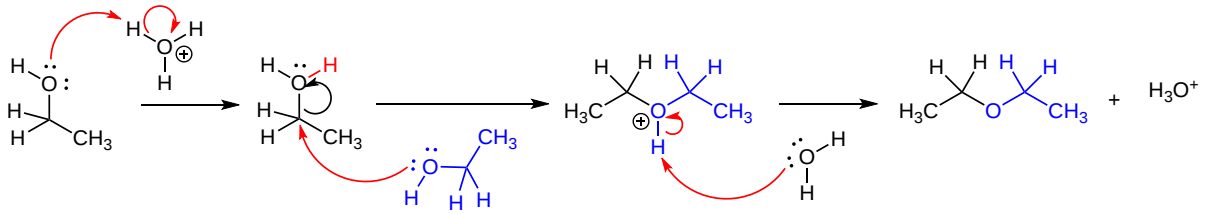
ETHER FORMATION THOUGH DEHYDRATION

Acid-catalyzed dehydration of small 1º-alcohols constitutes a specialized industrial method of preparing symmetrical ethers. This reaction **cannot** be employed to prepare unsymmetrical ethers because a mixture of products is likely to be obtained. Also, 2º and 3º alcohols cannot be used for this reaction because they dehydrate to form alkenes by an E1 mechanism (**Section 17-6**).

$$2\,CH_3CH_2{-}OH + H_2SO_4 \xrightarrow{130\ ^\circ C} CH_3CH_2{-}O{-}CH_2CH_3 + H_2O \qquad (18.2.1)$$

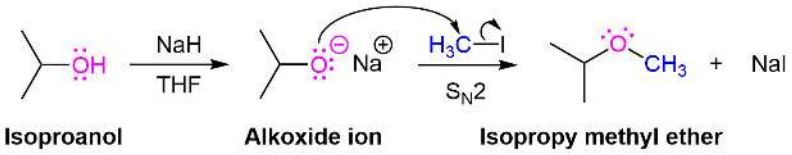
MECHANISM

In the first step of the reaction mechanism, one alcohol is protonated to become a good leaving group. In the second step, a second alcohol displaces water from the protonated alcohol during an S_N2 reaction yielding a protonated ether. In the final step, this intermediate is deprotonated to yield the symmetrical ether.



WILLIAMSON ETHER SYNTHESIS

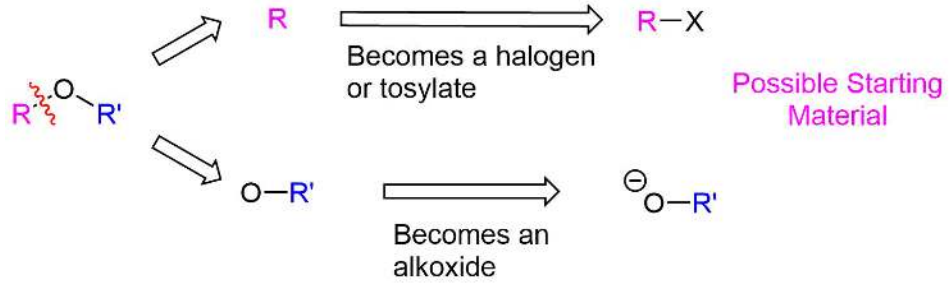
One important procedure, known as the **Williamson Ether Synthesis**, proceeds by an S_N2 reaction of an alkoxide nucleophile with a primary alkyl halide or tosylate. As previously discussed in **Section 17-2**, alkoxides are commonly created by deprotonating an alcohol with a strong base, such as sodium hydride (NaH). Simple alcohols can be used a solvent during a Williamson ether synthesis and with their alkoxide created through the addition of sodium metal ($Na_{(s)}$).



PLANNING A WILLIAMSON ETHER SYNTHESIS

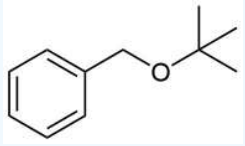
The Williamson ether synthesis has the same limitations as other S_N2 reactions, as discussed in **Section 11-3**. Since alkoxide anions are strong bases, utilizing 2° or 3° halogen leaving groups could possibly produce an E2 elimination product. When considering the synthesis of an unsymmetrical ether, there are two different combinations of reactants possible and each should be carefully considered. In general, the pathway which utilizes the least sterically hindered halogen will be preferred.

The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alkoxide. The other fragment will become a halogen or tosylate.



? WORKED EXAMPLE 18.2.1

How would you prepare the following molecule using a Williamson Ether Synthesis?

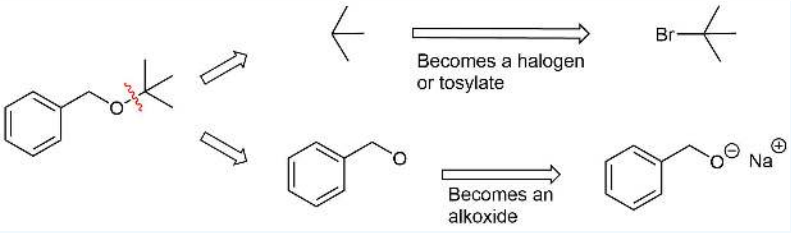


Answer

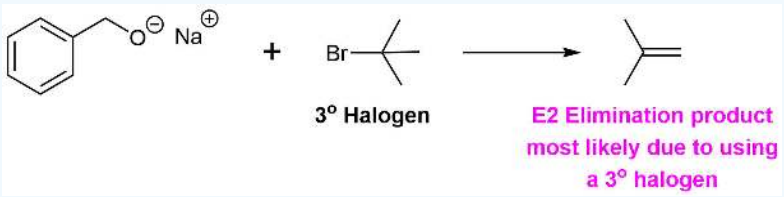
Analysis: The ether is asymmetrical so each of the C-O bonds can be broken to create a different set of possible reactants. After cleavage of the C-O bond, pathway 1 shows a 3° halogen as the starting material. This reaction will most likely not be effective due to alkoxides reacting with 3° halogens to preferable form an alkenes by E2 elimination. Pathway 2 shows a 1° halogen as a starting material which is favorable for S_N2 reactions.

Pathway 1

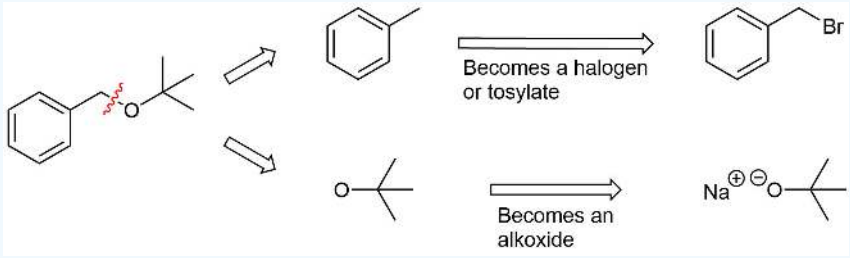
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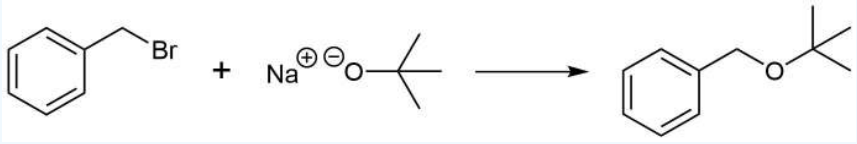
Solution 1



Pathway 2

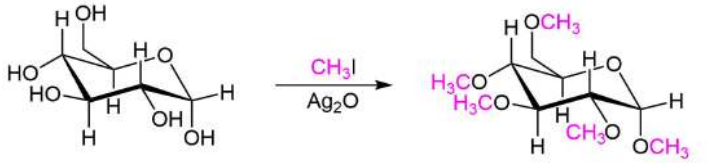


Solution 2



ETHER SYNTHESIS USING SILVER OXIDE

A variation of the Williamson ether synthesis uses silver oxide (Ag_2O) in the place of the strong base. The conditions of this variation are milder than the typical Willamson synthesis because a strong base and the formation of an alkoxide intermediate are not necessary. This reaction is particually useful when converting the -OH groups on a sugar into ethers.



α-D-Glucopyranose

Methyl 2,3,4,6-tetra-*O*-methyl-α-D-Glucopyranoside

MECHANISM

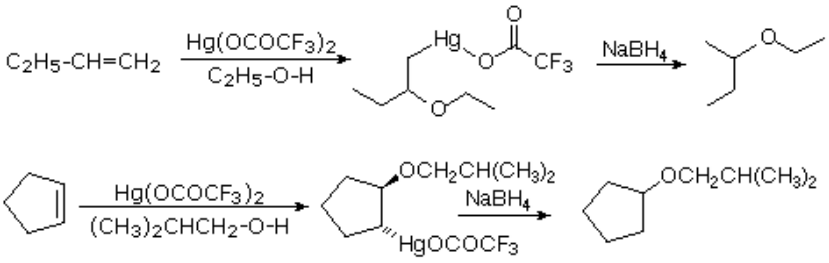
During this reaction a partial positively charged silver in Ag_2O gives draws electron density from the iodine in CH_3I. This correspondingly removes electron density from the adjacent carbon increasing its partial positive charge which increases its electrophlicity. This allows the alcohol to act as a nucleophile in the subsequent S_N2 reaction.



Alcohol Polarized C-I Bond Ether

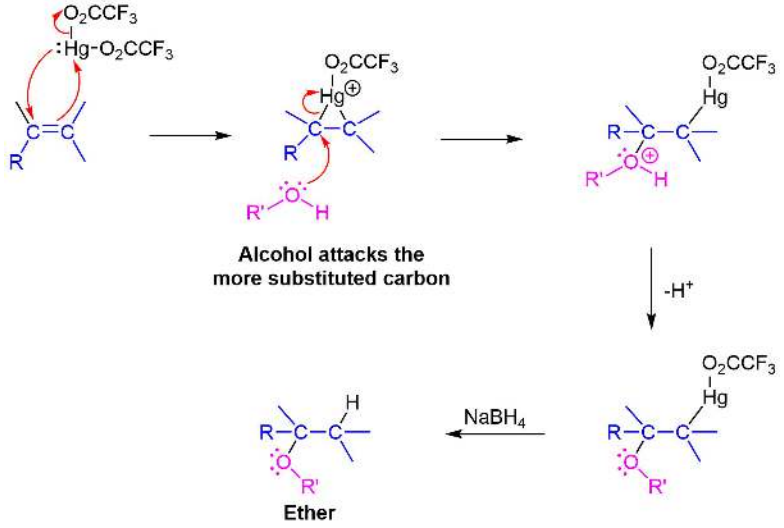
ETHER SYNTHESIS USING ALKOXYMERCURATION

Alkoxymercuration, is patterned after the oxymercuration reaction discussed in Section 8-4. Reaction of an alkene with an alcohol in the presence of a trifluoroacetate mercury (II) salt [$(CF_3CO_2)_2Hg$] prodcues an alkoxymercuration product. Demercuration using sodium borohydride ($NaBH_4$) yields an ether product. Overall, this reaction allows for the Markovnikov addition of an alcohol to an alkene to create an ether. Note that the alcohol reactant is used as the solvent, and a trifluoroacetate mercury (II) salt is used in preference to the mercuric acetate (trifluoroacetate anion is a poorer nucleophile than acetate). Most 1°, 2°, 3° alcohols can be successfully used for this reaction.



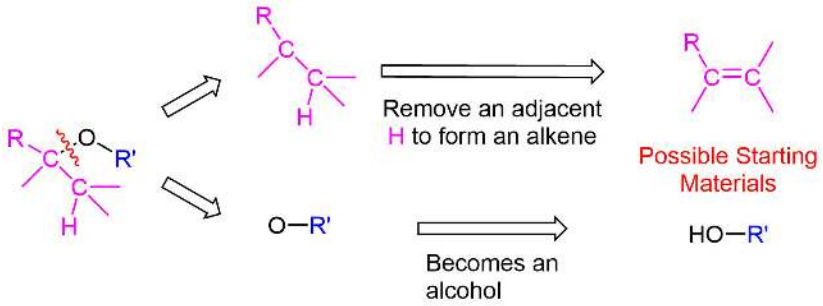
MECHANISM

The mechanism of alkoxymercuration is similar to that of oxymercuration, with electrophillic addition of the mercuric species to the alkene. The alcohol nucleophile attacks the more substituted carbon of the three-membered ring via a S_N2 reaction. Finally, sodium borohydride ($NaBH_4$) provides a reductive demercuration to form the ether product.



PLANNING THE SYNTHESIS OF AN ETHER USING ALKOXYMERCURATION

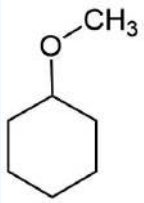
The key bond cleavage in the target molecule involves a C-O bond. Because unsymmetrical ethers have two unique C-O bonds, each can be broken to provide a unique set of reactants. After cleavage, the fragment with the oxygen will become an alcohol. The alkyl fragment will lose a hydrogen from a adjacent carbon to form an alkene. The main point to consider when choosing a possible synthesis pathways is the ability of the alkyl fragment to form an alkene.



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WORKED EXAMPLE 18.2.2

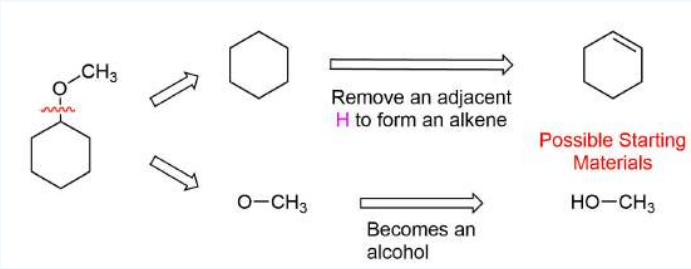
How would you prepare the following molecule using a alkoxymercuration?



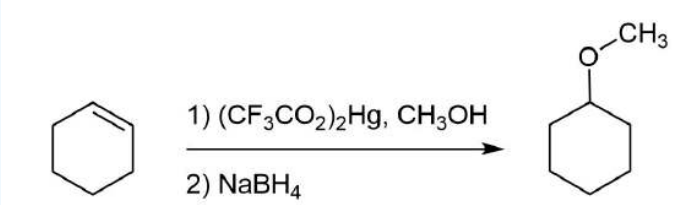
Answer

Analysis: The ether is symmetrical so each C-O bond of the ether can be cleaved to produce a set of starting materials for consideration. Pathway one shows a set of starting material which should work well for this reaction. The alcohol, methanol, can easily be used as a solvent. Although the alkene does not have a defined more and less substituted side, its symmetry will prevent a mixture of product from forming. The fragmentation for pathway 2 shows starting material which are not viable for this reaction. The alkyl fragment only has one carbon which cannot be used to form an alkene starting material. This means pathway 2 is not a viable method for the synthesis of the target molecule.

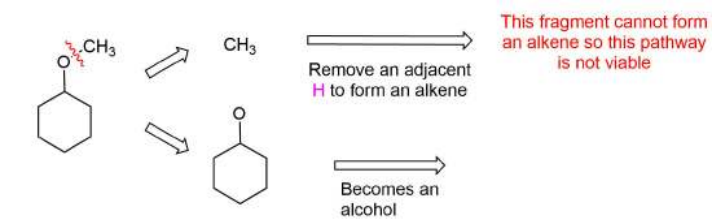
Pathway 1



Solution 1



Pathway 2



EXERCISE 18.2.1

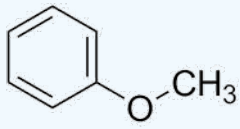
When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

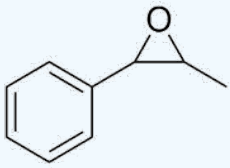
Answer

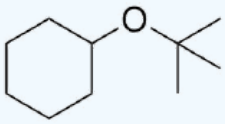
The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions from occurring. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions from occurring.

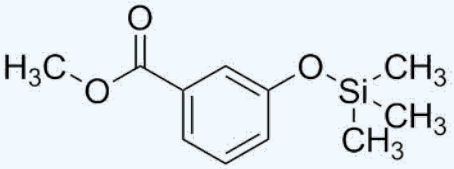
EXERCISE 18.2.2

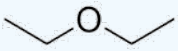
How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

(c) 

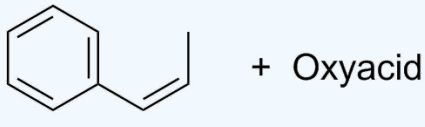
(d) 

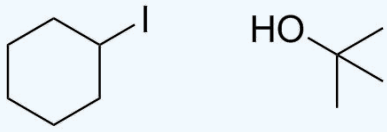
(e) 

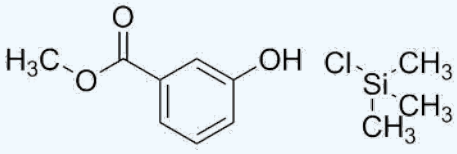
Answer

The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

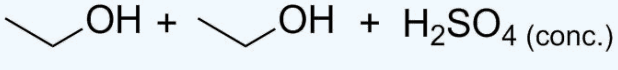
(a) 

(b) 

(c) 

(d) 

Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

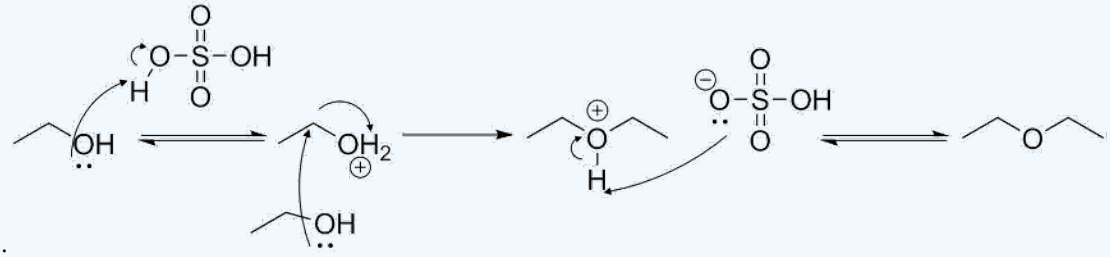
(e) 

EXERCISE 18.2.3

Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer

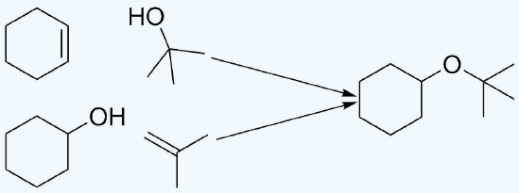
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EXERCISE 18.2.4

t-butoxycyclohexane can be prepared two different ways from an alkene and an alcohol, draw both possible reactions.

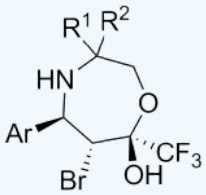
Answer



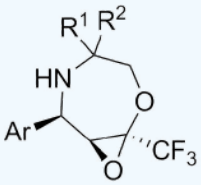
While both are possible, the top route is likely easier because both starting materials are a liquid.

EXERCISE 18.2.5

Epoxides are often formed intramolecularly. Take for example this large ring, in a publication from 2016 [*J. Org. Chem.*, **2016**, *81 (20)*, pp 10029–10034]. If subjected to base, what epoxide would be formed? (Include stereochemistry)



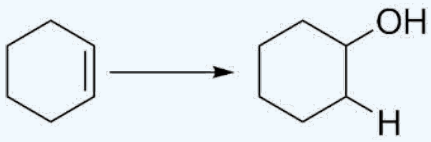
Answer



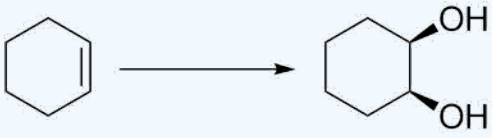
EXERCISE 18.2.6

What reagents would you use to perform the following transformations?

(a)



(b)

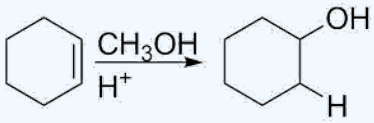


(c)

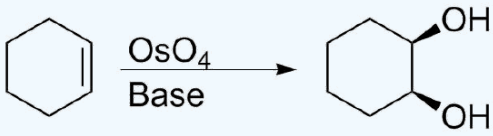


Answer

(a)

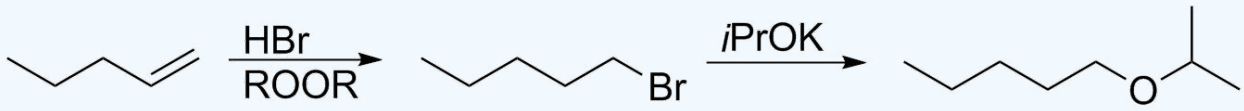


(b)



Note the cis addition

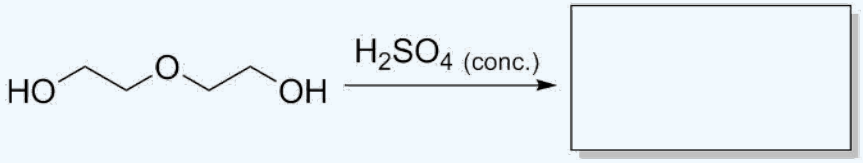
(c)



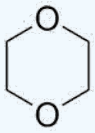
An oxidation to an alcohol through hydroboration, and subsequent substitution with 2-bromopropane could also work, but this route provides the least likelihood of an elimination reaction occurring.

? EXERCISE 18.2.7

Predict the product of the following.



Answer



The result is the production of dioxane, a common solvent.

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18.3: REACTIONS OF ETHERS - ACIDIC CLEAVAGE

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the acidic cleavage of an ether.
2. identify the products formed when a given ether is cleaved by a strong acid.
3. identify the reagent needed to bring about cleavage of a given ether.
4. deduce the structure of an unknown ether, given the products of acidic cleavage of the ether.
5. write the detailed mechanism for the acidic cleavage of a given ether.

STUDY NOTES

There are a number of points in this section that require additional explanations.

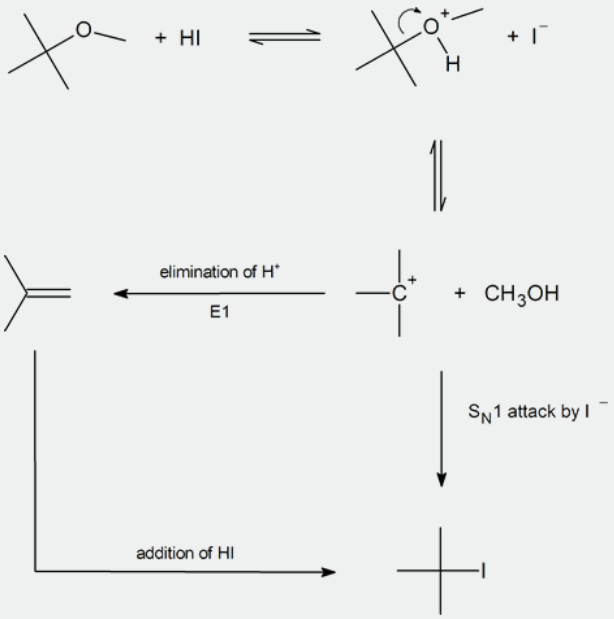
First, if an excess of HI (or HBr) is used in the cleavage reaction, the alcohol formed is converted by a nucleophilic substitution reaction to the appropriate alkyl halide:

$$\mathrm{ROH + HI \longrightarrow RI + H_2O}$$

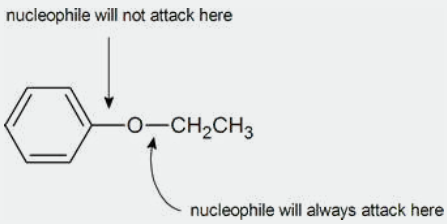
In view of this substitution, some textbooks simplify the overall cleavage process as:

$$\mathrm{R{-}O{-}R' + 2\,HI \longrightarrow RI + R'I + H_2O}$$

Second, we should consider in detail how certain ethers (those containing tertiary alkyl, benzyl or allyl groups) cleave by an S_N1 mechanism:



Finally, notice that an aryl alkyl ether will always produce a phenol and an alkyl halide, never an aryl halide and an alcohol. This is because we rarely see a nucleophile attacking an aromatic ring carbon in preference to an aliphatic carbon:



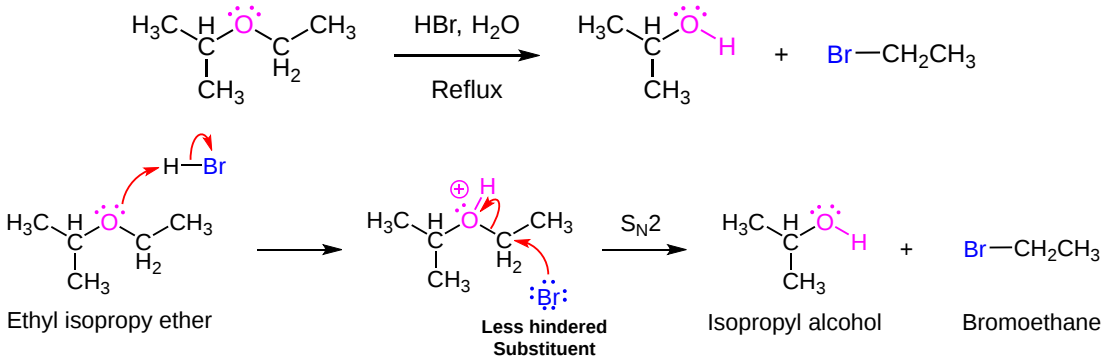
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As phenols do not undergo nucleophilic substitution reactions, even if an excess of HX is used, the products from the cleavage of an aryl alkyl ether are a phenol and an alkyl halide. Diaryl ethers are not cleaved by acids.

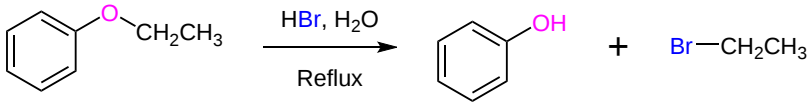
Ethers are known to be unreactive towards most reagents which makes them excellent reaction solvents. The most common reaction of ethers is cleavage of the C–O bond by using strong acids. During acidic cleavage the ether oxygen is protonated to form a good leaving groups which can be eliminated as part of an S_N2, S_N1, or E1 reaction mechanism. The mechanistic pathway is primarily determined by the strong acid used and the type of substituents attached to the ether.

ACIDIC CLEAVAGE OF ETHERS

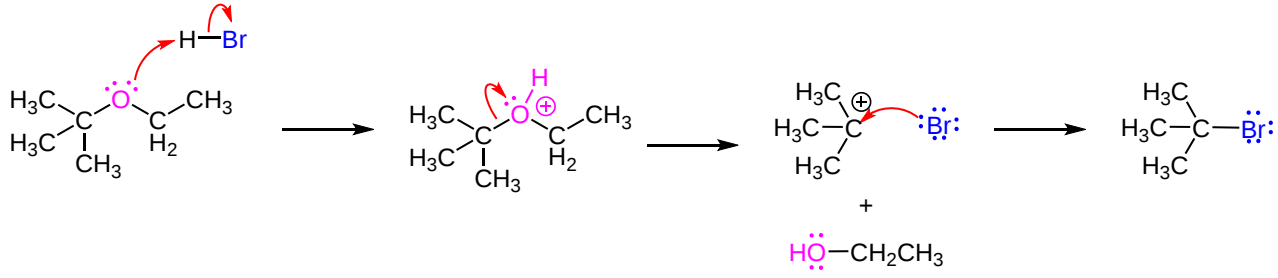
Aqueous solutions of HBr or HI (but not HCl) tend to cleave ethers into alcohol and an alkyl halide product by either an S_N2 or S_N1 mechanism. If the ether is attached to only primary, secondary, or methyl alkyl groups, a selective cleavage will typically take place using an S_N2 mechanism. First, the strong acid protonates the ether oxygen. Then resulting halide conjugate base attacks the protonated ether at the less sterically hindered alkyl substituent forming a halogen product. The ether's more sterically hindered alkyl substituent is ejected as a leaving group and forms an alcohol product. The example below show that when ethyl isopropyl ether is cleaved with hydrobromic acid the products isopropyl alcohol and bromoethane are produced. The bromide nucleophile preferably attacks the ether's ethyl substituent because it is less hindered (1°) than the isopropyl substituent (2°).



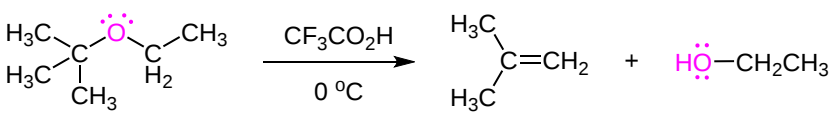
It is important to note that a phenyl substituent on an ether is not capable of participating in the S_N2 reaction of an acidic cleavage. If a phenyl group is present it will become a phenol in the product due to the halide nucleophile preferably attacking the other alkyl substituent.



When using HBr or HI, the acidic cleavage of ethers with tertiary, benzylic, or allylic substituents tend to occur by an S_N1 mechanism. The ability of these substituents to produce relatively stable carbocations promotes the S_N1 mechanism. The change in mechanism causes the tertiary, benzylic, or allyic group to preferably become the halogen product of the acidic cleavage. This makes the ether's other alkyl substituent become the alcohol product.

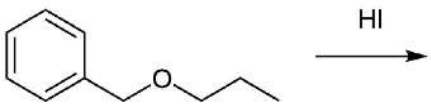


When using a strong acid whose conjugate base is a poor nucleophile, such as trifluoroacetic acid (CF_3CO_2H), for the the acidic cleavage of an ether with a tertiary alkyl substituent, the mechanism will often be E1. In this case the tertiary alkyl substituent will lose an adjacent hydrogen to form an alkene product. The ether's other alkyl substituent will form an alcohol product.



WORKED EXAMPLE 18.3.1

Predict the products of the following reaction:



Answer

Analysis: When considering the acidic cleavage of ethers it is important to realize that S_N2, S_N1, or E1 reactions are possible depending on the conditions. First, identify if the ether has a substituent which can easily form a carbocation: tertiary, benzylic, or allylic substituents. If none of these substituents are present the reaction will most likely be S_N2. However, if one of the substituents is present the reaction will most likely be S_N1 or E1. Next, identify if the reaction conditions will allow for an E1 reaction. These are the presence of a tertiary alkyl substituent on the ether along with the use of a strong acid which has a poor nucleophile as a conjugate base. If this set of conditions is not present the reaction will most likely be S_N1.

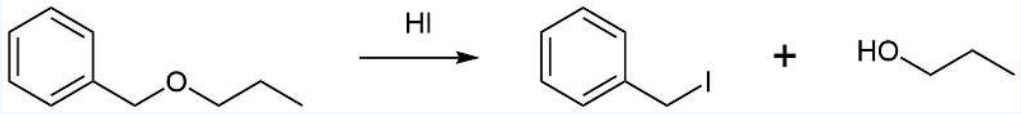
For a S_N2 reaction: The less hindered alkyl substituent of the ether will become a halogen. The other alkyl substituent will become an alcohol.

For a S_N1 reaction: The substituent which easily forms a carbocation will become a halogen and the other alkyl substituent will become an alcohol.

For an E1 reaction: The tertiary alkyl substutent will form an alkene and the other alkyl substiutent will become an alcohol.

For the reaction proposed above, the reactant contains a benzylic substituent so the reaction will most likely be S_N1. Consequently, the benzylic substituent will become and Iodide product and the propyl substituent will become an alcohol.

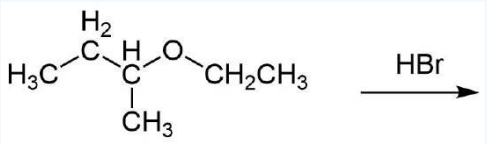
Solution



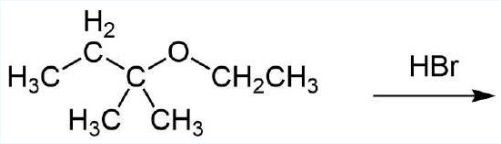
EXERCISES 18.3.1

1) Predict the product of the following reactions:

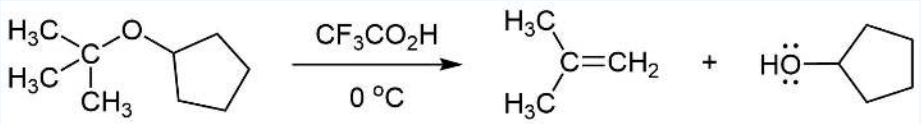
a)



b)



2) Please draw the mechanism for the following reaction:

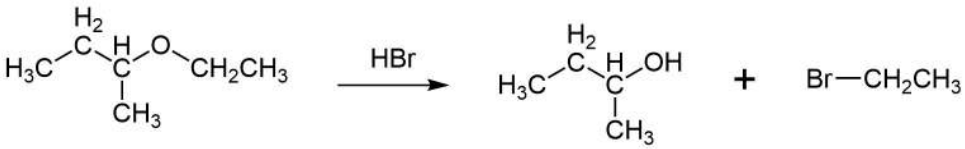


3) Why is HCl less effective at cleaving ethers than HBr or HI?

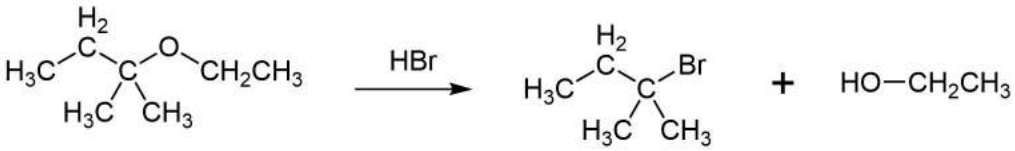
Answer

1)

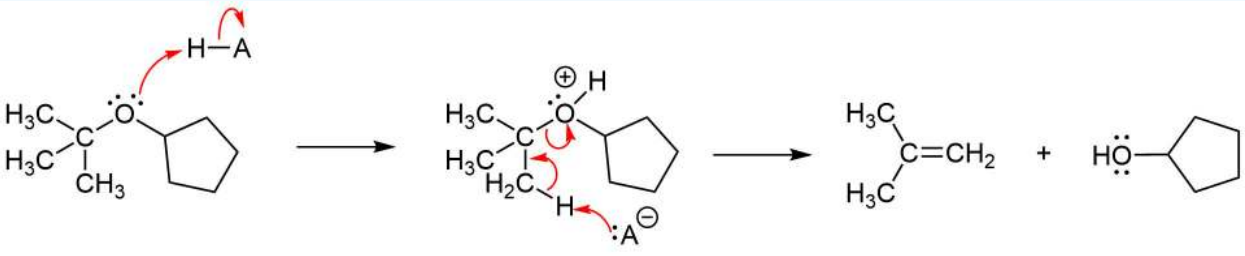
a)



b)



2)



3) HCl's conjugate base Cl^- is a poor nucleophile when compared to Br^- and I^-. The chloride anion is not a strong enough nucleophile to promote the acidic cleavage of ethers.

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18.4: REACTIONS OF ETHERS - CLAISEN REARRANGEMENT

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the Claisen rearrangement of allyl phenyl ester.
2. account for the formation of a specific product from a Claisen rearrangement, without giving mechanistic details.

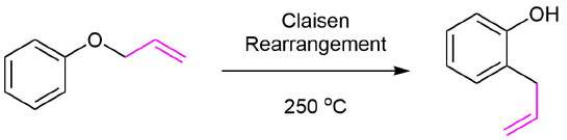
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Claisen rearrangement

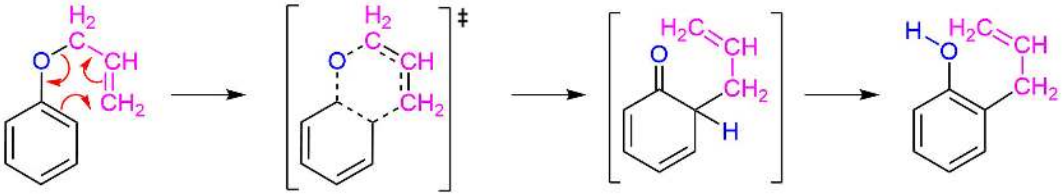
CLAISEN REARRANGEMENTS

The Claisen rearrangement is a key organic reaction that involves the thermal rearrangement of allyl vinyl ethers to form β-aryl allyl ethers. This reaction is specific to ally aryl ethers and allyl vinyl ethers. Heating an allyl aryl ether to 250 ^{o}C causes an intramolecular rearrangement to produce an *o*-allylphenol.



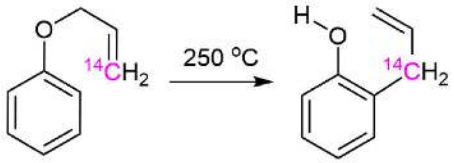
Allyl phenyl ether **o-Allylphenol**

The Claisen rearrangement takes place through a concerted mechanism in which a C-C bond forms between the C3 of the allyl group and the ortho position of the benzene ring at the same time that the C-O bond of the ether breaks. This rearrangement initially produces the non-aromatic 6-allyl-2,4- cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the concerted movement of six bonding electrons in the first step. The presence of six electrons in a ring suggests that the transition state may have aromatic characteristics. The Claisen rearrangement is part of a broader class of reactions called sigmatropic rearrangements which will be discussed in more detail in **Section 30-8**.



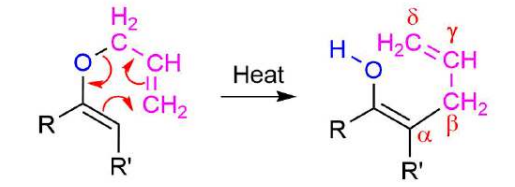
Transition State **Intermediate**

Evidence for this mechanism was provided by performing the rearrangement with allyl group with a ^{14}C label at C3. The product of this reaction was shown to have the ^{14}C labeled carbon exclusively bonded to the ring.



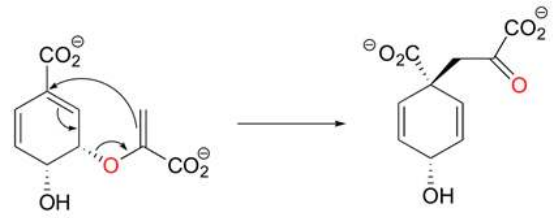
Only Product

Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



An allyl vinyl ether — A γ,δ-unsaturated Ketone

Claisen rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.

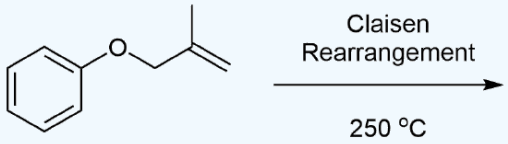


chorismate — prephenate

EXERCISE 18.4.1

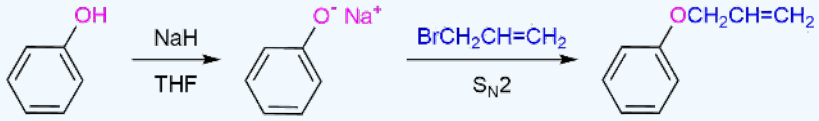
1) Show how you could synthesize allyl phenyl ether from allyl bromide and phenol.

2) What would be the expected product of the following Claisen rearrangement?

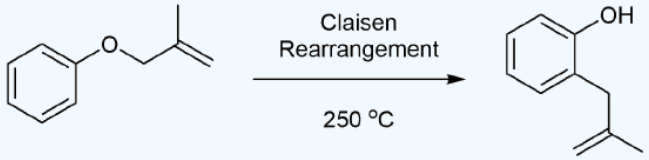


Answer

1)



2)



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18.5: CYCLIC ETHERS - EPOXIDES

OBJECTIVES

After completing this section, you should be able to

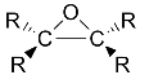
- write an equation to describe the industrial preparation of ethylene oxide.
- list two important industrial uses of ethylene oxide.
- write an equation to describe the normal laboratory preparation of an epoxide.
- identify the epoxide produced from the reaction of a given alkene with a peroxyacid.
- identify the alkene, the reagent, or both, needed to prepare a given epoxide.
- write an equation to describe the preparation of an epoxide from an alkene via a halohydrin.

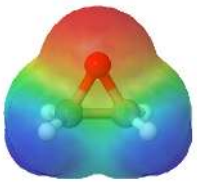
KEY TERMS

Make certain that you can define, and use in context, the key term below.

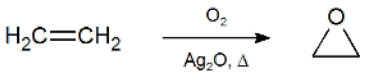
- epoxide (oxirane)

Epoxides (also known as **oxiranes**) are three-membered ring structures in which one of the vertices is an oxygen and the other two are carbons. Epoxides behave differently than other ethers due to the strain created by the three-membered ring.



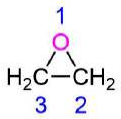


The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air. Ethylene oxide is used as an important chemical feedstock in the manufacturing of ethylene glycol, which is used as antifreeze, liquid coolant and solvent. In turn, ethylene glycol is used in the production of polyester and polyethylene terephthalate (PET) the raw material for plastic bottles.



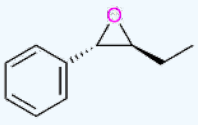
NOMENCLATURE OF EPOXIDES

The name ethylene oxide is not systematic but common. Epoxides are systematically named as an oxirane ring system much like the other cyclic ethers discussed in Section 18.1. The oxygen is numbered in the 1 position.



Oxirane

EXAMPLE 18.5.1



trans-2-Ethyl-3-phenyloxirane



cis-2,3-Dimethyloxirane

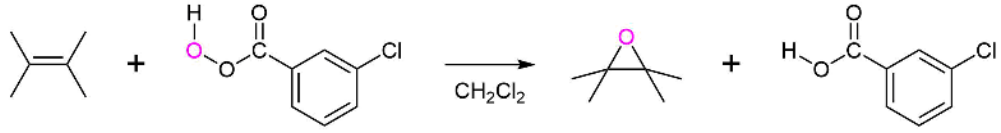


2,2-Dimethyloxirane

SYNTHESIS OF EPOXIDES

As discussed in Section 8-7, epoxides are typically prepared by the reaction of an alkene and a peroxycarboxylic acid (RCO_3H), such as *meta*-chloroperbenzoic acid (MCPBA). The peroxycarboxylic acid has the unique property of having an electropositive oxygen atom on the CO_3H group. The reaction is initiated by the electrophilic oxygen atom reacting with the nucleophilic carbon-carbon double bond. The mechanism involves a concerted reaction with a four-part, circular transition state. The result is that the originally electropositive oxygen atom ends up in the oxacyclopropane ring and the CO_3H group becomes CO_2H.

General Reaction

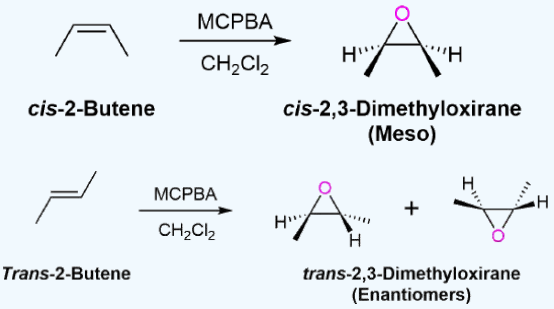


Alkene | *meta*-Chloroperoxy-benzoic acid (MCPBA) | Epoxide | *meta*-Chloro-benzoic acid

Stereochemical Consideration

The oxygen addition to the alkene is a syn addition and is stereospecific. The substituents of a *cis*-alkene will appear in the *cis* configuration on the epoxide ring. Likewise, Substituents of a *trans*-alkene will appear in the *trans* configuration on the epoxide ring. During this reaction the sp^2 hybridized carbons of the alkene are converted to sp^3 hybridized carbons in the epoxide. Thus, there is the possibility of two new chiral carbons forming in the epoxide product. In most cases, epoxidation of an alkene will product a mixture of enantiomers in the product, due to the electrophilic oxygen being able to attack from above or below the plane of the alkene. One major exception is the epoxidation of symmetrical cis-alkene which produces a meso compound product.

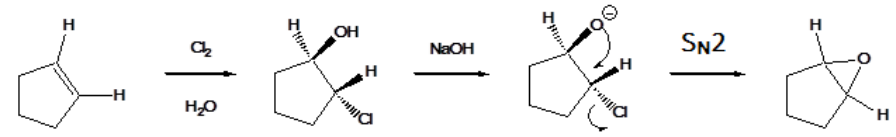
EXAMPLE 18.5.2



cis-2-Butene | *cis*-2,3-Dimethyloxirane (Meso)

Trans-2-Butene | *trans*-2,3-Dimethyloxirane (Enantiomers)

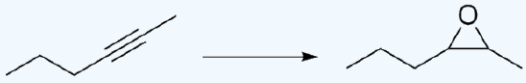
Treatment of an alkene with X_2 & H_2O creates a halohydrin (Section 8-3). When a halohydrin is treated with a base the alcohol is deprotonated to from an alkoxide. This causes an intramolecular Williamson ether synthesis to produce an epoxide along with the elimination of HX. Note, that this reaction generally forms a mixture of enantiomeric products unless a meso compound is produced.



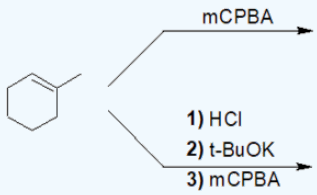
Alkene | Halohydrin | Epoxide

EXERCISE 18.5.1

1) What reagents would you use to perform the following transformation?



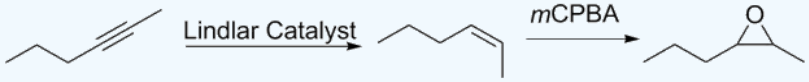
2) Predict the products of the following reactions:



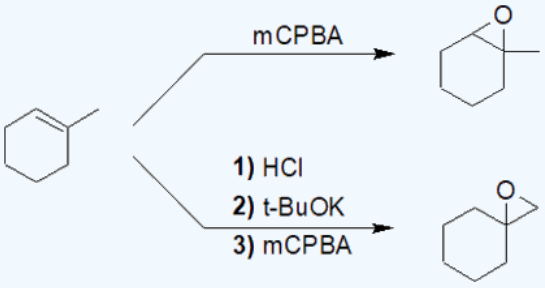
3) Predict the product of the following reaction. Be sure to include proper stereochemistry.

Answer

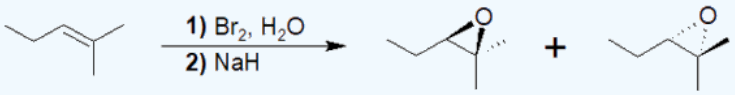
1) Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.



2)



3)



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18.6: REACTIONS OF EPOXIDES - RING-OPENING

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the opening of an epoxide ring under mildly acidic conditions.
   a. identify the product formed from the hydrolysis of an epoxide.
   b. write the mechanism for the opening of an epoxide ring by an aqueous acid, paying particular attention to the stereochemistry of the product.
   c. identify the product formed when an epoxide ring is opened by a hydrogen halide under anhydrous conditions.
2. predict the major product from the acidic cleavage of a given unsymmetrical epoxide.
3. write an equation to illustrate the cleavage of an epoxide ring by a base.
   a. identify the product formed from the reaction of a given epoxide with given base.
   b. explain why epoxides are susceptible to cleavage by bases, whereas other cyclic ethers are not.

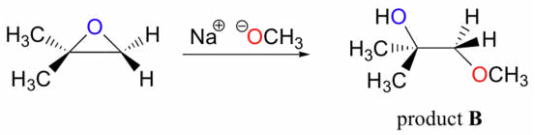
STUDY NOTES

In the discussion on base-catalyzed epoxide opening, the mechanism is essentially S_N2. While oxygen is a poor leaving group, the ring strain of the epoxide really helps to drive this reaction to completion. Indeed, larger cyclic ethers would not be susceptible to either acid-catalyzed or base-catalyzed cleavage under the same conditions because the ring strain is not as great as in the three-membered epoxide ring.

EPOXIDE RING-OPENING BY ALCOHOLYSIS

The ring-opening reactions of epoxides provide a nice overview of many of the concepts discussed in earlier chapters of this book. Ring-opening reactions can proceed by either S_N2 or S_N1 mechanisms, depending on the nature of the epoxide and on the reaction conditions. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes alcoholysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic attack, leading to what we will refer to as product B:

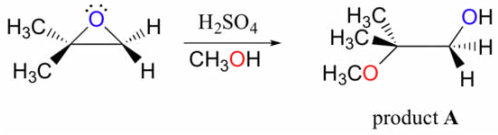
basic ring-opening:



product **B**

Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon is the site of attack. As a result, product A predominates.

acidic ring-opening:

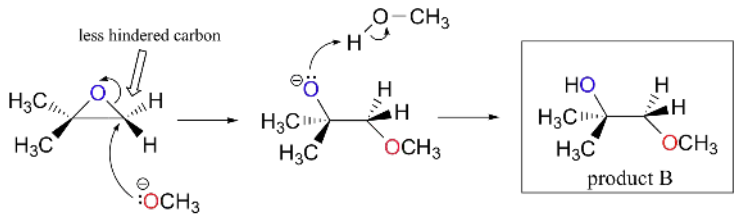


product **A**

These are both good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively).

BASIC EPOXIDE RING-OPENING BY ALCOHOLYSIS

In the basic, S_N2 reaction, the leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group (**Section 11-3**), and thus the ring is unlikely to open without a 'push' from the nucleophile.

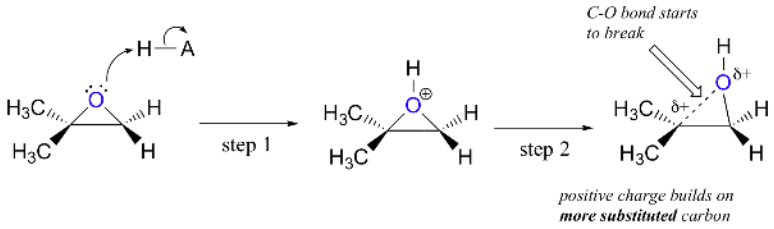


The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

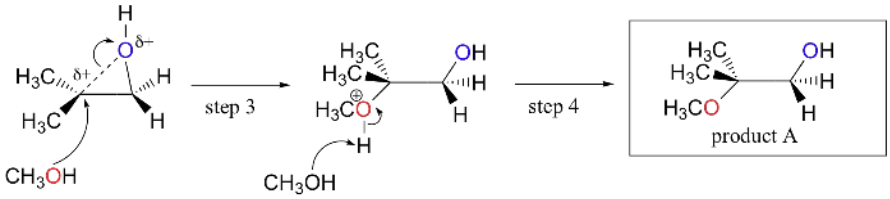
There are two electrophilic carbons in the epoxide, but the best target for the nucleophile in an S_N2 reaction is the carbon that is *least hindered*. This accounts for the observed regiochemical outcome. Like in other S_N2 reactions, nucleophilic attack takes place from the backside, resulting in inversion at the electrophilic carbon.

ACID-CATALYZED EPOXIDE RING-OPENING BY ALCOHOLYSIS

The best way to depict the acid-catalyzed epoxide ring-opening reaction is as a hybrid, or cross, between an S_N2 and S_N1 mechanism. First, the oxygen is protonated, creating a good leaving group (step 1 below). Then the carbon-oxygen bond begins to break (step 2) and positive charge begins to build up on the more substituted carbon. Recall that alkyl substituents can donate electron density through hyper conjugation and stabilize a positive charge on a carbon.



Unlike in an S_N1 reaction, the nucleophile attacks the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

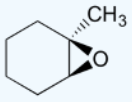


Attack takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks attack from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile attacks the more substituted carbon because it is this carbon that holds a greater degree of positive charge.

EXAMPLE 18.6.1

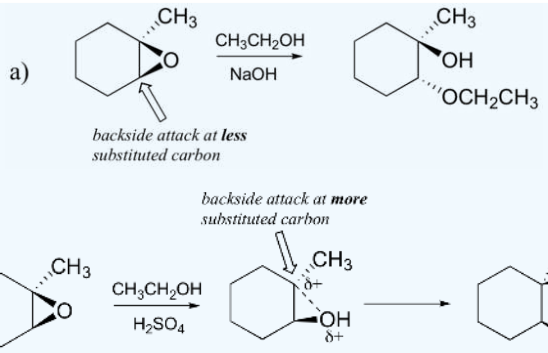
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



Hint: be sure to consider both regiochemistry **and** stereochemistry!

Answer



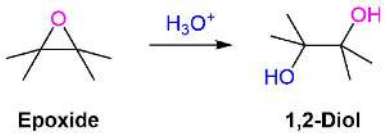
EPOXIDE RING-OPENING BY HYDROLYSIS

Epoxides may be cleaved by hydrolysis to give ***trans*-1,2-diols** (1,2 diols are also called **vicinal diols or vicinal glycols)**. The reaction can be preformed under acidic or basic conditions which will provide the same regioselectivity previously discussed.

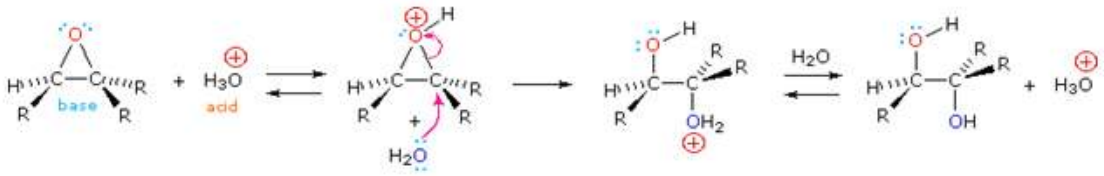
ACID CATALYZED HYDROLYSIS

Under aqueous acidic conditions the epoxide oxygen is protonated and is subsequently attacked by a nucleophilic water. After deprotonation to reform the acid catalyst a 1,2-diol product is formed. If the epoxide is asymmetric, the incoming water nucleophile will preferably attack the more substituted epoxide carbon. The epoxide ring is opened by an S_N2 like mechanism so the two -OH groups will be *trans* to each other in the product.

GENERAL REACTION



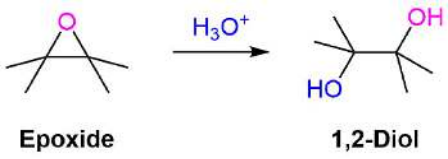
MECHANISM



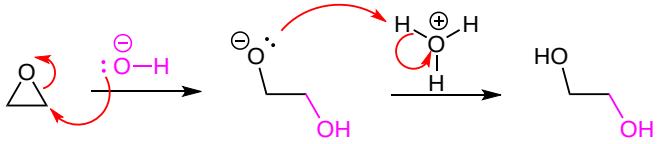
BASIC HYDROLYSIS

Under aqueous basic conditions the epoxide is opened by the attack of hydroxide nucleophile during an S_N2 reaction. The epoxide oxygen forms an alkoxide which is subsequently protonated by water forming the 1,2-diol product. If the epoxide is asymmetric the incoming hydroxide nucleophile will preferable attack the less substituted epoxide carbon. Because the reaction takes place by an S_N2 mechanism the two -OH groups in the product will be *trans* to each other.

GENERAL REACTION



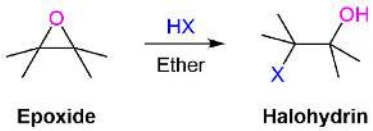
MECHANISM



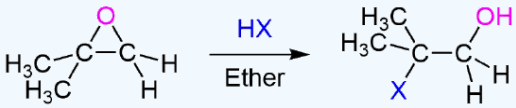
EPOXIDE RING-OPENING BY HX

Epoxides can also be opened by anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will attack the less substituted carbon through an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertiary carbon in an S_N1 like reaction.

GENERAL REACTION

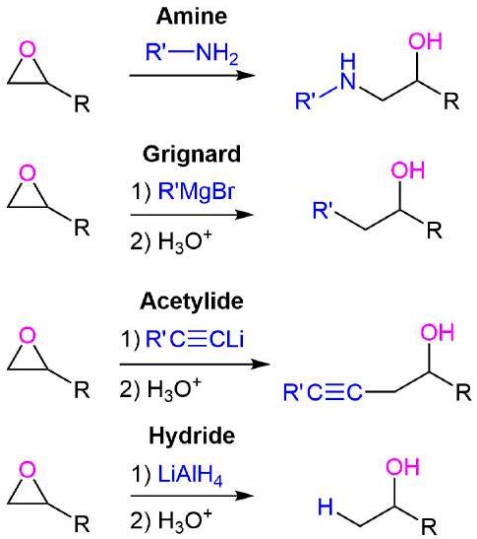


EXAMPLE 18.6.2

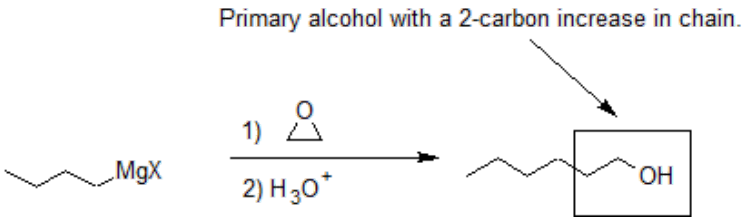


EPOXIDE RING-OPENING BY OTHER BASIC NUCLEOPHILES

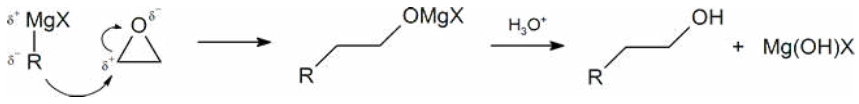
A wide variety of basic nucleophiles can be used for the ring opening of an epoxide including, amines, hydrides, Grignard reagents, acetylide anions, and hydride. These ring openings generally take place by an S_N2 mechanism.



Reacting Grignard reagents with ethylene oxide is a particularly useful reaction because it produces a primary alcohol containing two more carbon atoms than the original Grignard reagent.

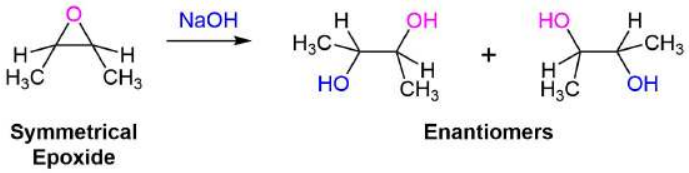


This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases. The first step of the mechanism of this reaction involves the S_N2 attack of the Grignard reaction to open the epoxide to form an alkoxide. The second step of the mechanism involves the protonation of the alkoxide to form an alcohol.



ADDITIONAL STEREOCHEMICAL CONSIDERATIONS OF RING-OPENING

During the ring-opening of an asymmetrical epoxide, the regiochemical control of the reaction usually allows for one stereoisomer to be produced. However, if the epoxide is symmetrical, each epoxide carbon has roughly the same ability to accept the incoming nucleophile. When this occurs the product typically contains a mixture of enantiomers.



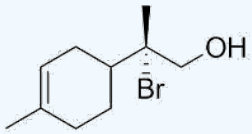
EXERCISES

? EXERCISE 18.6.1

Given the following, predict the product assuming only the epoxide is affected. (Remember to show stereochemistry)



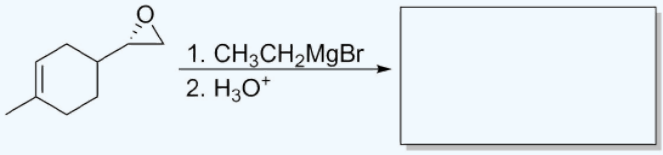
Answer



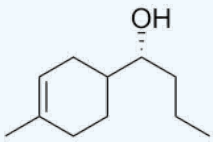
Note that the stereochemistry has been inverted

? EXERCISE 18.6.2

Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

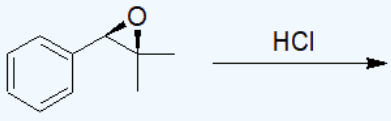


Answer

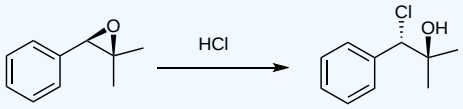


? EXERCISE 18.6.3

Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



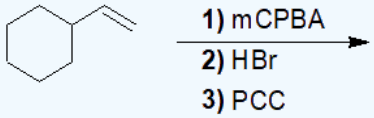
Answer



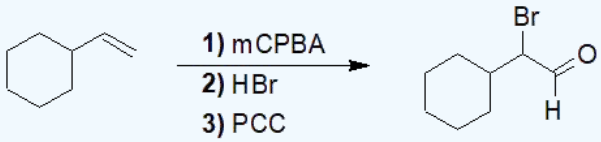
The ring side of the protonated epoxide intermediate will better stabilize a partial positive charge, so would be the more likely carbon for the chloride ion to attack.

EXERCISE 18.6.4

Predict the product of the following reaction.

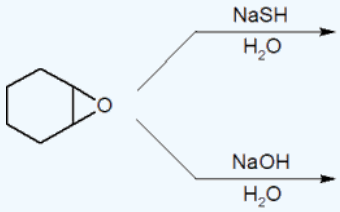


Answer

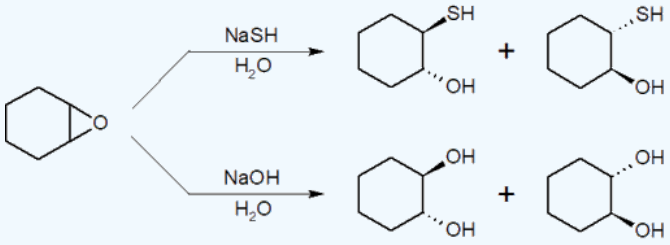


EXERCISE 18.6.5

Provide the final products of the following reactions.



Answer



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18.7: CROWN ETHERS

OBJECTIVES

After completing this section, you should be able to

1. write the normally accepted name for a crown ether, given its structure.
2. draw the structure of a crown ether, given its normally accepted name.
3. describe, briefly, the uses of crown ethers.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

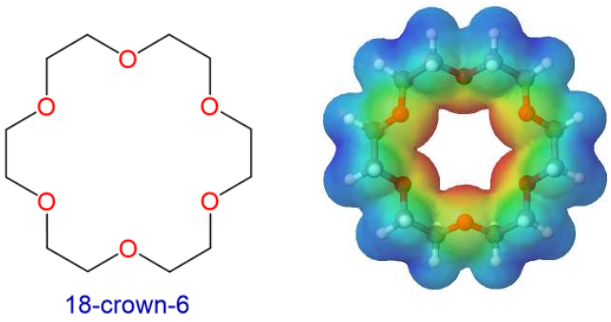
- crown ether

STUDY NOTES

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. As we have indicated in the objectives above, a detailed knowledge of these compounds is not required in this course.

CROWN ETHERS

Crown ethers are cyclic polyethers with four or more oxygen atoms each separated by two or three carbon atoms. Crown ethers have the general formula of $(OCH_2CH_2)_n$ or $(OCH_2CH_2CH_2)_n$ and are named using both the total number of atoms in the ring and the number of oxygen atoms. Thus 18-crown-6 is an 18-membered ring with six oxygen atoms. All crown ethers have a cavity in the center this is lined with oxygen atoms and can accommodate a alkali metal ion, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. The negative character of center cavity of 18-crown-6 can be seen by looking at its electrostatic potential map shown below. The presence of high electron density is shown by a red color.



Crown ethers are useful for dissolving ionic substances in organic solvents, such as $KMnO_4$ dissolving in toluene, by sequestering the cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic.

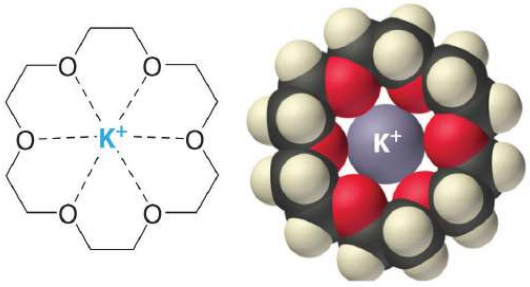
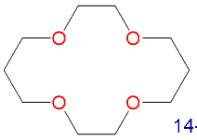
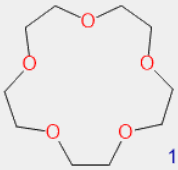
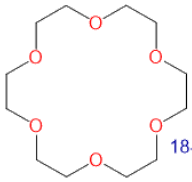
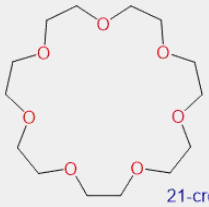


Figure **18.7.1**: Potassium complex of the crown ether 18-crown-6. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity. Crown ethers prefer to bind alkali metal cations with sizes that match that of their binding cavity. For instance, as shown in Table **18.7.1**, 14-

crown-4 preferentially binds to Li^+, 15-crown-5 preferentially binds to Na^+, 18-crown-6 preferentially binds to K^+, and 21-crown-7 preferentially binds to Cs^+.

Table **18.7.1**: Crown ethers preferentially bind cations with sizes that match the cavity size of their crown-shaped conformers.

Crown Ether	Cavity Diameter (A˚)	Preferred Cation	Cation Diameter (A˚)
 14-crown-4	1.2-1.5	Li^+	1.36
 15-crown-5	1.7-2.2	Na^+	1.94
 18-crown-6	2.6-3.2	K^+	2.66
 21-crown-7	3.4-4.3	Cs^+	3.34

CRYPTANDS

Cryptands (from the Greek *kryptós*, meaning “hidden”) are variations of crown ethers comprised of two nitrogens connected by three polyether strands. A common nomenclature is used where the numbers preceding the word cryptan indicate the number of oxygen atoms in each strand of the molecule.

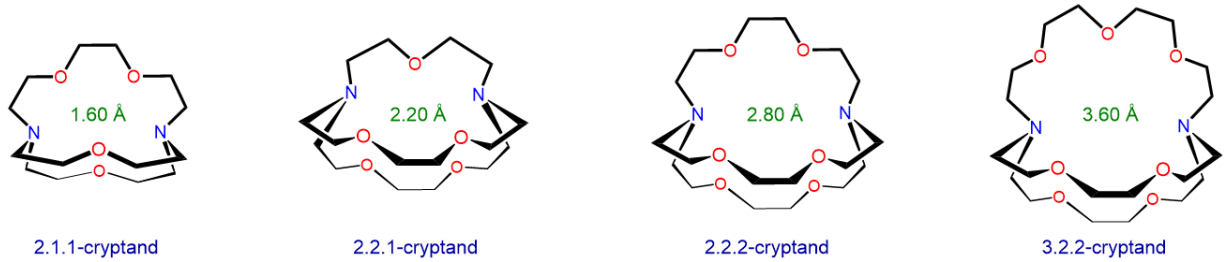


Figure **18.7.2**: Structures and approximate binding cavity diameters for several cryptands.

Like crown ethers, cryptands are compounds that contains a central cavity that can completely surround a cation with lone pair electrons from oxygen and nitrogen atoms. Also, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them. Similar to crown ethers, cryptands prefer to bind with alkali metal cations whose diameter matches the size of their binding cavity.

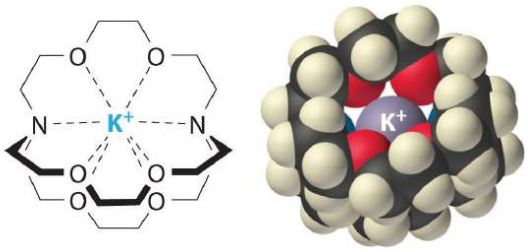


Figure **18.7.3**: Potassium complex of 2,2,2-cryptand. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

? EXERCISE 18.7.1

Cryptand ligands also preferentially bind alkali metal ions with sizes that match the size of their binding cavities. The structure and approximate cavity sizes of several cryptands are shown above. Use the information in Table **18.7.1** to predict which alkali metal ion each cryptand will preferentially bind.

Answer

The cryptands might be expected to selectively bind the largest ion which fits within the cavity. Predicted selectivity of crown ethers for alkali metal cations based on the hypothesis that they will selectively bind the largest ion which fits their binding cavity are listed below.

Cryptand	Cavity Diameter of (Å)	Preferred Cation	Cation Diameter (Å)
2.1.1-cryptand	1.60	Li^+	1.36
2.2.1-cryptand	2.20	Na^+	1.96
2.2.2-cryptand	2.80	K^+	2.66
3.2.2-cryptand	3.60	Cs^+	3.34

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18.8: THIOLS AND SULFIDES

OBJECTIVES

After completing this section, you should be able to

1. a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   d. write an equation to illustrate the preparation of a thiol by the reaction of thiourea with an alkyl halide.
2. write an equation to show the interconversion between thiols and disulfides.
3. a. write the name of a sulfide, given its structure.
   b. draw the structure of a sulfide, given its name.
   c. write an equation showing how a sulfide may be prepared by the reaction of a thiolate anion on an alkyl halide.
   d. identify the product from the reaction of a given alkyl halide with a given thiolate anion.
   e. identify the reagents necessary to prepare a given sulfide.
   f. write an equation to illustrate the formation of a trialkylsulfonium salt from a sulfide and an alkyl halide.

KEY TERMS

Note: All of these terms are defined in the "Study Notes," below.

- disulfide
- mercapto group
- (organic) sulfide
- sulfone
- sulfoxide
- thiol
- thiolate anion
- trialkylsulfonium ion (trialkylsulfonium salt)

STUDY NOTES

The chemistry of sulfur-containing organic compounds is often omitted from introductory organic chemistry courses. However, we have included a short section on these compounds, not for the sake of increasing the amount of material to be digested, but because much of the chemistry of these substances can be predicted from a knowledge of their oxygen-containing analogues.

A thiol is a compound which contains an SH functional group. The SH group itself is called a mercapto group. A disulfide is a compound containing an S-S linkage.

(Organic) sulfides have the structure R-S-R′, and are therefore the sulfur analogues of ethers. The nomenclature of sulfides can be easily understood if one understands the nomenclature of the corresponding ethers. Notice that the term "thio" is also used in inorganic chemistry. For example, SO_4^{2-} is the sulfate ion; while $S_2O_3^{2-}$, in which one of the oxygen atoms of a sulfate ion has been replaced by a sulfur atom, is called thiosulfate. Thiolate anions, RS^-, are analogous to alkoxy anions, RO^-. Thiolate anions are better nucleophiles than are alkoxy anions.

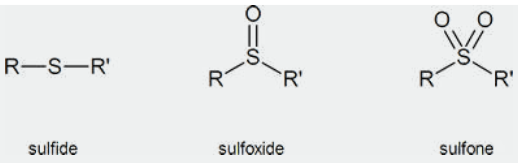
If you have trouble understanding why trialkylsulfonium ions are formed, think of them as being somewhat similar to the hydronium ions that are formed by protonating water:



hydronium ion trialkylsulfonium ion

Later we shall see examples of tetraalkylammonium ions, R_4N^+, which again may be regarded as being similar to hydronium ions.

Sulfoxides and sulfones are obtained by oxidizing organic sulfides. You need not memorize the methods used to carry out these oxidations.



sulfide sulfoxide sulfone

Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

Table **18.8.1**: Comparison of compounds containing oxygen and sulfur

Oxygen-containing Compound	Sulfur Analogue
ether, R-O-R′	sulfide, R-S-R′
alkoxy anion, RO^-	thiolate anion, RS^-
alcohol, ROH	thiol, RSH
hydroxy group, OH^-	mercapto group, SH^-
peroxide, R-O-O-R′	disulfide, R-S-S-R′

Note that when we name thiols, we include the “e” of the alkane name. Thus, CH_3CH_2SH is called “ethanethiol,” not “ethanthiol.”

Thiols and sulfides are the "sulfur equivalent" of alcohols and ethers. You can replace the oxygen atom of an alcohol with a sulfur atom to make a thiol; similarly, you can replace the oxygen atom in an ether with S to make the corresponding alkyl sulfide. This is because thiols contain the C-S-H functional group, while sulfides contain the C-S-C group.

OXIDATION STATES OF SULFUR COMPOUNDS

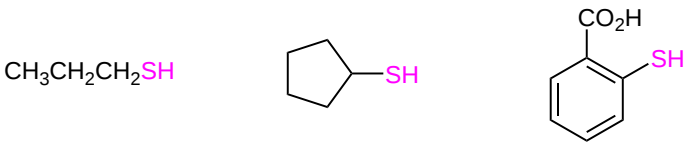
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

Sulfur Oxidation States in Organic Compounds

-2	-1	0	+2	+4	+6
H_2S R–S–H thiols R–S–R sulfides R–S(+)(R)–R sulfonium ions	R–S–S–R disulfides	S elemental R–S(=O)–R sulfoxides R–S–OH sulfenic acids	R–S(=O)(=O)–R sulfones R–S(=O)–OH sulfinic acids	SO_2 R–S(=O)(=O)–OH sulfonic acids R-O–S(=O)–O-R sulfite esters	SO_3 R-O–S(=O)(=O)–O-R sulfate esters

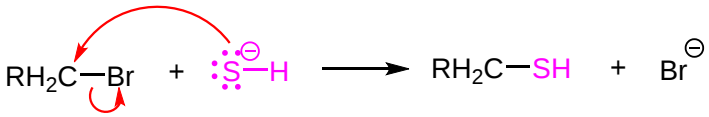
THIOLS

Thiols are often called “mercaptans,” a reference to the Latin term mercurium captans (capturing mercury), since the -SH group forms strong bonds with mercury and its ions. Thiols are analogous to alcohols. Thiols are weakly acidic (pK_a ~ 10) and are much stronger acids than alcohols (pKa ~ 16). However, thiols usually do not form hydrogen bonds due to the sulfur atom not have sufficient electronegativity. Thiols named using the same rules as alcohols except the parent chain is named as alkane with the suffix -thiol added. As a substituent the -SH group is called a **mercapto** group.



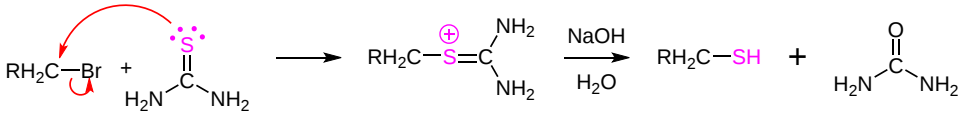
Propanethiol **Cyclopentanethiol** ***o*-Mercaptobenzoic acid**

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



Hydrosulfide ion **Thiol**

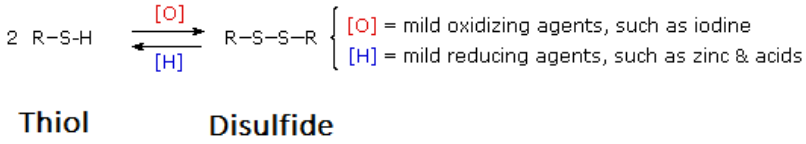
One problem with this reaction is that the thiol product can deprotonate and undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The S_N2 reaction first produces an alkyl isothiourea salt as an intermediate. This salt is then hydrolyzed to form the thiol by a reaction with aqueous base.



Thiourea **Thiol** **Urea**

DISULFIDES

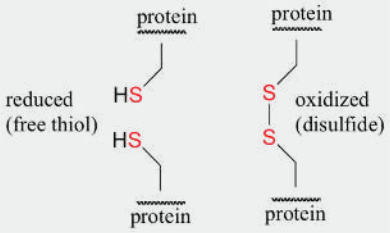
Thiols (R-S-H) can be oxidized to form disulfides (R-S-S-R') through reaction with Br_2 or I_2. Note, an equivalent oxidation of alcohols (R-O-H) to peroxides (R-O-O-R') is not normally observed. The reasons for this different behavior becomes clear when looking at bond strengths. The S–S single bond in disulfides is nearly twice as strong as the O–O bond in peroxides. Also, the O–H bond in alcohols is more than 25 kcal/mole stronger than the S–H bond in thiols. Thus, thermodynamics favors disulfide formation over peroxide. Disulfides can easily be reduced back to a thiols through reaction with zinc and acid.



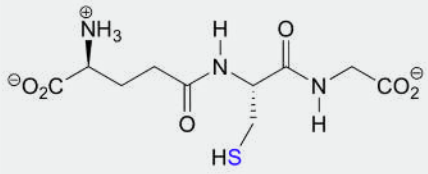
Thiol **Disulfide**

DISULFIDE BRIDGES IN PROTEINS

Disulfide (sulfur-sulfur) linkages between two cysteine residues are an integral component of the three-dimensional structure of many proteins. The interconversion between thiols and disulfide groups is a redox reaction: the thiol is the reduced state, and the disulfide is the oxidized state.

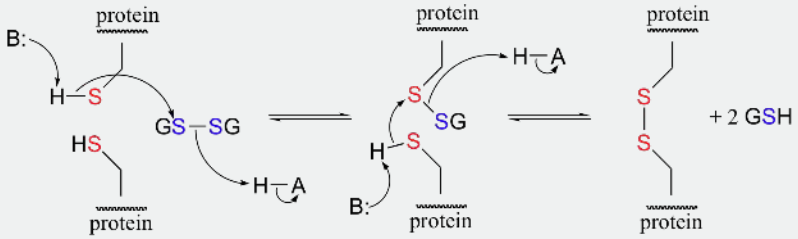


Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme. Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure below. In its reduced (free thiol) form, glutathione is abbreviated 'GSH'.



Glutathione (GSH)

In its oxidized form, glutathione exists as a dimer of two molecules linked by a disulfide group, and is abbreviated 'GSSG'. A new disulfide in a protein forms via a 'disulfide exchange' reaction with GSSG, a process that can be described as a combination of two S_N2-like attacks. The end result is that a new cysteine-cysteine disulfide forms at the expense of the disulfide in GSSG.



In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

SULFIDES

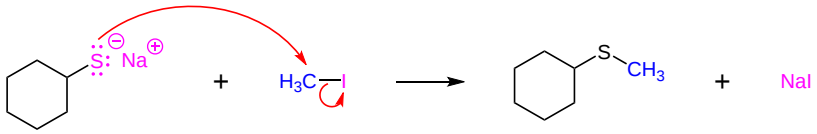
Sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substances, alkylthio is used in place of alkoxy.



Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

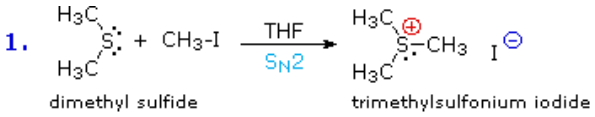
Sulfur analogs of ethers are called **sulfides**. Sulfides are less common than thiols as naturally occurring compounds. However, sulfides—especially disulfides (C-S-S-C)—have important biological functions, mainly in reducing agents (antioxidants).

Since thiols are weakly acidic their conjugate bases, called thiolate ions, can be easily formed through reaction with a strong base such as NaH. Thiolates have proven to be excellent nucleophiles and easily undergo S_N2 reactions with primary and secondary alkyl halides to form sulfides. The reaction is analogous to the Williamson ether synthesis previously discussed in this chapter (**Section 18-2**)



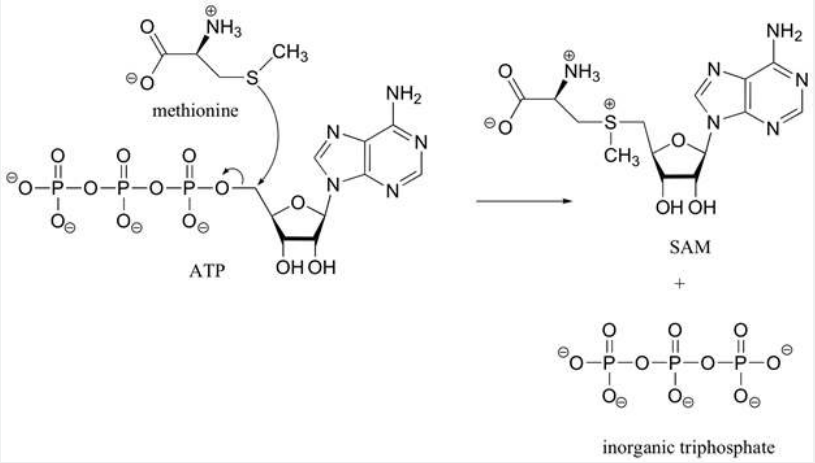
Cyclohexanethiolate **Cyclohexyl methyl sulfide**

The chemical behavior of sulfides contrasts with that of ethers in some important ways. Because sulfur's valence electrons involve 3P orbitals they are further away and less tightly held than the valence electrons on oxygen which involve 2P orbitals. This makes the nucleophilicity of sulfur atoms much greater than that of oxygen, leading to a number of interesting and useful electrophilic substitutions of sulfur that are not normally observed for oxygen. For instance, sulfides, unlike ethers, easily react with primary alkyl halides through an S_N2 mechanism to give ternary sulfonium ions (R_3S^+) in the same manner that 3º-amines can be alkylated to form quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.

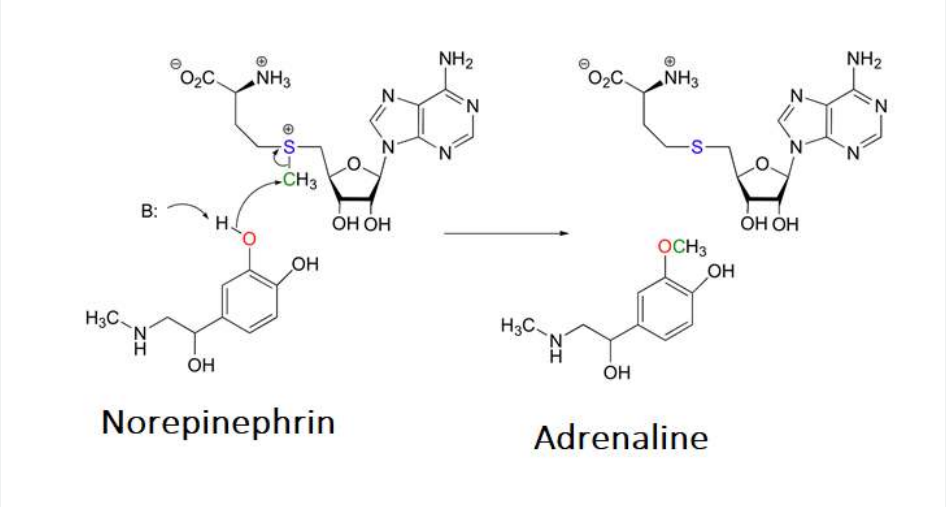


BIOLOGICAL SULFONIUM ION FORMATION

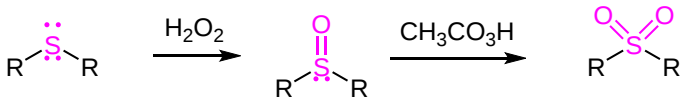
In biological systems the sulfonium ion, *S*-adenosylmethionine (SAM), is formed by a S_N2 reaction between the nucleophilic sulfur atom of the amino acid methionine and the electrophilic methene (CH_2) carbon of adenosine triphosphate (ATP). This reaction is unusually in that the triphosphate ion is removed from ATP as a leaving group. In most cases biological nucleophiles attack an electrophilic phosphorus on ATP causing a diphosphate ion to be removed as the leaving group.



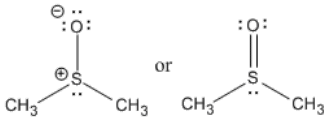
The sulfonium ion in SAM is an effective methylating agent. Through an S_N2 reaction, biological nucleophiles can attack the electrophilic methyl group bonded to the positively charged sulfonium ion and cause the removal of a neutral sulfide as a leaving group. An example of this reaction is the catechol-O-methyltransferase catalyzed O-methylation of norepinephrin by SAM to produce adrenaline.



Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room temperature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid, such as peracetic acid (CH_3CO_3H), to produce the sulfone (R_2SO_2).



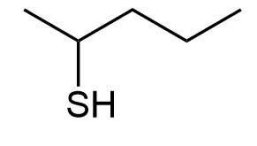
A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is considered a polar aprotic solvent.



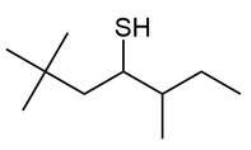
EXERCISE 18.8.1

Give IUPAC names the following compounds:

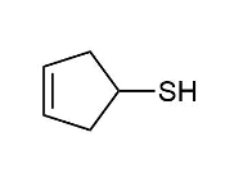
a)



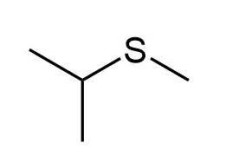
b)



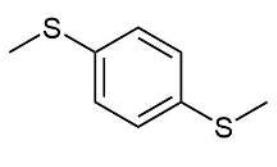
c)



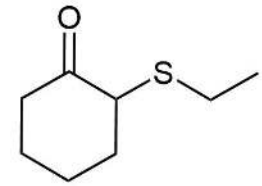
d)



e)



f)



Answer

a) 2-Pentanethiol

b) 2,2,5-Trimethyl-4-heptanethiol

c) 3-Cyclopentene-1-thiol

d) Methyl isopropyl sulfide

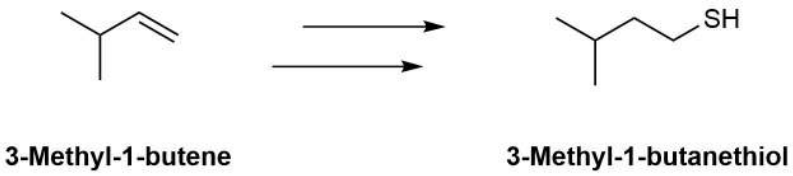
e) *p*-Di(methylthio)benzene

f) 2-(Ethylthio)cyclohexanone

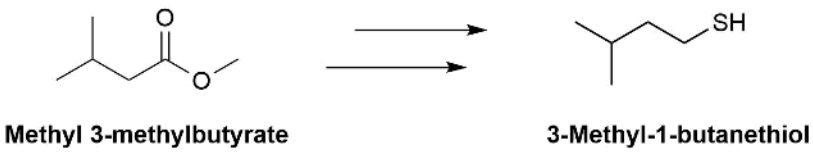
? EXERCISE 18.8.2

The molecule 3-methyl-1-butanethiol has been shown to be one of the components of skunk spray. How would make the following conversions?

a)



b)



Answers

a) 1) HBr & Peroxides, 2) $(NH_2)_2C=S$, 3) NaOH & H_2O

b) 1) $LiAlH_4$, 2) PBr_3, 3) $(NH_2)_2C=S$, 4) NaOH & H_2O

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18.9: SPECTROSCOPY OF ETHERS

OBJECTIVES

After completing this section, you should be able to

1. use the ^{1}H NMR spectrum of an unknown ether or epoxide to determine its identity.
2. identify the approximate chemical shift expected for protons attached to the carbon atoms that are bonded to oxygen in an ether or an epoxide.

INFRARED SPECTROSCOPY

Ethers and epoxides typically have a strong C-O stretch between 1000 and 1300 1/cm. Because this absorption appears in the fingerprint region of the IR is can be difficult to assign. In addition to the C-O peak, it is helpful to note if an IR spectrum has no C=O or O-H stretch peaks to confirms it is not aldehyde, ketone, or alcohol.

If you look at an IR spectrum of dibutyl ether, you will see:

- there are the usual sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong peak near 1100 cm^{-1}. This peak is due to the C-O stretching vibration.

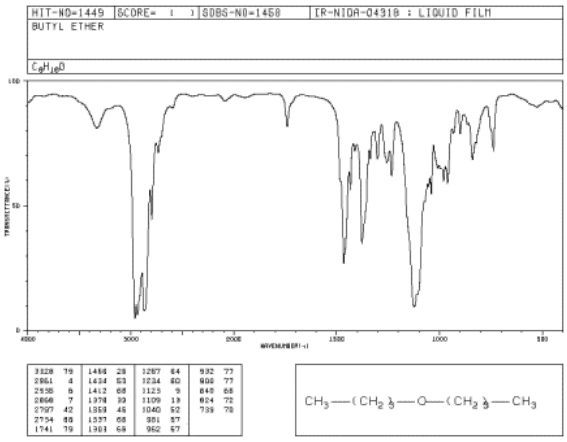
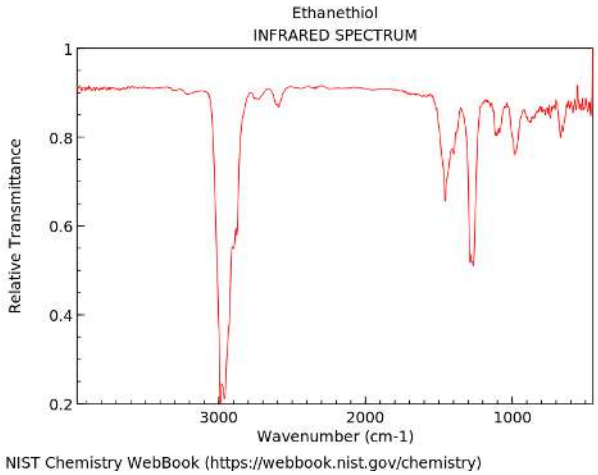


Figure IR7. *IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)*

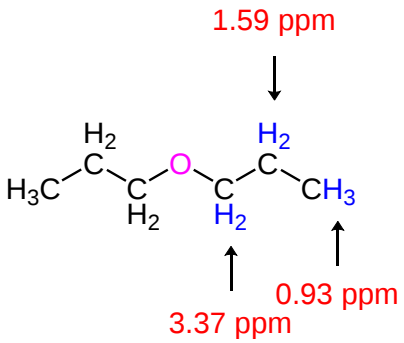
Although thios and sulfides do have a weak C-S stretch between 710 and 570 1/cm, the absorption is very difficult to assign. In addition thios have a weak S-H stretch at 2600-2550 1/cm.



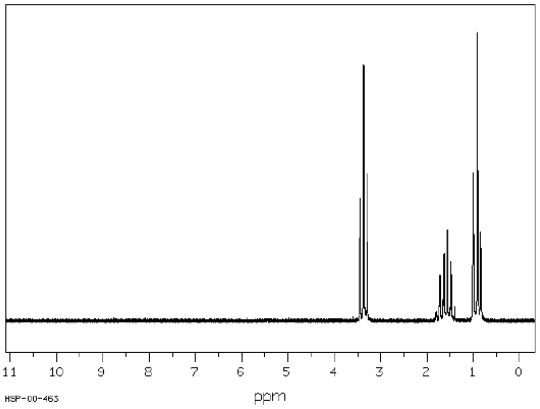
^{1}H NMR SPECTROSCOPY

- Hydrogens on carbon adjacent to the ether show up in the region of 3.4-4.5 ppm.
- Similar peaks in epoxides are shifted to a slightly higher field than other ethers. Hydrogens on carbons in and epoxide appear in the region of 2.5 to 3.5 ppm.
- Hydrogens on carbons adjacent to the sulfur in sulfides and thiols appear in the region of 2.0 to 2.5 ppm.
- The SH hydrogen of a thiol typically appears in the region of 1.3-1.5 ppm.

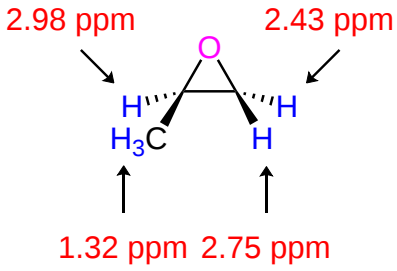
The ^{1}H NMR spectrum of dipropyl ether shows three signals with the triplet at 3.37 ppm assigned to the -CH_2- beside the ether and the other two signals upfield (1.59 and 0.93 ppm). Notice the protons closer to the electron withdrawing oxygen atom are further downfield indicating some deshielding. Protons at (A) and (C) are each coupled to two equivalent (B) protons. So, each of these signals appears as a triplet. The (B) protons in turn are coupled to a set of two and three equivalent protons and appears as a sextet. Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017).



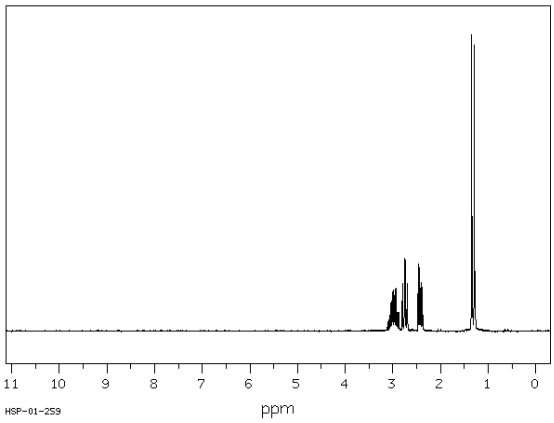
Dipropyl ether



Source: SDBSWeb : http://sdbs.db.aist.go.jp

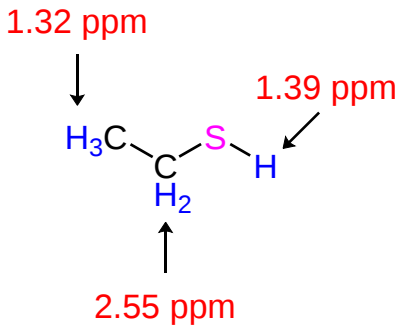


2-Methyloxirane

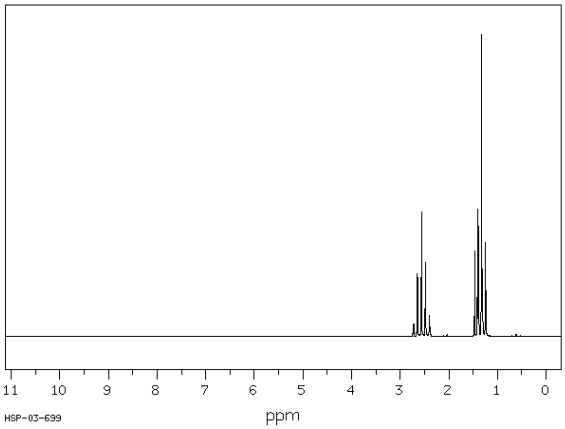


Source: SDBSWeb : http://sdbs.db.aist.go.jp

The methylene protons of this epoxide are diastereotopic and appear as two separate peak. When looking at the 3D structure of 2-methyloxirane it is clear that each methylene hydrogen is distinctly different. Also, hydrogens attached to the carbons in eposxides tend to display complex splitting patterns (Sections **13-7 and 13-8**).



Ethanethiol

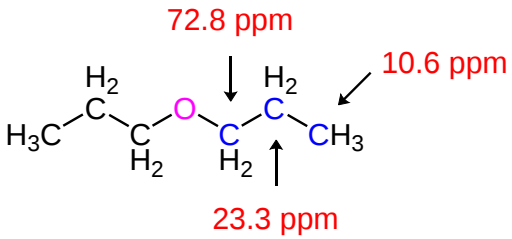


Source: SDBSWeb : http://sdbs.db.aist.go.jp

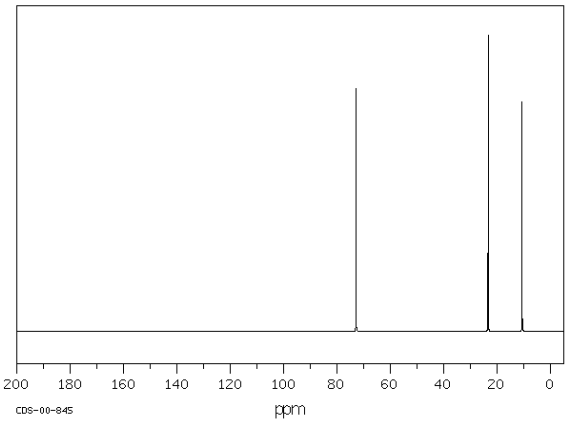
Note that in this ^{1}H NMR spectra the SH proton is actively involved in splitting. The SH proton peak at 1.39 ppm is split into a triplet and the methylene peak at 2.55 ppm is split into a quintet.

^{13}C NMR SPECTRA

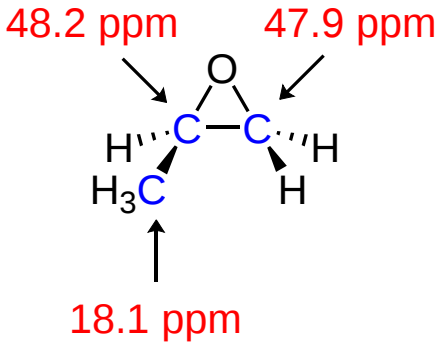
- Carbons adjacent to the ether appear in the region of 50-80 ppm.
- Carbons that are part of the epoxide appear in the region of 40-60 ppm.
- Carbons adjacent to the sulfur in sulfides and thiols appear in the region of 20-40 ppm.



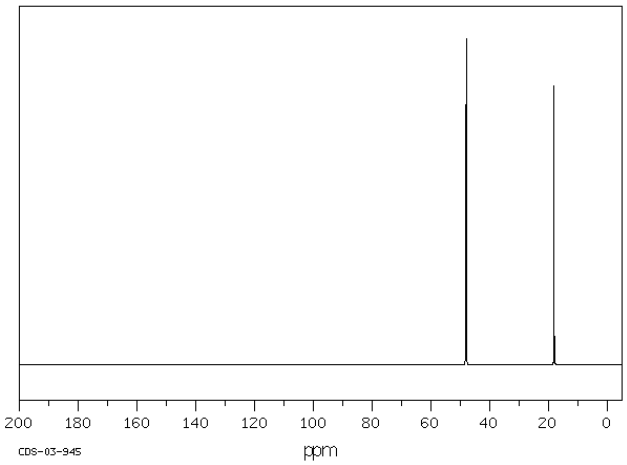
Dipropyl ether



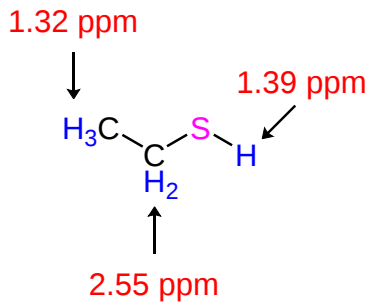
Source: SDBSWeb : http://sdbs.db.aist.go.jp



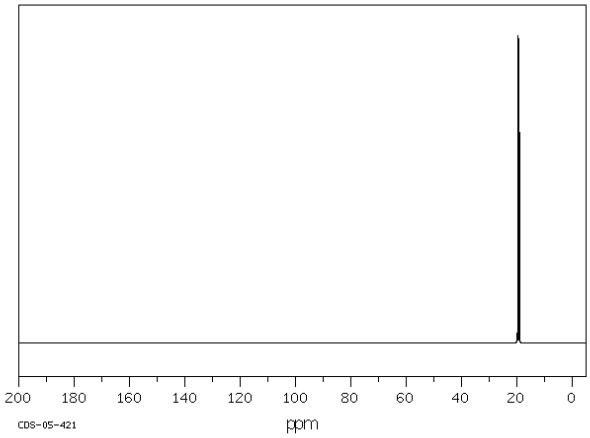
2-Methyloxirane



Source: SDBSWeb : http://sdbs.db.aist.go.jp



Ethanethiol



Source: SDBSWeb : http://sdbs.db.aist.go.jp

MASS SPECTRA

Ethers, sulfides, and epoxides all have similar fragmentation patterns in mass spectra with a few subtle variations.

ETHERS

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce $[H_2C{=}O\text{-}R]^+$
- They can also undergo an inductive cleavage to produce R^+

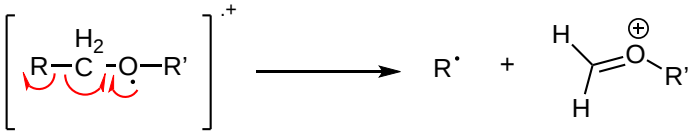
EPOXIDES

- The M^+ is typically weak or absent
- They primarily undergo alpha-cleavage to produce an alkyl radical

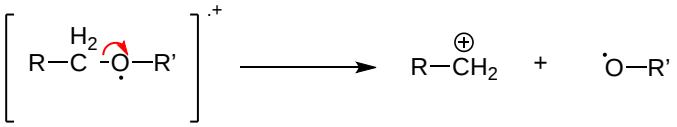
SULFIDES

- The M^+ is typically stronger than the corresponding ether
- They primarily undergo alpha-cleavage to produce an alkyl radical
- They can also undergo an inductive cleavage to produce R^+

FRAGMENTATION PATTERNS

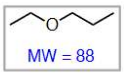


alpha-cleavage

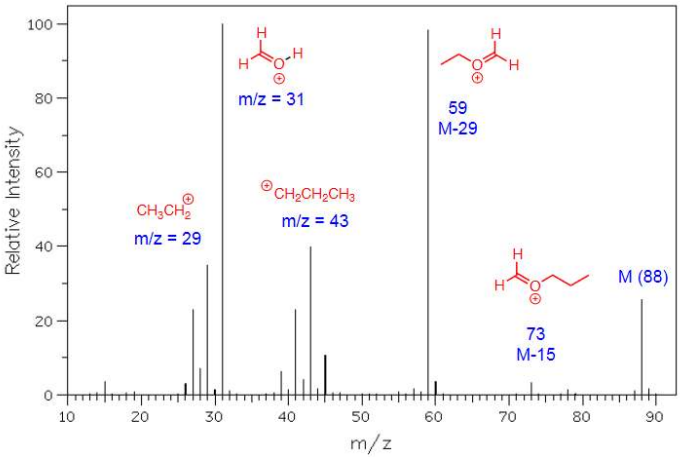


inductive cleavage

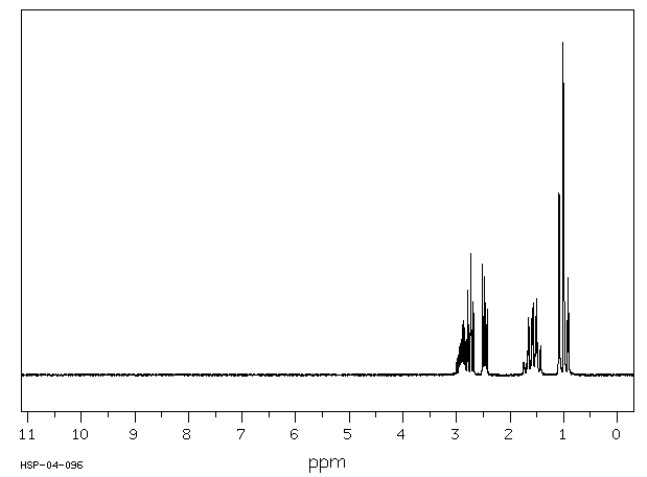
Ethers



ethyl propyl ether



? EXERCISE 18.9.1



Source: SDBSWeb : http://sdbs.db.aist.go.jp

Answer

2-Ethyloxirane

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18.10: INTERCHAPTER - A PREVIEW OF CARBONYL CHEMISTRY

So far, in our survey of the oxygen-containing organic compounds, we have studied the chemistry of ethers and alcohols. Now we turn our attention to a much larger group of compounds—those containing a carbonyl group:



The variety of carbonyl compounds is so wide, and their chemistry so extensive, that we shall need the next five chapters to discuss them thoroughly. One advantage of this course is that we have divided up the discussion of carbonyl compounds so that this large amount of factual material can be studied in small, readily digestible blocks.

The purpose of this chapter is to provide a general outline of what is to follow in the next five chapters: the various types of carbonyl compounds are introduced, the nature of the carbonyl group is explained, and the four most common mechanisms by which carbonyl groups react are described in general terms.

CHAPTER OBJECTIVES

When you have completed this chapter, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. identify the various types of carbonyl compounds.
3. write the mechanism of each of the four general types of reactions discussed in the chapter.
4. define, and use in context, the key terms introduced in this chapter.

INTRODUCTION

OBJECTIVES

After completing this section, you should be able to give examples of the wide variety of biologically important, pharmaceutical and industrial compounds that contain one or more carbonyl groups.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- carbonyl group

STUDY NOTES

A “carbonyl group” consists of an sp^2-hybridized carbon atom that is joined to an oxygen atom by a double bond.

NATURAL OCCURRENCE OF ALDEHYDES AND KETONES

Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain a aldehyde or ketone functional group are shown in the following two figures. The compounds in the figure 1 are found chiefly in plants or microorganisms and those in the figure 2 have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author’s favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-Muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, Cortisone.

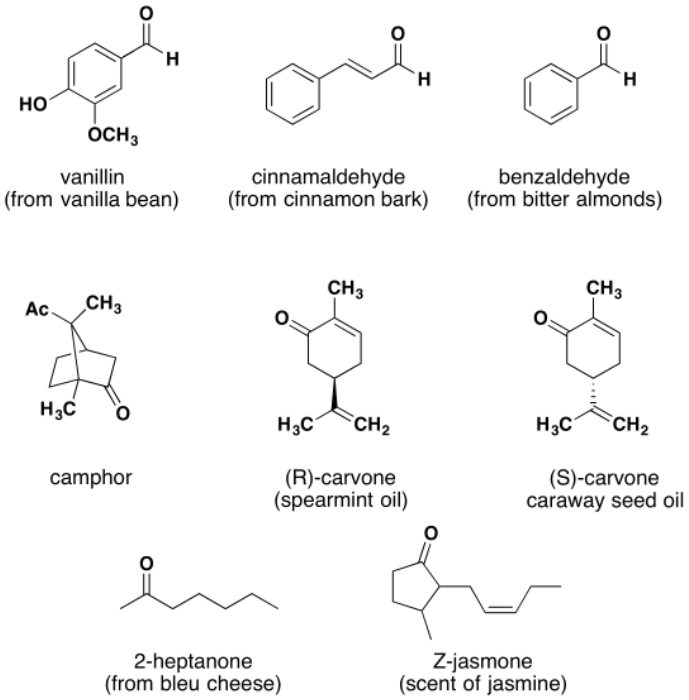


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

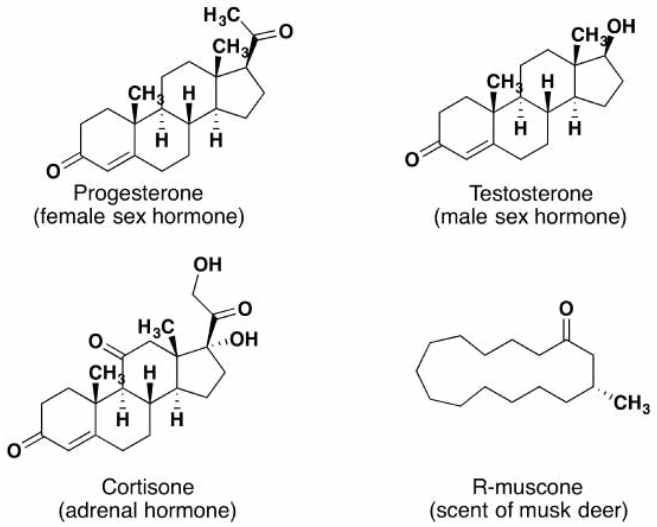


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

I KINDS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. identify the following types of compounds as containing carbonyl groups: aldehydes, ketones, carboxylic acids, acid chlorides, acid anhydrides, esters, lactones, amides and lactams.
2. identify the important difference between aldehydes and ketones, and the other types of compounds listed under Objective 1, above.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- acyl fragment or acyl group

STUDY NOTES

The idea of an “acyl group”

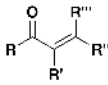
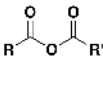


is not really new. Recall that in Chapter 16 we discussed the introduction of acyl groups into benzene rings by means of the Friedel-Crafts acylation reaction.

Note the use of the word “moiety” as an alternative to “group” or “fragment.”

Study the different types of carbonyl compounds listed in the table so that you can immediately recognize to which type a given compound belongs.

SOME CARBONYL COMPOUNDS

Compound	Aldehyde	Ketone	Formaldehyde	Carboxylic Acid	Ester	Amide	Enone	Acyl Halide	Acid Anhydride
Structure									
General Formula	RCHO	RCOR'	CH_2O	RCOOH	RCOOR'	RCONR'R''	RC(O)C(R')CR''R'''	RCOX	$(RCO)_2O$

One should also add to this list lactones (cyclic esters) and lactams (cyclic amides).

II NATURE OF THE CARBONYL GROUP

OBJECTIVES

After completing this section, you should be able to describe the electronic structure, polarity, and geometry of the carbonyl group.

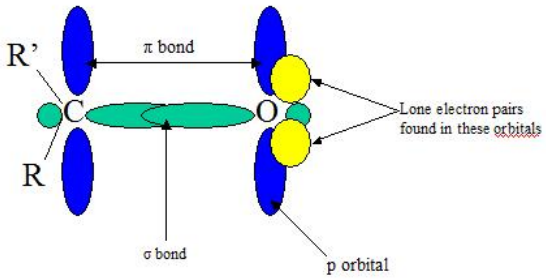
A carbonyl group is a chemically organic functional group composed of a carbon atom double-bonded to an oxygen atom --> [**C=O**] The simplest carbonyl groups are aldehydes and ketones usually attached to another carbon compound. These structures can be found in many aromatic compounds contributing to smell and taste.

INTRODUCTION

Before going into anything in depth be sure to understand that the **C=O** entity itself is known as the "Carbonyl group" while the members of this group are called "carbonyl compounds" --> **X**-C=O. The carbon and oxygen are usually sp^2 hybridized and planar.

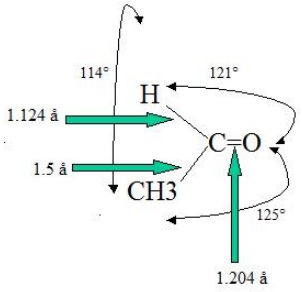
CARBONYL GROUP DOUBLE BONDS

The double bonds in alkenes and double bonds in carbonyl groups are VERY different in terms of reactivity. The C=C is *less* reactive due to C=O electronegativity attributed to the oxygen and its two lone pairs of electrons. One pair of the oxygen lone pairs are located in 2s while the other pair are in 2p orbital where its axis is directed perpendicular to the direction of the pi orbitals. The Carbonyl groups properties are directly tied to its electronic structure as well as geometric positioning. For example, the electronegativity of oxygen also polarizes the pi bond allowing the single bonded substituent connected to become electron withdrawing.



**Note: Both the pi bonds are in phase (top and botom blue ovals)*

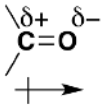
The double bond lengths of a carbonyl group is about 1.2 angstroms and the strength is about 176-179 kcal/mol). It is possible to correlate the length of a carbonyl bond with its polarity; the longer the bond meaing the lower the polarity. For example, the bond length in C=O is larger in acetaldehyde than in formaldehyde (this of course takes into account the inductive effect of CH_3 in the compound).



POLARIZATION

As discussed before, we understand that oxygen has two lone pairs of electrons hanging around. These electrons make the oxygen more electronegative than carbon. The carbon is then partially postive (electrophillic) and the oxygen partially negative (nucleophillic). The polarizability is denoted by a lowercase delta and a positive or negative superscript depending. For example, carbon would have d+ and oxygen delta^(-). The polarization of carbonyl groups also effects the boiling point of aldehydes and ketones to be higher than those of hydrocarbons in the same amount. The larger the carbonyl compound the less soluble it is in water. If the compound exceeds six carbons it then becomes insoluble.

**For more information about carbonyl solubility, look in the "outside links" section*



**Amides are the most stable of the carbonyl couplings due to the high-resonance stabilization between nitrogen-carbon and carbon-oxygen.*

III GENERAL REACTIONS OF CARBONYL COMPOUNDS

OBJECTIVES

After completing this section, you should be able to

1. list the four general reaction mechanisms that dominate the chemistry of carbonyl compounds.
2. discuss nucleophilic addition reactions of aldehydes and ketones (Chapter 19).
    a. write a general mechanism for nucleophilic addition to a carbonyl compound.
    b. write a detailed mechanism for the addition of a given nucleophile (e.g., a Grignard reagent) to an aldehyde or ketone.
3. discuss nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21).
    a. write a general mechanism to illustrate nucleophilic acyl substitution reactions.
    b. write a detailed mechanism for the reaction of a given carbonyl-containing compound with a given nucleophile through a nucleophilic acyl substitution.
4. discuss alpha substitution reactions (Chapter 22).
    a. write a general mechanism to illustrate alpha-substitution of a carbonyl compound through the formation of an enol or enolate anion.
    b. explain the stability and ease of formation of enolate anions.
    c. write the detailed mechanism for the formation of an alpha-substituted carbonyl compound from the overall reaction of a carbonyl compound with a primary alkyl halide.
5. discuss carbonyl condensation reactions (Chapter 23).
    a. write a general mechanism to illustrate the condensation reaction that can occur between two molecules of a carbonyl compound; for example, the reaction of two molecules of acetaldehyde to form one molecule of aldol.

KEY TERMS

Note: All of these terms are defined in the “Study Notes,” below.

- aldol reaction
- alkylation
- alpha substitution
- carbonyl condensation
- enol
- enolate anion
- nucleophilic acyl substitution
- nucleophilic addition reaction

STUDY NOTES

A “nucleophilic addition reaction” (of a carbonyl compound) involves the initial attack of a nucleophile on the slightly positive carbonyl-carbon atom to form a tetrahedral intermediate.

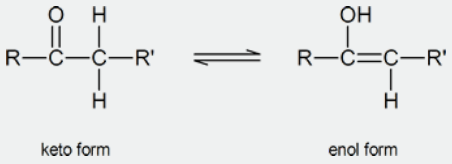
In a “nucleophilic acyl substitution reaction,” a nucleophile attacks the carbonyl carbon of a carboxylic acid derivative



and initially produces a tetrahedral intermediate. The intermediate then reacts by expelling the leaving group, X, thereby forming a new carboxylic acid derivative.

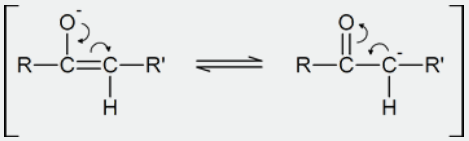
In an “alpha substitution reaction” of a carbonyl compound, one of the hydrogen atoms attached to a carbon atom adjacent to the carbonyl group is removed and replaced by some other group.

Alpha substitution reactions of carbonyl compounds involve the “enol” form of the compound. Keto-enol tautomerism was briefly introduced in Section 9.4. Review this section if necessary.



keto form enol form

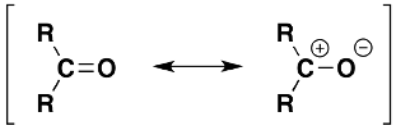
As you can see from the above diagram, the enol form has a hydroxyl group attached to one of the sp^2 hybridized carbon atoms of a carbon-carbon double bond. Removal of the proton from the hydroxyl group produces a resonance-stabilized “enolate anion”:



A “carbonyl condensation reaction” is one in which two carbonyl- containing molecules condense together (i.e., join together), often with the elimination of water. The reaction involves the formation of an enolate anion from one carbonyl-containing molecule, followed by the subsequent nucleophilic attack by this enolate anion on the carbonyl carbon atom of the second molecule.

NUCLEOPHILIC ADDITION TO A CARBONYL GROUP

C=O is prone to additions and nucleophillic attack because or carbon's positive charge and oxygen's negative charge. The resonance of the carbon partial positive charge allows the negative charge on the nucleophile to attack the Carbonyl group and become a part of the structure and a positive charge (usually a proton hydrogen) attacks the oxygen. Just a reminder, the nucleophile is a good acid therefore "likes protons" so it will attack the side with a positive charge.



**Remember: due to the electronegative nature of oxygen the carbon is partially positive and oxygen is partially negative*

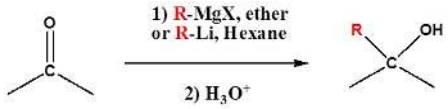


1 2 3

1. The Nucleophile (Nu) attacks the positively charged carbon and pushes one of the double bond electrons onto oxygen to give it a negative charge.
2. The Nucleophile is now a part of the carbon structure with a negatively charged oxygen and a Na^+ "floating" around.
3. The negatively charged oxygen attacks the proton (H^+) to give the resulting product above.

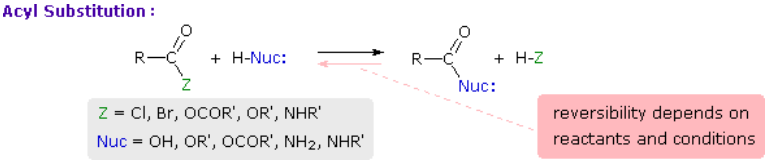
An Organometallic Example

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

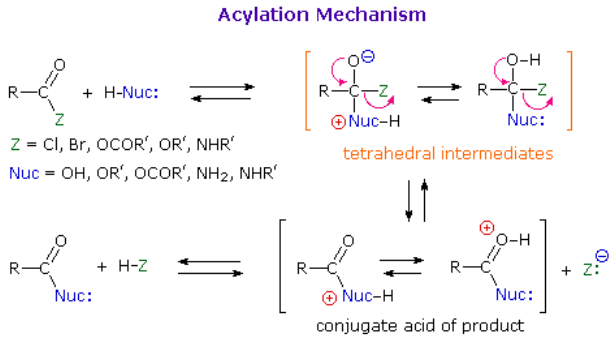


NUCLEOPHILIC ACYL SUBSTITUTION

This is probably the single most important reaction of carboxylic acid derivatives. The overall transformation is defined by the following equation, and may be classified either as **nucleophilic substitution at an acyl group** or as **acylation of a nucleophile**. For certain nucleophilic reagents the reaction may assume other names as well. If Nuc-H is water the reaction is often called **hydrolysis**, if Nuc–H is an alcohol the reaction is called **alcoholysis**, and for ammonia and amines it is called **aminolysis**.



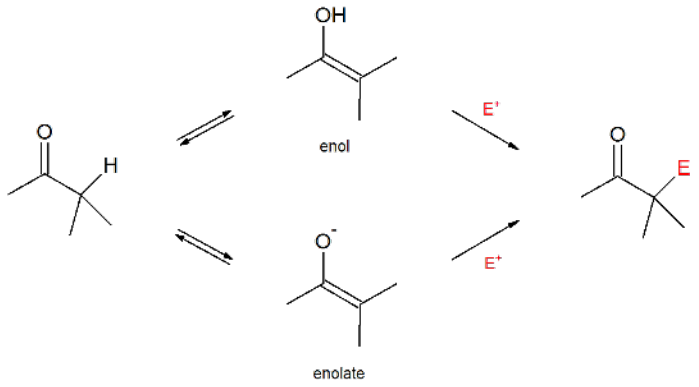
As illustrated in the following diagram, acylation reactions generally take place by an **addition-elimination process** in which a nucleophilic reactant bonds to the electrophilic carbonyl carbon atom to create a tetrahedral intermediate. This tetrahedral intermediate then undergoes an elimination to yield the products. In this two-stage mechanism bond formation occurs before bond cleavage, and the carbonyl carbon atom undergoes a hybridization change from sp^2 to sp^3 and back again. The facility with which nucleophilic reagents add to a carbonyl group was noted earlier for aldehydes and ketones.



Mechanism Toggle

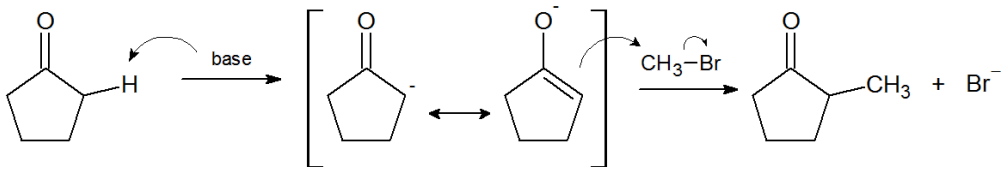
ALPHA-SUBSTITUTION REACTIONS

Now we will investigate reactions which occur a the carbon alpha to the carbonyl groups. These reactions involve two new nucleophilic species the enol and the enolate.



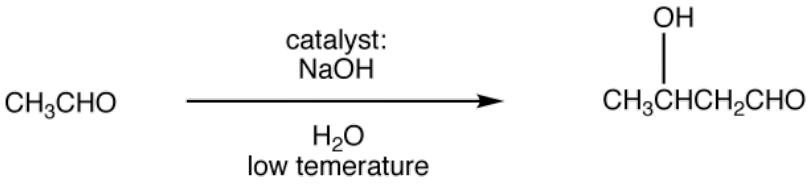
Note! The electrophile replaces the hydrogen on the alpha carbon.

The following is a specific example of this type of reaction. Here we methylate the carbon alpha to the carbonyl group through an enolate intermediate. The hydrogen on the alpha carbon is acidic because of the presence of the C=O group and is therefore preferentially abstracted by the base.



CARBONYL CONDENSATION REACTIONS

Enolizable aldehydes and enolizable ketones, in the presence of an acid or base catalyst usually in aqueous medium at low temperature, undergo a reaction, giving an aldol as the major product. This reaction is known as aldol reaction. The base-catalyzed aldol reaction, in which the catalyst is usually the hydroxide ion, is more common. Careful control of reaction temperature is critical because high temperatures promote aldol condensation. The optimum temperature depends on the nature of the aldehyde or ketone. Typically, heating the reaction mixture results in aldol condensation. For example:

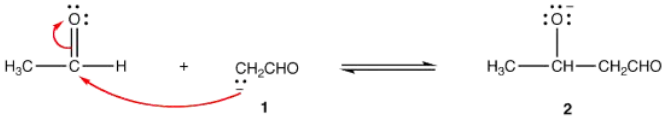


Mechanism:

Step 1: The hydroxide ion deprotanates the aldehyde reversibly.



Step 2: Enolate ion 1 adds to the unreacted aldehyde.



Step 3: Alkoxide ion 2 is protonated by water.



Since all three steps are reversible, the overall reaction is reversible and its equilibrium constant depends on the nature of the aldehyde or ketone. The reactions of aldehydes in which the α-carbon is a secondary carbon usually have large equilibrium constants; those of other aldehydes and ketones have small equilibrium constants. These observations suggest that the equilibrium constant of aldol reaction is sensitive to steric hindrance at the carbonyl carbon in the aldehyde or ketone.

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18.S: ETHERS AND EPOXIDES; THIOLS AND SULFIDES (SUMMARY)

CONCEPTS & VOCABULARY

18.0 Introduction

- Ethers are molecules containing oxygen which is bonded to two carbon groups.
- Thiols are sulfur analogues of alcohols with an SH group instead of OH.
- Sulfides are sulfur analogues of ethers with sulfur bonded to two carbon groups instead of oxygen.

18.1 Names and Properties of Ethers

- Ether groups are named as alkoxy groups.
- Ethers do not have intramolecular hydrogen bonding (unlike alcohols), therefore ethers have significantly reduced intermolecular forces causing boiling points that are much lower than similar sized alcohols.

18.2 Preparing Ethers

- Alkoxymercuration can be used to prepare an ether from an alkene.

18.3 Reactions of Ethers: Acidic Cleavage

- The carbon-oxygen bonds of ethers can be cleaved with strong acids through either nucleophilic substitution or elimination reactions.

18.4 Reactions of Ethers: Claisen Rearrangement

- The Claisen rearrangement is a [3, 3] sigmatropic rearrangement reaction that converts aryl or enol ethers into carbonyl compounds (though the aromatic version rearranges into a phenol to re-establish aromaticity.

18.5 Cyclic Ethers: Epoxides

- Epoxides, also called oxiranes, have a three-membered ring structure with one oxygen and two carbon atoms.
- Epoxides can be formed from alkenes by reaction with peroxy acids (MCPBA for example).
- Epoxides can be formed from halohydrin molecules by reaction with a base, which causes an intramolecular Williamson ether synthesis.

18.6 Reactions of Epoxides: Ring Opening

- When epoxides are ring opened under basic conditions, they follow S_N2 mechanism leading to the nucleophile adding to the less substituted side of the epoxide.
- When epoxides are ring opened under acidic conditions, they follow S_N1 mechanism leading to the nucleophile adding to the more substituted side of the epoxide.
- When epoxides are ring opened in aqueous reactions, the result is an anti-diol.
- Halo acids can be added to epoxides to form anti-halohydrins.

18.7 Crown Ethers

- Crown ethers are cyclic ethers containing several oxygen atoms.
- Crown ethers are named by the number of total atoms in the ring, followed by the word crown and finally the number of oxygen atoms (18-crown-6 for example).

18.8 Thiols and Sulfides

- Thiols can be prepared from alkyl halides through reaction with hydrosulfide ion (SH^-) or through a more complicated series of reactions including thiourea.
- Thiols can be oxidized with mild oxidizing agents to form disulfides.
- Disulfide bridges link cysteine residues in protein structures.
- Sulfides are sulfur analogues of ether, though are much better nucleophiles with sulfur in place of oxygen.

18.9 Spectroscopy of Ethers

- Ethers show standard C-H stretches and bends in IR along with a strong C-O stretch around 1000 cm^{-1}.
- In ^1H NMR, hydrogens on carbons adjacent to the oxygen typically appear between 3.4-4.5 ppm.
- Hydrogens on carbons of an epoxide ring typically appear between 2.5-3.5 ppm in ^1H NMR.

18.10 Interchapter: A Preview of Carbonyl Chemistry

- Carbonyl groups are one of the most important features in organic chemistry and consist of a sp^2 carbon double-bonded to oxygen.
- Carbonyl groups are present in ~10 different functional groups.

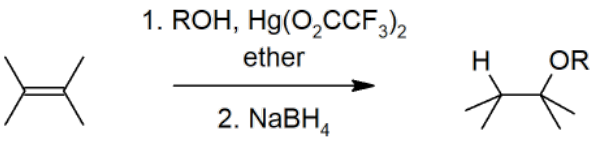
- Carbonyl groups are polarized with a partial positive charge on carbon and partial negative charge on oxygen. This makes the carbon atom an electrophile, while the oxygen can act as a nucleophile.
- Carbonyl groups can react through several mechanisms including nucleophilic addition and nucleophilic acyl substitution, alpha substitution and condensation.

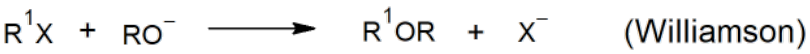
SKILLS TO MASTER

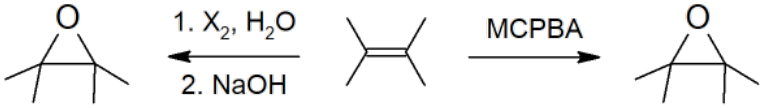
- Skill 18.1 Name ethers using common naming and IUPAC.
- Skill 18.2 Write reaction equations for preparation of ethers.
- Skill 18.3 Write mechanisms for reactions of ethers with strong halogen acids.
- Skill 18.4 Draw mechanisms for Cope and Claisen rearrangements.
- Skill 18.5 Draw mechanisms for ring-opening epoxides under acidic and basic conditions.
- Skill 18.6 Draw and name crown ethers.
- Skill 18.7 Explain how disulfide bridges contribute to protein structure.
- Skill 18.8 Give an example of S-adenosyl methionine activity in biological systems.
- Skill 18.9 Use IR and NMR spectra to identify ethers.

SUMMARY OF REACTIONS

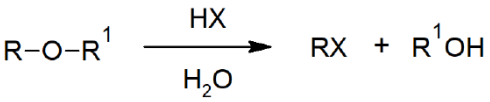
Ether and Epoxide Preparation

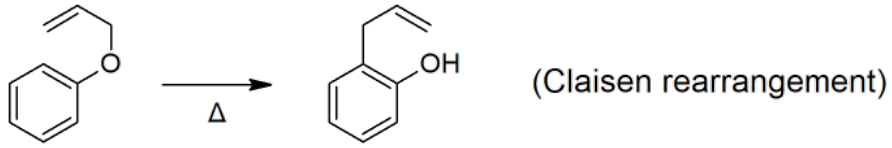


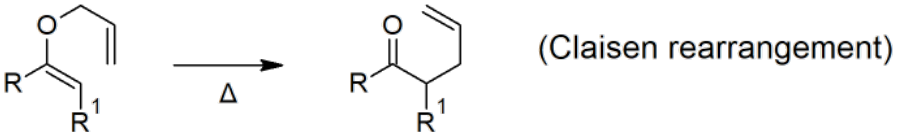




Ether Reactions

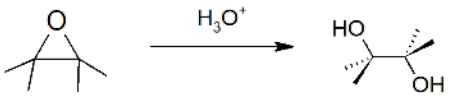


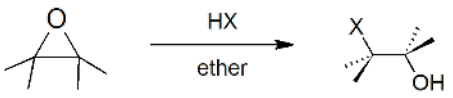


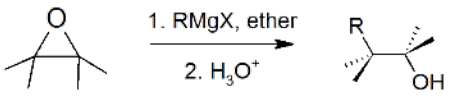


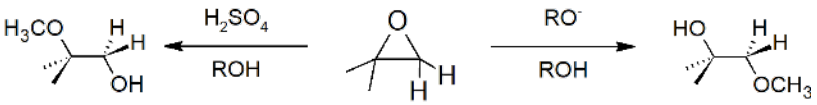
Epoxide Reactions

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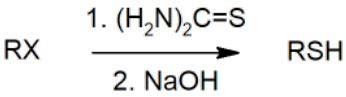


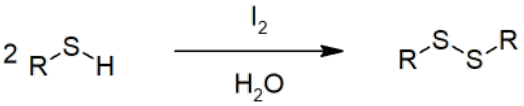


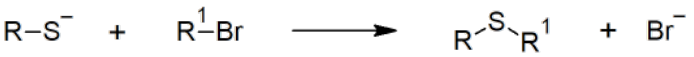


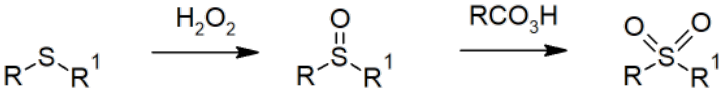


Sulfur Compound Reactions









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CHAPTER OVERVIEW

19: ALDEHYDES AND KETONES- NUCLEOPHILIC ADDITION REACTIONS

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19.1: Naming Aldehydes and Ketones
19.2: Preparing Aldehydes and Ketones
19.3: Oxidation of Aldehydes and Ketones
19.4: Nucleophilic Addition Reactions of Aldehydes and Ketones
19.5: Nucleophilic Addition of Water - Hydration
19.6: Nucleophilic Addition of HCN - Cyanohydrin Formation
19.7: Nucleophilic Addition of Hydride and Grignard Reagents - Alcohol Formation
19.8: Nucleophilic Addition of Amines - Imine and Enamine Formation
19.9: Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction
19.10: Nucleophilic Addition of Alcohols - Acetal Formation
19.11: Nucleophilic Addition of Phosphorus Ylides - The Wittig Reaction
19.12: Biological Reductions
19.13: Conjugate Nucleophilic Addition to α, β-unsaturated Aldehydes and Ketones
19.14: Spectroscopy of Aldehydes and Ketones
19.S: Aldehydes and Ketones (Summary)

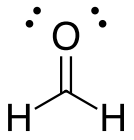
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19.0: CHAPTER OBJECTIVES AND PREVIEW OF CARBONYL CHEMISTRY

OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design a multi-step synthesis in which you may have to use any of the reactions discussed in this chapter together with any number of reactions from previous chapters.
- solve “road-map” problems that require a knowledge of the chemistry of aldehydes and ketones.
- use evidence from any combination of infrared spectroscopy, nuclear magnetic resonance spectroscopy, mass spectroscopy and chemical reactions to determine the structure of an unknown aldehyde or ketone.
- define, and use in context, the key terms introduced in this chapter.

In 1969 the molecule formaldehyde was discovered to be the first polyatomic organic molecule present in interstellar space by the National Radio Astronomy Observatory. The reactivity of formaldehyde gives it a wide variety of uses from embalming fluid to finger nail polish. Formaldehyde contain a C=O bond called a carbonyl, which is fundamental to study of organic chemistry. In this chapter we will begin a multi-chapter discussion on the chemistry of the carbonyl bond starting with aldehyde and ketone functional groups.



formaldehyde

In Chapter 19, we make a comprehensive study of the chemistry of aldehydes and ketones. Aldehydes and ketones are discussed together because their chemistry is very similar. However, as you work through the chapter, be sure to look for specific instances where the chemistry of these two classes of compounds differs.

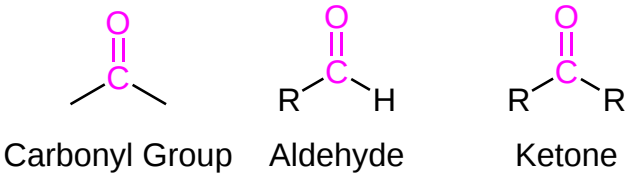
As usual, we begin the chapter with a discussion of nomenclature. This introduction is followed by descriptions of the methods used to prepare aldehydes and ketones in the laboratory. You will notice that a number of these reactions have already appeared in previous units. Note that an important difference between aldehydes and ketones is the resistance of ketones to oxidation.

A large part of this chapter is concerned with the addition of various nucleophiles to the carbonyl group of aldehydes and ketones. In particular, we discuss the addition of a variety of nitrogen-containing compounds, alcohols and phosphorus ylides. Many of these reactions are important to chemists concerned primarily with the synthesis of new organic compounds.

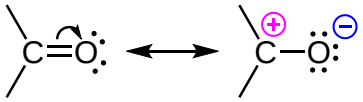
We also describe the Cannizzaro reaction and conjugate addition to α, β-unsaturated carbonyl compounds. We mention the occurrence of nucleophilic addition reactions in biological systems, and conclude the unit with a look at the use of spectroscopic techniques in the analysis of aldehydes and ketones.

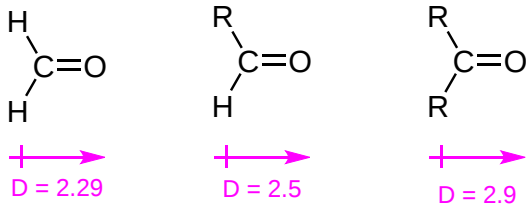
PREVIEW OF CARBONYL CHEMISTRY

Aldehydes and ketones are organic compounds which incorporate a carbonyl functional group, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an aldehyde. If both are carbons, the compound is a ketone.

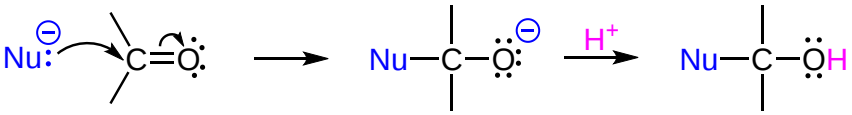


Because of the greater electronegativity of oxygen, the carbonyl group is polar, and aldehydes and ketones have larger molecular dipole moments (D) than do alkenes. The resonance structures below illustrate this polarity, and the relative dipole moments of formaldehyde, other aldehydes and ketones.





This polarity causes the carbonyl carbon to be partially positive (electrophillic) and the oxygen partially negative (nucleophillic). The C=O bond is prone to nucleophillic attack because or carbon's positive charge and oxygen's negative charge. In general, nucleophiles attack the electrophilic carbon and become a part of the structure while the oxygen is protonated forming a hydroxyl group.



Aldehydes and ketones are widespread in nature and are often combined with other functional groups. Examples of naturally occurring molecules which contain an aldehyde or ketone functional group are shown in the following two figures. The compounds in the **figure 1** are found chiefly in plants or microorganisms and those in the **figure 2** have animal origins. Many of these molecular structures are chiral.

When chiral compounds are found in nature they are usually enantiomerically pure, although different sources may yield different enantiomers. For example, carvone is found as its levorotatory (R)-enantiomer in spearmint oil, whereas, caraway seeds contain the dextrorotatory (S)-enantiomer. In this case the change of the stereochemistry causes a drastic change in the perceived scent. Aldehydes and ketones are known for their sweet and sometimes pungent odors. The odor from vanilla extract comes from the molecule vanillin. Likewise, benzaldehyde provides a strong scent of almonds and is this author's favorite chemical smell. Because of their pleasant fragrances aldehyde and ketone containing molecules are often found in perfumes. However, not all of the fragrances are pleasing. In particular, 2-heptanone provides part of the sharp scent from blue cheese and (R)-muscone is part of the musky smell from the Himalayan musk deer. Lastly, ketones show up in many important hormones such as progesterone (a female sex hormone) and testosterone (a male sex hormone). Notice how subtle differences in structure can cause drastic changes in biological activity. The ketone functionality also shows up in the anti-inflammatory steroid, cortisone.

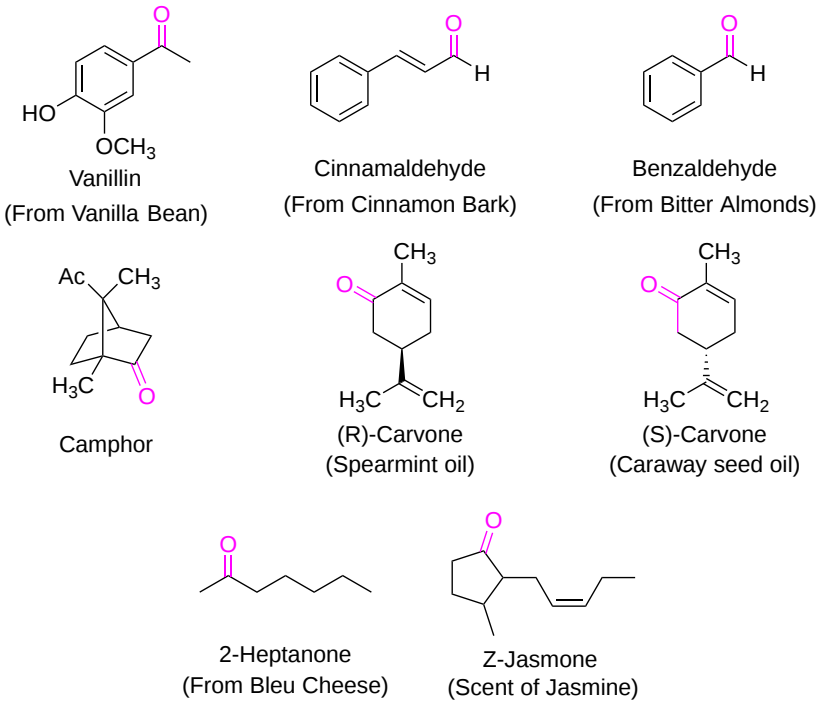


Figure 1. Aldehyde and ketone containing molecules isolated from plant sources.

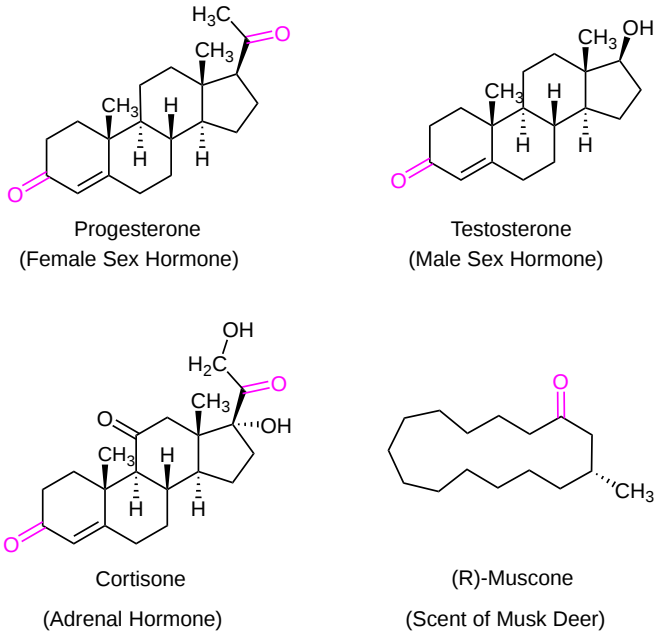


Figure 2. Aldehyde and ketone containing molecules isolated from animal sources.

CONTRIBUTORS AND ATTRIBUTIONS

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
-
- Layne Morsch (University of Illinois Springfield)

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19.1: NAMING ALDEHYDES AND KETONES

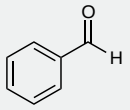
OBJECTIVES

After completing this section, you should be able to

- provide the IUPAC name of an aldehyde or ketone, given its Kekulé, condensed, or skeletal structure.
- draw the structure of an aldehyde or ketone, given its IUPAC name.
- draw the structure of the following aldehydes and ketones, given their common names: formaldehyde, acetaldehyde, benzaldehyde, acetone, acetophenone, benzophenone.

STUDY NOTES

We will only use those common names listed under Objective 3, above. We will use systematic names in all other cases. For example, the systematic name of the compound shown below is benzenecarbaldehyde, but it has the common name of benzaldehyde.



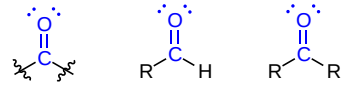
benenecarbaldehyde
(benzaldehyde)

When naming unsaturated aldehydes and ketones, you must give the carbonyl group "priority" over the double bond when you are deciding which end of the carbon chain to begin numbering The carbonyl-carbon of an aldehyde will always be at the end of the carbon chain in an acyclic compound; and therefore numbering always starts at this carbon. It is for this reason, too, that the number "1" is not required when naming a compound such as 2-ethyl-4-methylpentanal.

The most potent and varied odors are aldehydes. Ketones are widely used as industrial solvents. Aldehydes and ketones contain the carbonyl group. Aldehydes are considered the most important functional group. They are often called the formyl or methanoyl group. Aldehydes derive their name from the *dehyd*ration of *al*cohols. Aldehydes contain the carbonyl group bonded to at least one hydrogen atom. Ketones contain the carbonyl group bonded to two carbon atoms.

INTRODUCTION TO NAMING CARBONYLS

Aldehydes and ketones are organic compounds which incorporate a **carbonyl functional group**, C=O. The carbon atom of this group has two remaining bonds that may be occupied by hydrogen, alkyl or aryl substituents. If at least one of these substituents is hydrogen, the compound is an **aldehyde**. If neither is hydrogen, the compound is a **ketone**.

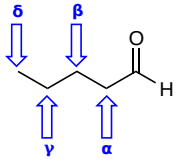


carbonyl group | aldehyde | ketone

NAMING ALDEHYDES

The IUPAC system of nomenclature assigns a characteristic suffix ***-al*** to aldehydes. For example, $H_2C{=}O$ is methan**al**, more commonly called formaldehyde. Since an aldehyde carbonyl group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name. There are several simple carbonyl containing compounds which have common names which are retained by IUPAC.

Also, there is a common method for naming aldehydes and ketones. For aldehydes common parent chain names, similar to those used for carboxylic acids, are used and the suffix ***–aldehyde*** is added to the end. In common names of aldehydes, carbon atoms near the carbonyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.



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If the aldehyde group (-CHO) is attached to a ring the suffix ***–carbaldehyde*** is added to the name of the ring. The carbon attached to this group will get the #1 location number in naming the ring.

SUMMARY OF ALDEHYDE NOMENCLATURE RULES

1. Aldehydes take their name from their parent alkane chains. The ***-e*** is removed from the end and is replaced with ***-al***.
2. The aldehyde funtional group is given the #1 numbering location and this number is not included in the name.
3. For the common name of aldehydes start with the common parent chain name and add the suffix ***-aldehyde***. Substituent positions are shown with Greek letters.
4. When the -CHO functional group is attached to a ring the suffix ***-carbaldehyde*** is added, and the carbon attached to that group is C1.

EXAMPLE 19.1.1

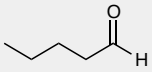
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



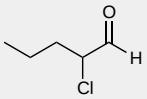
methanal
(formaldehyde)



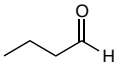
ethanal
(acetaldehyde)



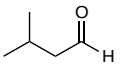
pentanal
(valeraldehyde)



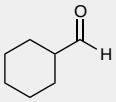
2-chloropentanal
(α-chlorovaleraldehyde)



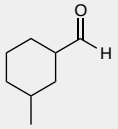
butanal
(butyraldehyde)



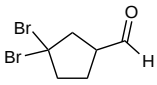
3-methylbutanal
(isovaleraldehyde)



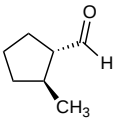
cyclohexanecarbaldehyde



3-methylcyclohexanecarbaldehyde



3,3-dibromocyclopentanecarbaldehyde



trans-2-methylcyclopentanecarbaldehyde

NAMING KETONES

The IUPAC system of nomenclature assigns a characteristic suffix of **-one** to ketones. A ketone carbonyl function may be located anywhere within a chain or ring, and its position is usually given by a location number. Chain numbering normally starts from the end nearest the carbonyl group. Very simple ketones, such as propanone and phenylethanone do not require a locator number, since there is only one possible site for a ketone carbonyl function

The common names for ketones are formed by naming both alkyl groups attached to the carbonyl then adding the suffix **-ketone**. The attached alkyl groups are arranged in the name alphabetically.

SUMMARY OF KETONE NOMENCLATURE RULES

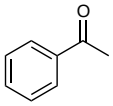
1. Ketones take their name from their parent alkane chains. The ending ***-e*** is removed and replaced with ***-one***.
2. The common name for ketones are simply the **substituent groups listed alphabetically + *ketone*.**
3. Some simple ketones are known by their common names. Such as *propanone* which is commonly referred to as *acetone*.

EXAMPLE 19.1.2

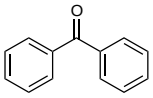
The IUPAC system names are given on top while the common name is given on the bottom in parentheses.



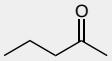
propanone
(acetone)



acetophenone
(methyl phenyl ketone)



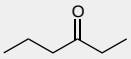
benzophenone
(diphenyl ketone)



2-pentanone
(methyl propyl ketone)



3-methyl-2-butanone
(methyl isopropyl ketone)

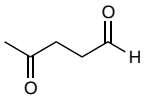


3-hexanone
(ethyl propyl ketone)

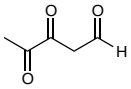
NAMING ALDEHYDES AND KETONES IN THE SAME MOLECULE

As with many molecules with two or more functional groups, one is given priority while the other is named as a substituent. Because aldehydes have a higher priority than ketones, molecules which contain both functional groups are named as aldehydes and the ketone is named as an **"oxo"** substituent. It is not necessary to give the aldehyde functional group a location number, however, it is usually necessary to give a location number to the ketone.

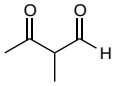
EXAMPLE 19.1.3



4-oxopentanal



3,4-dioxopentanal

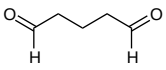


2-methyl-3-oxobutanal

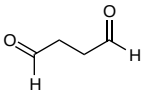
NAMING DIALDEHYDES AND DIKETONES

For dialdehydes the location numbers for both carbonyls are omitted because the aldehyde functional groups are expected to occupy the ends of the parent chain. The ending **–dial** is added to the end of the parent chain name.

EXAMPLE 19.1.4



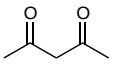
pentanedial



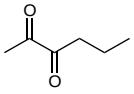
butanedial

For diketones both carbonyls require a location number. The ending **-dione** is added to the end of the parent chain.

EXAMPLE 19.1.5



2,4-pentanedione



2,3-hexanedione

NAMING CYCLIC KETONES AND DIKETONES

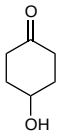
In cyclic ketones the carbonyl group is assigned location position #1, and this number is not included in the name, unless more than one carbonyl group is present. The rest of the ring is numbered to give substituents the lowest possible location numbers. Remember the prefix **cyclo** is included before the parent chain name to indicate that it is in a ring. As with other ketones the **–e** ending is replaced with the **–one** to indicate the presence of a ketone.

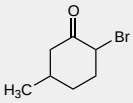
With cycloalkanes which contain two ketones both carbonyls need to be given a location numbers. Also, an **–e** is not removed from the end but the suffix **–dione** is added.

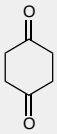
EXAMPLE 19.1.6


cyclopentanone


2-bromocyclopentanone


4-hydroxycyclohexanone


2-bromo-5-methylcyclohexanone

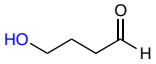

1,4-cyclohexanedione

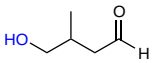

1,2-cyclopentanedione

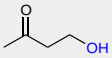
NAMING CARBONYLS AND HYDROXYLS IN THE SAME MOLECULE

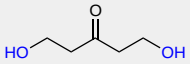
When an aldehyde or ketone is present in a molecule which also contains an alcohol functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of alcohols the **OH** is named as a **hydroxyl** substituent. However, the **l** in hydroxyl is generally removed.

EXAMPLE 19.1.7


4-hydroxybutanal


4-hydroxy-3-methylbutanal


4-hydroxy-2-butanone


1,5-dihydroxy-3-pentanone

NAMING CARBONYLS AND ALKENES IN THE SAME MOLECULE

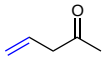
When an aldehyde or ketone is present in a molecule which also contains an alkene functional group the carbonyl is given nomenclature priority by the IUPAC system. This means that the carbonyl is given the lowest possible location number and the appropriate nomenclature suffix is included.

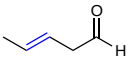
When carbonyls are included with an alkene the following order is followed:

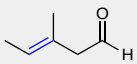
(Location number of the alkene)-(Prefix name for the longest carbon chain minus the **-ane** ending)-(an **-en** ending to indicate the presence of an alkene)-(the location number of the carbonyl if a ketone is present)-(either an **–one** or and **-anal** ending).

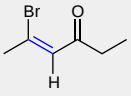
Remember that the carbonyl has priority so it should get the lowest possible location number. Also, remember that cis/tran or E/Z nomenclature for the alkene needs to be included if necessary.

EXAMPLE 19.1.8


4-penten-2-one


trans-3-pentenal

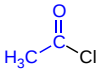

(*E*)-3-methyl-3-pentenal


(*Z*)-5-bromo-4-hexen-3-one

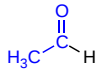
ALDEHYDES AND KETONES AS FRAGMENTS

- **Alkanoyl** is the common name of the R-C=O fragment, though the older naming, *acyl*, is still widely used.
- **Formyl** is the common name of the H-C=O fragment.
- **Acetyl** is the common name of the CH_3-C=O- fragment.

EXAMPLE 19.1.9



acetyl chloride



acetylaldehyde

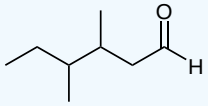


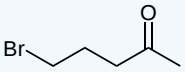
formyl fluoride

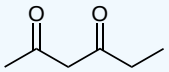
EXERCISES

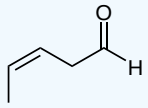
EXERCISE 19.1.1

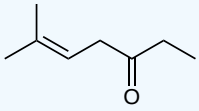
Give the IUPAC name for each compound:

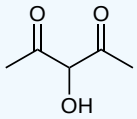
a) 

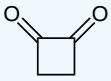
b) 

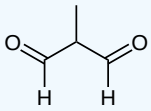
c) 

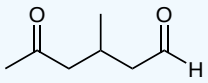
d) 

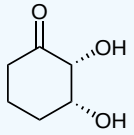
e) 

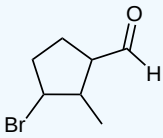
f) 

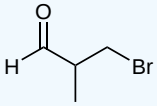
g) 

h) 

i) 

j) 

k) 

l) 

Answer

a. 3,4-dimethylhexanal
b. 5-bromo-2-pentanone
c. 2,4-hexanedione
d. *cis*-3-pentenal
e. 6-methyl-5-hepten-3-one
f. 3-hydroxy-2,4-pentanedione
g. 1,2-cyclobutanedione
h. 2-methyl-propanedial
i. 3-methyl-5-oxo-hexanal
j. *cis*-2,3-dihydroxycyclohexanone
k. 3-bromo-2-methylcyclopentanecarboaldehyde

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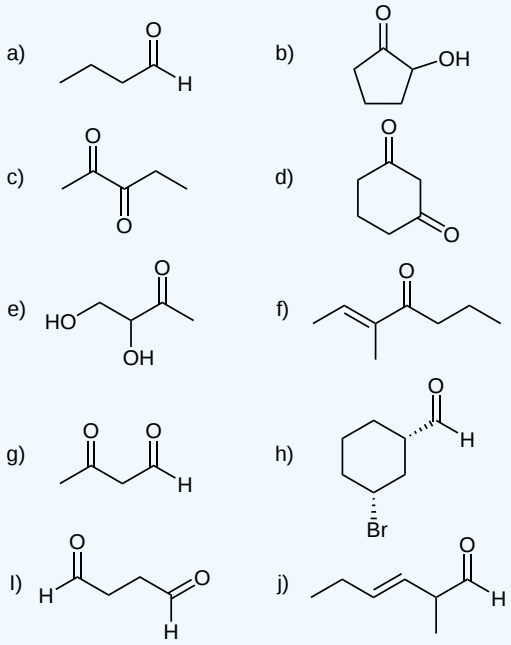
l. 3-bromo-2-methylpropanal

EXERCISE 19.1.2

Give the structure corresponding to each IUPAC name:

a. butanal
b. 2-hydroxycyclopentanone
c. 2,3-pentanedione
d. 1,3-cyclohexanedione
e. 3,4-dihydoxy-2-butanone
f. 3-methyl-2-hepten-4-one
g. 3-oxobutanal
h. *cis*-3-bromocyclohexanecarboaldehyde
i. butanedial
j. *trans*-2-methyl-3-hexenal

Answer



REFERENCES

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry. 5th ed. New York: W.H. Freeman, 2007.
2. Zumdahl, Steven S., and Susan A. Zumdahl. Chemistry. 6th ed. Boston: Houghton Mifflin College Division, 2002.

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19.2: PREPARING ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

1. describe in detail the methods for preparing aldehydes discussed in earlier units (i.e., the oxidation of primary alcohols and the cleavage of alkenes).
2. write an equation to describe the reduction of an ester to an aldehyde.
   a. identify the product formed when a given ester is reduced with diisobutylaluminum hydride.
   b. identify the reagents and conditions used in the reduction of an ester to an aldehyde.
   c. identify the disadvantages of using diisobutylaluminum hydride to reduce an ester to an aldehyde.
3. describe in detail the methods for preparing ketones discussed in earlier units (i.e., the oxidation of secondary alcohols, the ozonolysis of alkenes, Friedel-Crafts acylation, and the hydration of terminal alkynes).
   a. write an equation to illustrate the formation of a ketone through the reaction of an acid chloride with a dialkylcopper lithium reagent.
   b. identify the ketone produced from the reaction of a given acid chloride with a specified dialkylcopper lithium reagent.
   c. identify the acid chloride, the dialkylcopper lithium reagent, or both, needed to prepare a specific ketone.

STUDY NOTES

You may wish to review the sections in which we discuss the oxidation of alcohols (17.7) and the cleavage of alkenes (8.8). A third method of preparing aldehydes is to reduce a carboxylic acid derivative; for example, to reduce an ester with diisobutylaluminum hydride (DIBAL-H).

There are essentially five methods of preparing ketones in the laboratory. Four of them have been discussed in earlier sections:

1. the oxidation of a secondary alcohol—Section 17.7.
2. the ozonolysis of an alkene—Section 8.8.
3. Friedel-Crafts acylation—Section 16.3.
4. the hydration of a terminal alkyne—Section 9.5.

The "new" method we introduce in this section involves the reaction of an acid chloride with a diorganocopper reagent. The latter substances were discussed in Section 10.9, which you might now wish to review.

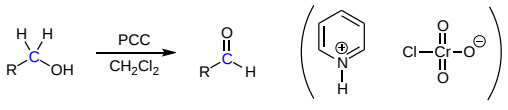
Aldehydes and ketones can be prepared using a wide variety of reactions. Although these reactions are discussed in greater detail in other sections, they are listed here as a summary and to help with planning multistep synthetic pathways. Please use the appropriate links to see more details about the reactions.

FORMATION OF ALDEHYDES

OXIDATION OF 1^{O} ALCOHOLS TO FORM ALDEHYDES (SECTION 17.7)

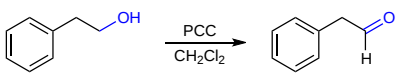
PCC

Pyridinium chlorochromate (PCC) is a milder version of chromic acid. PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids.



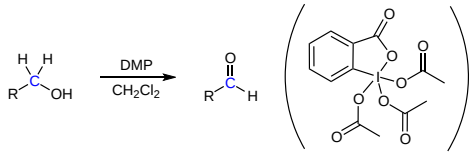
pyridinium chlorochromate (PCC)

Example oxidation of a primary alcohol to an aldehyde



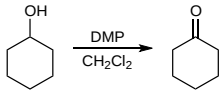
DESS-MARTIN PERIODINANE (DMP)

PCC is being replaced in laboratories by Dess-Martin periodinane (DMP), which has several practical advantages over PCC, such as producing higher yields and requiring less rigorous reaction conditions. DMP is named after Daniel Dess and James Martin, who developed it in 1983. Similar to PCC, it oxidizes primary alcohols to aldehydes without continuing the oxidation to a carboxylic acid. It can also be used to oxidize secondary alcohols to ketones.



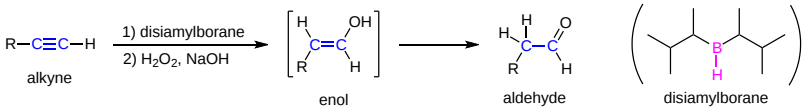
Dess-Martin periodinane

Example oxidation of an alcohol to a ketone using DMP

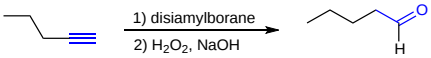


HYDRATION OF AN ALKYNES TO FORM ALDEHYDES (SECTION 9.5)

Anti-Markovnikov addition of a hydroxyl group to an alkyne forms an aldehyde. The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. This can be accomplished by hydroboration-oxidation reactions.

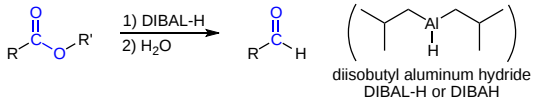


Example reaction of a terminal alkyne with disiamylborane followed by oxidation with hydrogen peroxide and hydroxide converting 1-pentyne to pentanal.



HYDRIDE REDUCTION OF ESTERS TO FORM ALDEHYDES (SECTION 21.8)

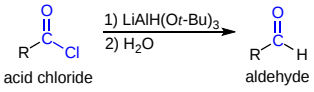
Various hydride sources allow for the partial reduction of some carboxylic acid derivatives to form aldehydes. These reactions are usually carried out at low temperatures (-78 ^{o}C) to prevent over reaction with the aldehyde product.



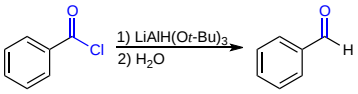
DIBAL-H reduction of methyl benzoate to benzaldehyde

HYDRIDE REDUCTION OF ACID CHLORIDES TO FORM ALDEHYDES (SECTIONS 21.6)

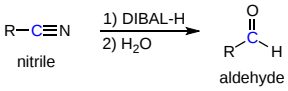
Reduction of acid chlorides to aldehydes requires hydride reagents with reduced reactivity as lithium aluminum hydride will continue reducing to the primary alcohol.



Example reduction of an acid halide to form an aldehyde



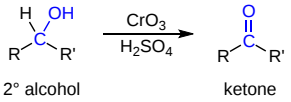
HYDRIDE REDUCTION OF A NITRILE TO FORM ALDEHYDES



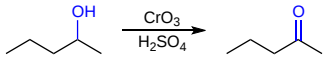
FORMATION OF KETONES

OXIDATION OF 2^{O} ALCOHOLS TO FORM KETONES (SECTION 17.7)

Oxidation of 2° alcohols to form ketones typically uses Jones reagent (CrO_3 in H_2SO_4) but many other oxidizing agents can be used.

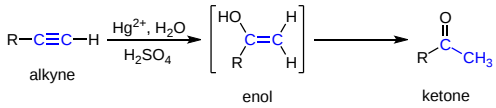


Example oxidation of a secondary alcohol to a ketone

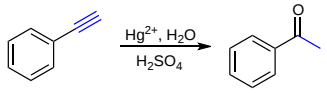


HYDRATION OF ALKYNES TO FORM KETONES (SECTION 9.4)

The addition of a hydroxyl group to an alkyne causes tautomerization which subsequently forms a carbonyl. Markovnikov addition of a hydroxyl group to an alkyne forms a ketone.

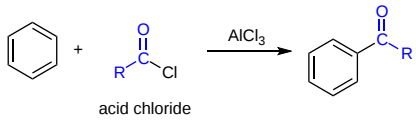


Example reaction of an alkyne with Hg^{2+}, H_2O, and H_2SO_4 to give a ketone

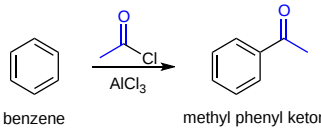


FRIEDEL-CRAFTS ACYLATION TO FORM A KETONE (SECTION 16.3)

Aromatic ketones can synthesized through Friedel–Crafts acylation of an aromatic ring with an acid chloride. Aluminum chloride ($AlCl_3$) is used as a Lewis acid catalyst.

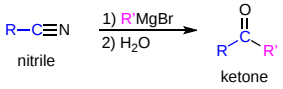


Example of Friedel-Crafts acylation to form a ketone from benzene.

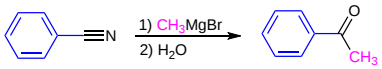


REACTION OF GRIGNARD REAGENTS WITH NITRILES TO FORM KETONES (SECTION 20.7)

Grignard reagents can attack the electophillic carbon in a nitrile to form an imine salt. This salt can then be hydrolyzed to become a ketone.

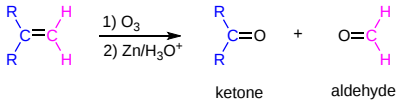


Example of Grignard addition to a nitrile to give a ketone.

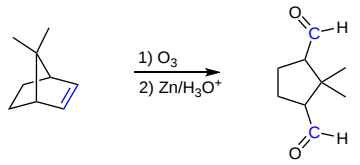


ALKENES CAN BE CLEAVED USING OZONE (O_3) TO FORM ALDEHYDES AND/OR KETONES (SECTION 8.8)

Ozonolysis is a method of oxidatively cleaving alkenes or alkynes using ozone (O_3), a reactive allotrope of oxygen. The process allows for carbon-carbon double or triple bonds to be replaced by double bonds with oxygen.

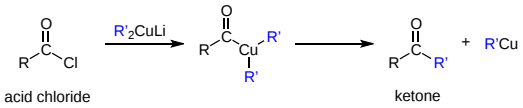


Example ozonolysis of an alkene to form aldehydes.

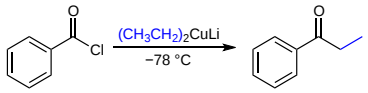


ORGANOCUPRATE REAGENTS CONVERT ACID CHLORIDES TO KETONES (SECTION 21.4)

An important reaction exhibited by lithium alkylcopper reagents (Gilman Reagents), is the nucleophilic addition to acid chlorides. Gilman reagents are a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of organocuprate reagents is slightly different and this difference is exploited to allow for a single nucleophilic addition to form a ketone.



Example of organocuprate addition to an acid chloride to generate a ketone.



? EXERCISE 19.2.1

What reagents would be required to prepare hexanal from the following starting materials?

a. $CH_3CH_2CH_2CH_2CH_2CH_2OH$
b. $CH_3CH_2CH_2CH_2CH_2CH{=}CH_2$
c. $CH_3CH_2CH_2CH_2CO_2CH_3$
d. $CH_3CH_2CH_2CH{=}CH_2$

Answer

a. Dess–Martin periodinane or PCC in CH_2Cl_2
b. 1. O_3, 2. Zn/H_3O^+
c. 1. DIBAH 2. H_2O
d. 1. BH_3 2. $H_2O_2/NaOH$; 2. Dess–Martin periodinane or PCC

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19.3: OXIDATION OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

- write an equation for the oxidation of an aldehyde using
  - CrO_3/sulphuric acid.
  - Tollens reagent.
- explain the difference in structure which makes aldehydes susceptible to oxidation and ketones difficult to oxidize.
- identify the carboxylic acid produced when a given aldehyde is oxidized.
- identify the aldehyde, the oxidizing agent, or both, needed to prepare a given carboxylic acid.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Tollens reagent

STUDY NOTES

An important difference between aldehydes and ketones is the ease with which the latter can be oxidized. Tollen's reagent is a classical organic laboratory technique to test for the presence of an aldehyde. The reagent consists of silver(I) ions dissolved in dilute ammonia. When the aldehyde is oxidized, the silver(I) ions are reduced to silver metal. When the reaction is carried out in a test-tube, the metallic silver is deposited on the walls of the tube, giving it a mirrorlike appearance. This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

WHY DO ALDEHYDES AND KETONES BEHAVE DIFFERENTLY?

Aldehydes have a proton attached to the carbonyl carbon which can be abstracted, allowing them to be easily oxidized to form carboxylic acids. The lack of this hydrogen, makes ketones generally inert to these oxidation conditions. Nevertheless, ketones can be oxidized but only under extreme conditions.

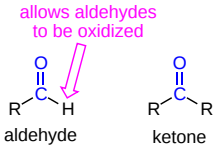


Figure **19.3.1**: This characteristic accounts for the term "silver mirror test" which is applied when this reaction is used to distinguish between aldehydes and ketones—the latter, of course, do not react.

A significant distinction between aldehydes and ketones lies in their susceptibility to oxidation, with aldehydes being more easily oxidized than ketones. One of the classic methods for identifying aldehydes in the laboratory is through the use of **Tollen's reagent** which consists of silver(I) ions dissolved in dilute ammonia. When an aldehyde is present, it undergoes oxidation, causing the silver(I) ions to be reduced to metallic silver. This reduction results in the deposition of silver on the surface of the test tube, forming a reflective, mirror-like coating. This reaction is commonly referred to as the "silver mirror test," and it serves as a reliable way to distinguish aldehydes from ketones. Ketones, in contrast, do not react with Tollen's reagent, making this test specific for aldehydes.

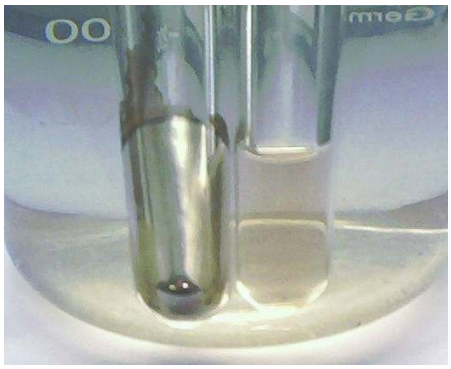
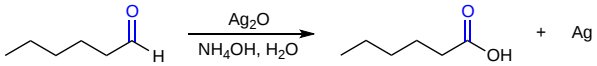


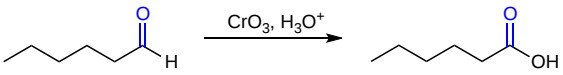
Figure **19.3.2**: Tollens test for Aldehyde. The left side is positive (silver mirror) and the right side is negative.



Oxidation of hexanal to form hexanoic acid using Tollens Reagent

OXIDATION OF ALDEHYDES

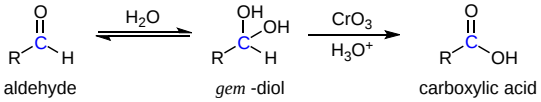
There are a wide variety of reagents which can cause the oxidation of aldehydes to carboxylic acids. The most common reagent for this conversion is CrO_3 in aqueous acid also called **Jones Reagent**. This reaction generally gives good yields at room temperature.



Example of the oxidation of hexanal to form hexanoic acid using Jones Reagent

MECHANISM

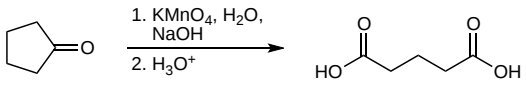
The oxidation of aldehydes occur through the reversible nucleophilic addition of water to the carbonyl to form a gem-diol functional group. This addition reaction is discussed in greater detail in Section 19.5. One of the OH groups of the *gem*-diol is oxidized to create a carbonyl (C=O) thereby forming a carboxylic acid.



aldehyde *gem* -diol carboxylic acid

OXIDATION OF KETONES AND BAEYER-VILLIGER OXIDATION

Because ketones do not have hydrogen atom attached to their carbonyl, they are resistant to oxidation. Only very strong oxidizing agents such as potassium manganate(VII) (potassium permanganate) solution oxidize ketones. However, this type of powerful oxidation occurs with cleavage, breaking carbon-carbon bonds and forming two carboxylic acids. Because of this destructive nature this reaction is rarely used.

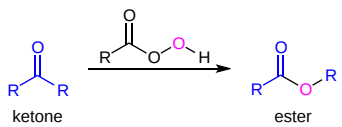


Oxidation of cyclopentanone to form pentanedioic acid

Peroxycarboxylic acids, such as **meta-chloroperoxybenzoic acid (mCPBA)**, are capable of oxidizing ketones to esters in a reaction known as the **Baeyer-Villiger oxidation**. Baeyer-Villiger oxidation has considerable synthetic utility because ketones normally are difficult to oxidize without degrading the structure to smaller fragments.

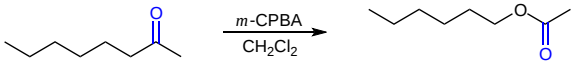


peroxycarboxylic acid *meta* -chloroperoxybenzoic acid

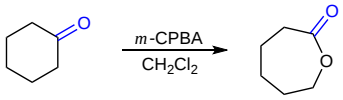


ketone ester

Baeyer-Villiger oxidations can be used with both straight chain ketones and cyclic ketones as shown in the following examples.



Baeyer-Villiger Oxidation of 2-octanone to form hexyl ethanoate

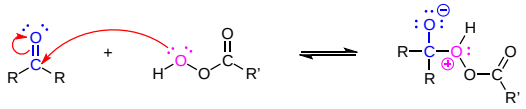


Baeyer-Villiger Oxidation of cyclohexanone to 6-hexanolactone

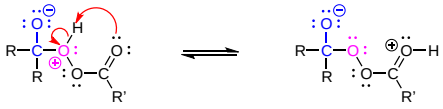
MECHANISM

The mechanism of the Baeyer-Villiger oxidation has been studied extensively and is of interest because it involves a rearrangement step in which a substituent group (R) moves from a carbon to an oxygen. In the first step, one oxygen from the peroxy carboxylic acid adds to the carbonyl group of the ketone. The adduct has multiple oxygen atoms on which protons can reside. An intramolecular proton transfer followed by protonation allows for generation of the Criegee intermediate. Migration of an alkyl group and elimination of a carboxylic acid, R^1CO_2H, then occur in the fourth step. This generates a protonated form of the ester product, which is deprotonated in the final step of the mechanism.

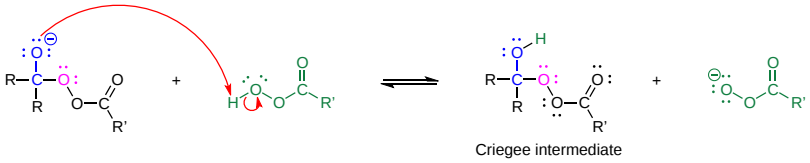
STEP 1: NUCLEOPHILIC ATTACK ON THE CARBONYL



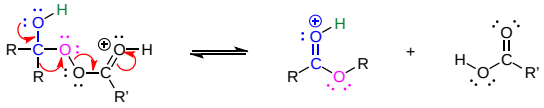
STEP 2: INTRAMOLECULAR PROTON TRANSFER



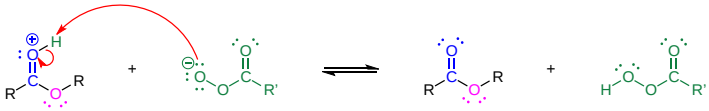
STEP 3: PROTONATION OF THE ALKOXIDE



STEP 4: MIGRATION OF AN ALKYL GROUP



STEP 5: DEPROTONATION



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19.4: NUCLEOPHILIC ADDITION REACTIONS OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

- give a general description of the nucleophilic addition reactions of aldehydes and ketones, identifying the two possible courses (or variations) that such reactions can take after the initial attack by the nucleophile.
- explain why, in general, aldehydes undergo nucleophilic addition reactions more readily than do ketones, and determine which of two given aldehydes or ketones will react most readily in such reactions.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

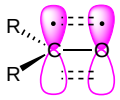
- nucleophilic addition reaction

STUDY NOTES

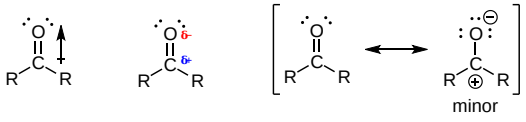
We have already discussed electrophilic addition reactions at some length; in this section nucleophilic addition reactions will be presented. Nucleophilic addition reactions involve the initial attack of a nucleophile on the slightly positive carbon center of the carbonyl group.

INTRODUCTION

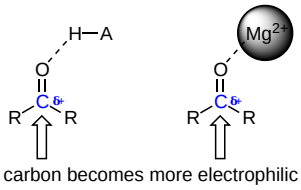
Before we consider in detail the reactivity of aldehydes and ketones, we need to look back and remind ourselves of what the bonding picture looks like in a carbonyl. Carbonyl carbons are sp^2 hybridized, with the three sp^2 orbitals forming three sigma bonds by overlapping with orbitals from the R groups (carbons or hydrogens) and an sp^2 hybrid orbital from oxygen. Due to the sp^2 orbitals, these three bonds adopt trigonal planar geometry seen in carbonyls. The carbonyl carbon's remaining unhybridized 2p orbital is perpendicular to this plane, and forms a 'side-by-side' pi bond by overlapping with a 2p orbital from the carbonyl oxygen.



The carbon-oxygen double bond is polar since oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow (pointing toward the more electronegative atom), or by showing the oxygen as holding a partial negative charge and the carbonyl carbon with a partial positive charge. A third way to illustrate the carbon-oxygen dipole is to consider the two main resonance contributors of a carbonyl group: the major form, which is what you typically see drawn in Lewis structures, and a minor but very important contributor in which both electrons in the pi bond are localized on the oxygen, giving it a full negative charge. The latter depiction shows the carbon with an empty 2p orbital and a full positive charge.



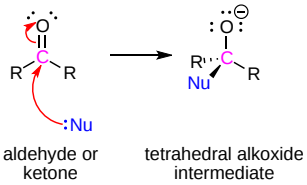
The result of carbonyl bond polarization, however it is depicted, is straightforward to predict. The carbon, because it is electron-poor, is an electrophile: it is a great target for attack by an electron-rich nucleophilic group. Because the oxygen end of the carbonyl double bond bears a partial negative charge, anything that can help to stabilize this charge by accepting some of the electron density will increase the bond's polarity and make the carbon more electrophilic. Very often a general acid group serves this purpose, donating a proton to the carbonyl oxygen. The same effect can also be achieved if a Lewis acid, such as a magnesium ion (Mg^{2+}), is located near the carbonyl oxygen.



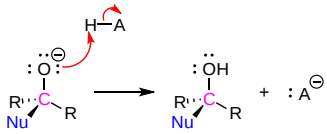
NUCLEOPHILIC ADDITION TO A CARBONYL

Most important reactions involving carbonyl groups characteristically have a nucleophilic addition as part of their mechanism. The generic mechanism for the nucleophilic addition of a negatively charged nucleophile to a carbonyl is shown below.

In the first step of the nucleophilc addition mechanism, the nucleophile forms a bond with the the electrophilic C=O carbon atom. This causes the rehybridization of the carbonyl carbon from sp^2 to sp^3. These reactions differ from nucleophilic substitution reactions since neither aldehydes nor ketones have a leaving group. Instead electrons in the pi bond are pushed up to the electronegative oxygen atom forming a tetrahedral alkoxide intermediate.

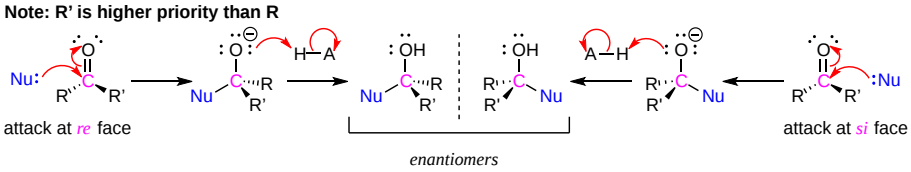


In the second step of the mechanism, the alkoxide is protonated by the addition of an acid to form an alcohol.



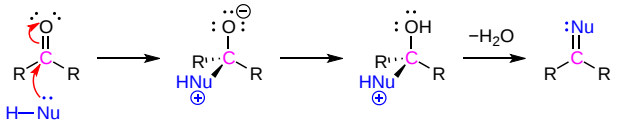
STEREOCHEMISTRY OF NUCLEOPHILIC ADDITION TO A CARBONYL

When the two groups adjacent to a carbonyl are not the same, we can distinguish between the **re** and **si** 'faces' of the planar structure. The concept of a trigonal planar group having two distinct faces comes into play when we consider the stereochemical outcome of a nucleophilic addition reaction. Notice that in the course of a carbonyl addition reaction, the hybridization of the carbonyl carbon changes from sp^2 to sp^3, meaning that the bond geometry changes from trigonal planar to tetrahedral. If the two R groups are not equivalent, then a chiral center is created upon addition of the nucleophile. The configuration of the new chiral center depends upon which side of the carbonyl plane the nucleophile attacks from. Reactions of this type often result in a 50:50 racemic mixture of stereoisomers, but it is also possible that one stereoisomer may be more abundant, depending on the structure of the reactants and the conditions under which the reaction takes place.



NUCLEOPHILIC ADDITION OF A NEUTRAL NUCLEOPHILE

Neutral nucleophiles can also undergo nucleophilic addition to carbonyls. The mechanism is slightly different than with a negatively charged nucleophile. The presence of an additional hydrogen atom in the nucleophile allows for the the carbonyl oxygen to be completely removed as water and a C=Nu bond to be formed.



RELATIVE REACTIVITY OF ALDEHYDES AND KETONES TO NUCLEOPHILIC ADDITION

In general, aldehydes are more reactive than ketones because they have a greater polarization of the carbonyl bond. The primary carbocation formed in the polarizing resonance structure of an aldehyde (shown below) is less stable and therefore more reactive than the secondary

carbocation formed in a similar resonance structure formed by a ketone. The stability difference in these resonance structures is due to the extra alkyl group present in the ketone. Alky groups stabilize carbocations through induction as discussed in Section 7.11.

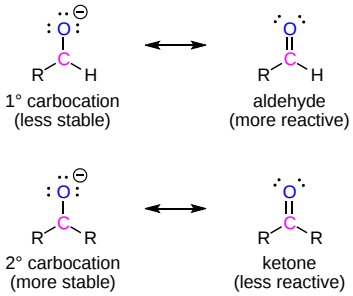


Figure 19.4.1). The carbonyl carbon of formaldehyde is more positive (more blue) and therefore more reactive towards nucleophlic addition than the carbonyl carbon in acetone which is less positive (more green). As discussed above, electron-attracting groups can further increase its positive character of a carbonyl carbon and thereby facilitate nucleophilic addition.

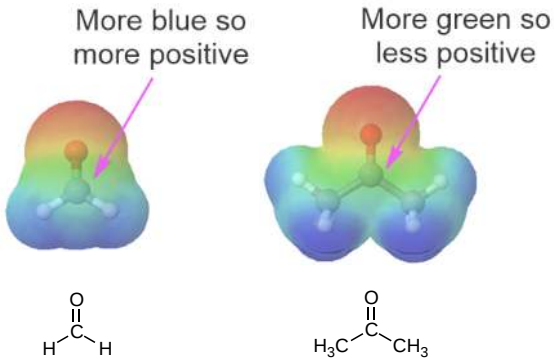


Figure 19.4.1: The Electrostatic Potential Map of Formaldehyde (Left) and Acetone (Right)

Another reason aldehydes tend to me more reactive to nucleophilic addition than ketones is steric hindrance. Ketones have two alkyl groups attached to their carbonyl carbon while aldehydes only have one. This means nucleophiles have a less sterically hindered path when attacking the carbonyl carbon of an aldehyde. Also, the transition state of the rate determining step for formation of the tetrahedral intermediate is less sterically crowded, lower in energy, and more kinetically favorable for an aldehyde than a ketone. The difference in sterics in the carbonyl carbon of an aldehyde and a ketone is easily seen when comparing the space filling models of acetaldehyde and acetone (Figure 19.4.2).

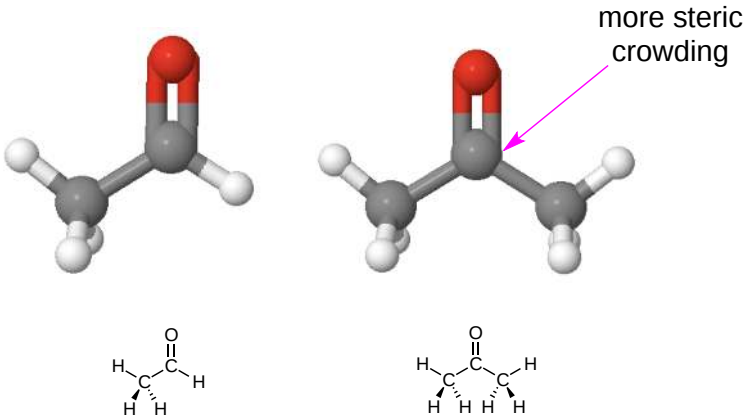
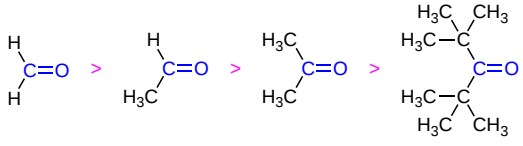


Figure 19.4.2: The Relative Steric Crowding of Acetaldehyde (Left) and Acetone (Right)

In fact, reactivity of a carbonyl toward nucleophilic addition decreases with increasing bulkiness of carbonyl substituents, as seen in the following series.



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EXERCISE 19.4.1

Benzaldehyde is less reactive to nucleophilic addition reactions than aliphatic aldehydes. Explain.

Answer

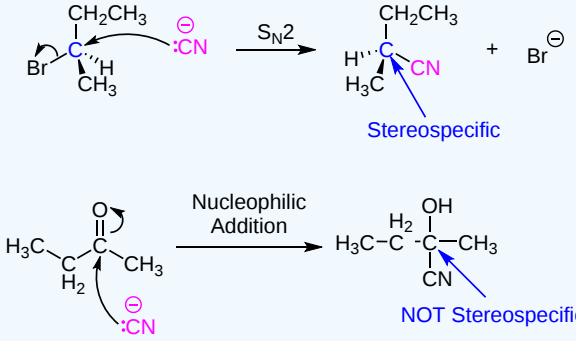
Aromatic rings act as an electron-donating group due to resonance effect. Electron donating groups make the carbonyl group in benzaldehyde less electrophilic.

EXERCISE 19.4.2

Compare the mechanisms of an S_N2 reaction between 2-bromobutane and cyanide and the tetrahedral complex formation between 2-butanone and cyanide.

Answer

In the S_N2 reaction the cyanide nucleophilic must undergo back side attack. This causes an inversion of stereochemistry and creates a product which is stereospecific. The carbonyl used in the nucleophilic addition is trigonal planar. This means the cyanide nucleophile can attack from either plane. This tends to create a racemic mixture of enantiomers.



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19.5: NUCLEOPHILIC ADDITION OF WATER - HYDRATION

OBJECTIVES

After completing this section, you should be able to

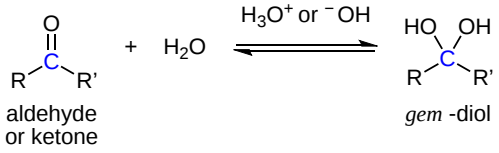
- write the step-wise mechanism for the base-catalyzed hydration of an aldehyde or ketone.
- write the step-wise mechanism for the acid-catalyzed hydration of an aldehyde or ketone.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- geminal (gem) diol

It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl group of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol, *gem*-diol, or 1,1-diol). The term hydrate implies the addition of water. The word germinal or abbreviation gem comes from the Latin word for twin, *geminus*.



aldehyde or ketone — *gem* -diol

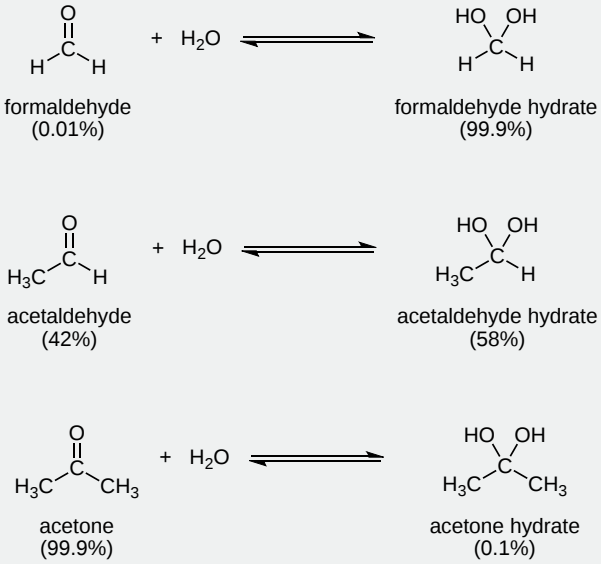
FACTORS AFFECTING THE HYDRATE EQUILIBRIUM

The equilibrium for hydrate formation depends both on steric and electrical factors of the carbonyl as discussed in the previous section. In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the small size of the hydrogen substituents relative to aldehydes and ketones favor hydrate formation. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. The addition of electron donating alkyl groups stabilized the partial positive charge on the carbonyl carbon and decreases the amount of *gem*-diol product at equilibrium. Because of this ketones tend to form less than 1% of the hydrate at equilibrium.

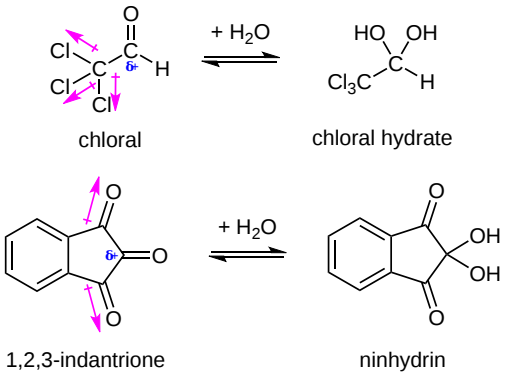


~100% *gem* -diol — <1% *gem* -diol

EQUILIBRIUM DISTRIBUTION OF COMMON ALDEHYDES AND KETONES WITH THEIR HYDRATE FORMS

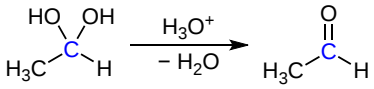


Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable hydrates. Two examples of this are chloral, and 1,2,3-indantrione. It should be noted that chloral hydrate is a sedative and has been added to alcoholic beverages to make a “knock-out” drink also called a Mickey Finn. Also, ninhydrin is commonly used by forensic investigators to reveal fingerprints.



REVERSIBILITY OF HYDRATE FORMATION

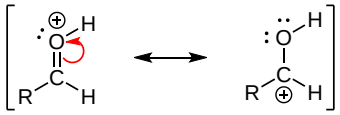
Isolation of hydrates is difficult because the reaction is reversible. Removal of water from the hydrate can cause the conversion of a gem-diol back to the corresponding carbonyl.



ACID OR BASE CATALYZED HYDRATE FORMATION

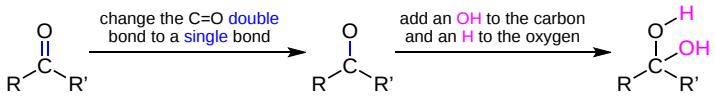
The nucleophilic addition of water to a carbonyl to form a hydrate is usually slow under neutral condition (pH = 7). The rate can be significantly increased through the addition of an acid or base as a catalyst.

The addition of an acid or base changes the mechanism and promote the nucleophilic addition of water to a carbonyl to form a hydrate. Basic conditions speed up the reaction because hydroxide is a better nucleophile than water. Acidic conditions speed up the reaction because the carbonyl becomes protonated. Protonation increases the polarity of the carbonyl bond which increase the partial positive charge on the carbon making it more electrophilic.

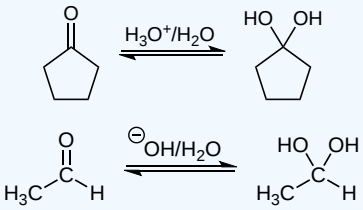


PREDICTING THE PRODUCT OF A HYDRATION

Overall, the C=O of the carbonyl in the starting material is removed and replaced by two single bonds both of which are attached to the original carbonyl carbon. Both of these single bonds are attached to OH groups in the product.



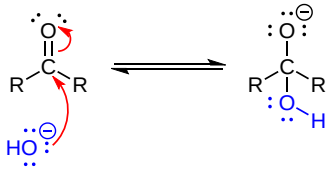
EXAMPLE 19.5.1



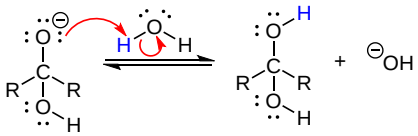
MECHANISM OF ACID OR BASE CATALYZED HYDRATE FORMATION

HYDRATE FORMATION UNDER BASIC CONDITIONS

Step 1: Basic conditions means there is a significant amount of hydroxide present. Hydroxide is a better nucleophile than water which speeds up the reaction. The negatively charged hydroxide forms a single bond with the electrophilic carbonyl carbon. This pushes the two electrons of the pi bond onto the electronegative oxygen forming an alkoxide ion intermediate.

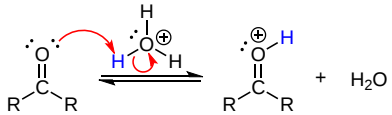


Step 2: Water acts as an acid and protonates the alkoxide ion to form a neutral hydrate while also regenerating hydroxide. The fact that hydroxide is not being used during the reaction is consistent with it acting as a catalyst.

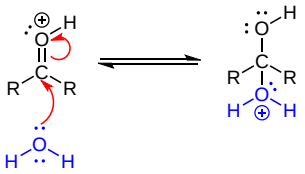


HYDRATE FORMATION UNDER ACIDIC CONDITIONS

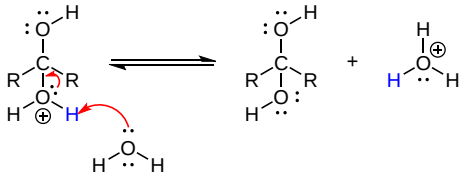
Step 1: Acidic conditions means there is a significant amount of hydronium present. Hydronium protonates the carbonyl oxygen thereby making the carbonyl carbon more electrophilic. After protonation the oxygen becomes positively charged.



Step 2: Under acidic conditions the most nucleophilic species is water. Water forms a single bond with the electrophilic carbon. This pushes the two electrons in the carbonyl pi bond onto the electronegative oxygen. The oxygen from the carbonyl becomes neutral while the oxygen from the water nucleophile become positively charged.

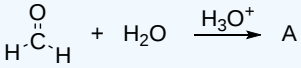


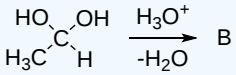
Step 3: Water acts as a base and deprotonates the intermediate to produce the neutrally charged hydrate while regenerating hydronium. The fact that hydronium is not being used during the reaction is consistent with it acting as a catalyst.

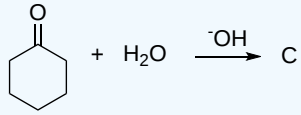


EXERCISE 19.5.1

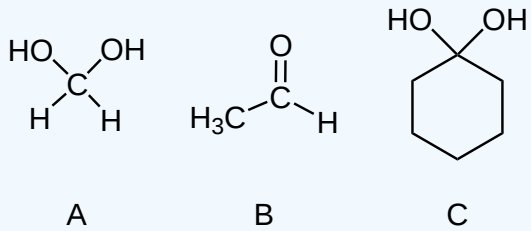
Draw the expected products of the following reactions.







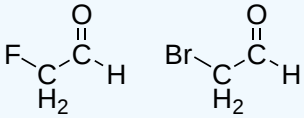
Answer



A B C

EXERCISE 19.5.2

Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

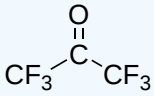


Answer

The compound on the left would. Fluorine is more electronegative than bromine and would remove more electron density from the carbonyl carbon. This would destabilize the carbonyl allowing for more gem-diol to form.

EXERCISE 19.5.3

Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

Although ketones tend to not form gem-diols, this compound exists almost entirely in the gem-diol form when placed in water. Ketones tend to not form gem-diols because of the stabilizing effect of the electron donating alkyl group. However, in this case the electron donating effects of the alkyl group is dominated by the presence of six highly electronegative fluorines turning these into electron withdrawing groups.

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19.6: NUCLEOPHILIC ADDITION OF HCN - CYANOHYDRIN FORMATION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the formation of a cyanohydrin from an aldehyde or ketone.
2. identify the cyanohydrin formed from the reaction of a given aldehyde or ketone with hydrogen cyanide.
3. identify the aldehyde or ketone, the reagents, or both, needed to prepare a given cyanohydrin.
4. write the detailed mechanism for the addition of hydrogen cyanide to an aldehyde or ketone.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- cyanohydrin

STUDY NOTES

For successful cyanohydrin formation it is important to have free cyanide ions available to react with the ketone or aldehyde. This can be achieved by using a salt (e.g. KCN or NaCN) or a silylated (e.g. Me_3SiCN) form of cyanide under acidic conditions or by using HCN with some base added to produce the needed CN^- nucleophile.

Hydrogen cyanide (HC≡N), adds reversibly to aldehydes and many ketones forming hydroxyalkanenitrile adducts commonly known and as **cyanohydrins**. Cyanohydrins have the structural formula of $R_2C(OH)CN$. The "R" on the formula represents an alkyl group, aryl group, or hydrogen.

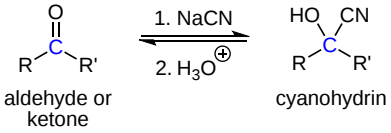
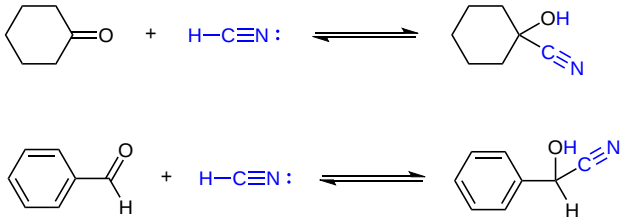


Figure 19.6.1: General Reaction of Cyanohydrin Formation

An important feature of cyanohydrin formation is that it requires a basic catalyst. Since hydrogen cyanide itself is a weak acid (pK_a = 9.25), the best results occur when a small amount of a strong base activates hydrogen cyanide by converting it to **cyanide ion ($^-$C≡N)**, which can function as a carbon nucleophile. In the absence of base, the reaction does not proceed, or is at best very slow. Cyanohydrin formation is weakly exothermic, and is favored for aldehydes, and unhindered cyclic and methyl ketones.



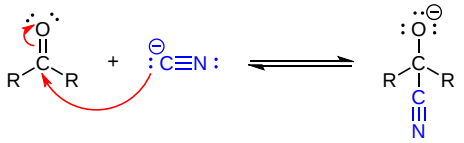
Examples of Cyanohydrin Formation

Hydrogen cyanide (HCN) is hazardous to handle because it is highly toxic. Therefore in many syntheses of cyanohydrins, HCN is created *in situ* by adding a strong acid to a mixture of sodium cyanide and the carbonyl compound, so that hydrogen cyanide is generated *in situ*. The amount of acid added should be insufficient to consume all the cyanide ion, therefore sufficiently alkaline conditions are maintained for rapid addition.

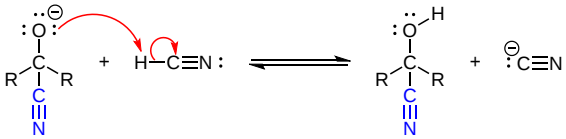
MECHANISM OF CYANOHYDRIN FORMATION

In the first step of the mechanism, the cyanide ion acts as a nucleophile and forms a C-C bond with the electrophillic carbonyl carbon. The two electrons in the carbonyl pi bond are pushed on to the electronegative oxygen forming a tetrahedral alkoxide ion intermediate. In the second step, the alkoxide ion is protonated by HCN which regenerates the cyanide ion.

STEP 1: NUCLEOPHILIC ATTACK

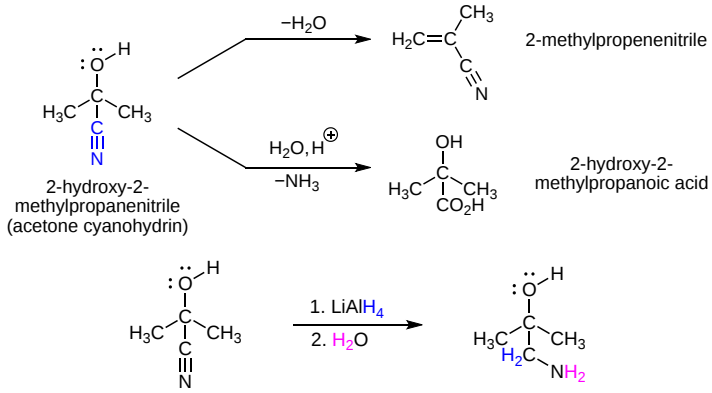


STEP 2: PROTONATION



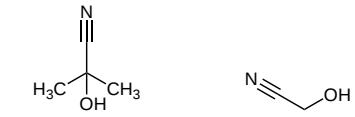
FURTHER CHEMISTRY OF CYANOHYDRINS

Cyanohydrin functional groups often prove useful because of the further chemistry that can be carried out due to the presence of a hydroxyl and a nitrile functionality. In particular, dehydration can convert the hydroxyl group into an alkene (Section 17.6). The nitrile can be converted into a carboxylic acid function group through reaction with a hot acidic aqueous solution (Section 20.7). Also, the nitrile can be reduced by the addition of $LiAlH_4$ to form a primary amine.



OTHER CYANOHYDRINS

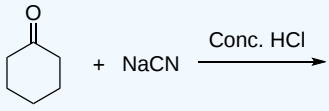
Other interesting cyanohydrins are: **acetone cyanohydrin**, and **glycolonitrile**.



Acetone cyanohydrin has the structure, $(CH_3)_2C(OH)CN$, and is used in the production of methyl methacrylate (also known as acrylic). Glycolonitrile is an organic compound with the structural formula of $HOCH_2CN$, which is the simplest cyanohydrin that is derived by formaldehydes.

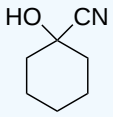
? EXERCISE 19.6.1

Complete the following reaction for cyanohydrins.



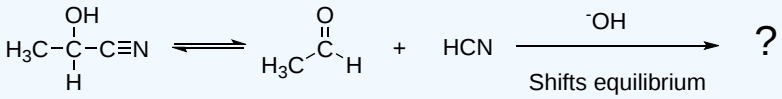
Answer

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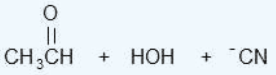


EXERCISE 19.6.2

Complete the following reaction for cyanohydrins.



Answer



EXERCISE 19.6.3

True or False: For a cyanohydrin to form, a *fast addition* of strong acid to cyanide salt is carried out to convert the salt into HCN.

Answer

False, slow addition

EXERCISE 19.6.4

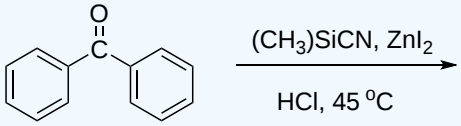
True or False: Cyanohydrin reactions are *irreversible*.

Answer

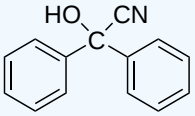
False, reversible

EXERCISE 19.6.5

What is the product for the overall reaction?



Answer



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19.7: NUCLEOPHILIC ADDITION OF HYDRIDE AND GRIGNARD REAGENTS - ALCOHOL FORMATION

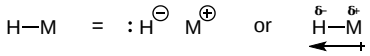
OBJECTIVES

After completing this section, you should be able to

1. write the equation to describe the nucleophilic addition reaction between a Grignard reagent and a carbonyl group.
2. write the general mechanism of nucleophilic addition of the "hydride ion" in the reduction of a carbonyl group.

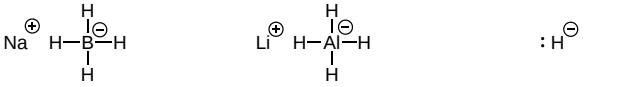
REDUCTION OF CARBONYLS TO ALCOHOLS USING METAL HYDRIDES

Like carbon, hydrogen can be used as a nucleophile if it is bonded to a metal in such a way that the electron density balance favors the hydrogen side. A hydrogen atom that carries a net negative charge and bears a pair of unshared electrons is called a **hydride ion.** How much negative charge density resides on hydrogen depends on the difference in electronegativity between hydrogen and the metal it's bonded to.



(M = metal)

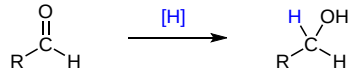
The most common sources of the hydride anion (:H) are **lithium aluminum hydride ($LiAlH_4$)** and **sodium borohydride ($NaBH_4$)**. Note! The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Also, each are capable of delivering up to 4 hydride equivalents. The reaction equation of hydride reductions are not typically balanced (*i.e.* it does not specify the stoichiometry of the reagent). Because aluminum is less electronegative than boron, the Al-H bond in $LiAlH_4$ is more polar, thereby, making $LiAlH_4$ a stronger reducing agent.

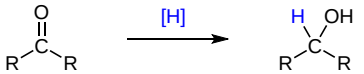


sodium borohydride | lithium aluminum hydride | hydride nucleophile

GENERAL REACTION

Nucleophilic addition of a hydride anion (:H) to an aldehyde or a ketone gives a tetrahedral alkoxide anion intermediate, which on protonation yields the corresponding alcohol. Aldehydes produce 1°-alcohols and ketones produce 2°-alcohols. Both $LiAlH_4$ and $NaBH_4$ are capable of reducing aldehydes and ketones to the corresponding alcohol.

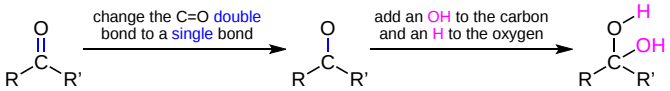




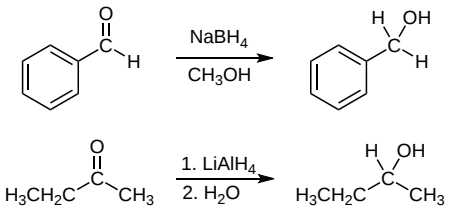
In metal hydrides reductions, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction water is usually added in a second step. The lithium, sodium, boron and aluminum end up as soluble inorganic salts at the end of either reaction.

PREDICTING THE PRODUCT OF A HYDRIDE ADDITION TO A CARBONYL

During the reduction, the C=O double bond in the reactant becomes a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two new single bonds in the product. One will be attached to the oxygen (O-H) and one to the carbon (C-H).



EXAMPLE

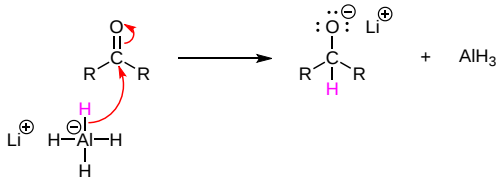


MECHANISM FOR THE REDUCTION OF CARBONYLS USING LIALH$_4$

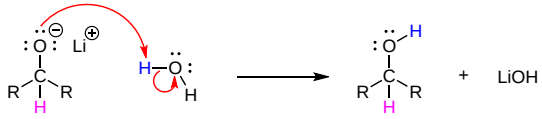
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of hydride. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and forming a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source (such as water). In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding.

Step 1: Nucleophilic attack to form a tetrahedral alkoxide intermediate



Step 2: Protonation to form an alcohol



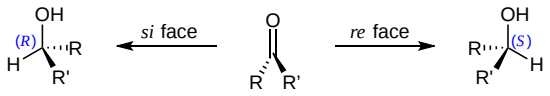
PROPERTIES OF HYDRIDE SOURCES

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride (LiAlH4) and sodium borohydride (NaBH4). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.

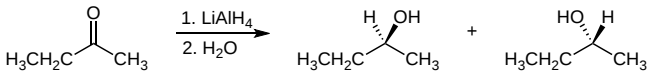
Reagent	Preferred Solvents	Functions Reduced	Reaction Work-up
Sodium Borohydride $NaBH_4$	ethanol; aqueous ethanol 15% NaOH; diglyme avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols inert to most other functional groups	**1)** simple neutralization **2)** extraction of product
Lithium Aluminum Hydride $LiAlH_4$	ether; THF avoid alcohols and amines avoid halogenated compounds avoid strong acids	aldehydes to 1º-alcohols ketones to 2º-alcohols carboxylic acids to 1º-alcohols esters to alcohols epoxides to alcohols nitriles & amides to amines halides & tosylates to alkanes most functional groups react	**1)** careful addition of water **2)** remove aluminum salts **3)** extraction of product

LIMITATIONS OF HYDRIDE REDUCTIONS

A hydride addition to an asymmetric ketone has the possibility of forming a chiral carbon that is not stereospecific. Attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to a mixture of the (*S*) and (*R*) alcohols. These reactions can be made to have stereochemical control by using several different methods including stereospecific reagents, sterics, and by the affect of an enzyme during a biological reduction.



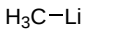
EXAMPLE



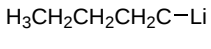
2-butanone (*S*)-2-butanol (*R*)-2-butanol

ORGANOMETALLIC REACTIONS

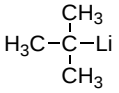
Lithium and magnesium metals reduce the carbon-halogen bonds of alkyl halides to form **organolithium reagents** and **Grignard reagents** respectively. In both cases, the carbon bonds to the metal and has characteristics similar to a carbanion ($R:^-$) nucleophile. Some common organometallic reagents are shown below:



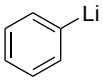
Methyl Lithium



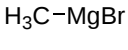
Butyl Lithium



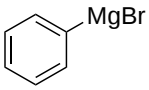
t-Butyl Lithium



Phenyl Lithium



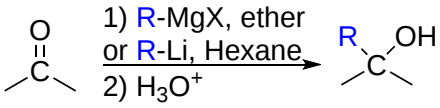
Methyl Magnesium Bromide



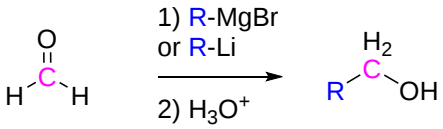
Phenylmagnesium Bromide

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. Aldehydes and ketones will undergo nucleophilic addition with organolithium and Grignard reagent nucleophiles. The nucleophilic carbon in the organometallic reagents forms a C-C single bond with the electrophilic carbonyl carbon. An alkoxide ion intermediate is formed which becomes an alcohol with subsequent protonation with an acid. Both Grignard and organolithium reagents will perform these reactions.

GENERAL REACTION

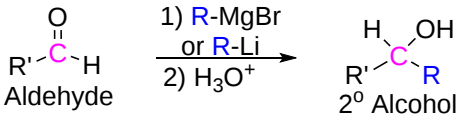


ADDITION TO FORMALDEHYDE GIVES 1^O ALCOHOLS

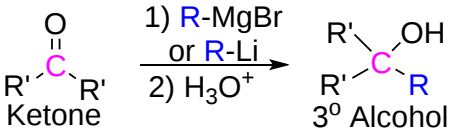


Formaldehyde 1° Alcohol

ADDITION TO ALDEHYDES GIVES 2^O ALCOHOLS

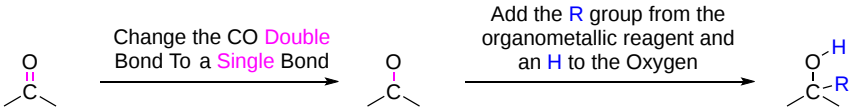


ADDITION TO KETONES GIVES 3° ALCOHOLS

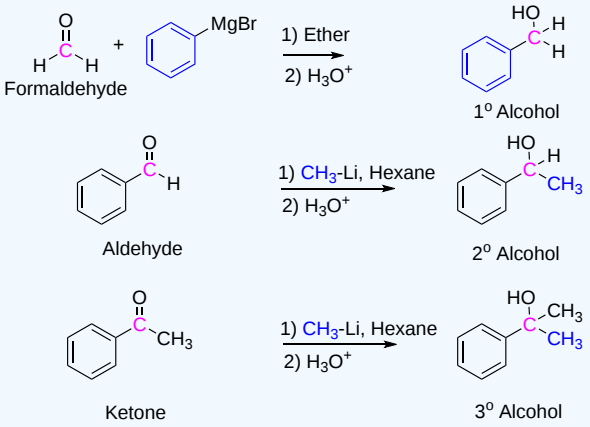


PREDICTING THE PRODUCT OF ADDITION OF ORGANOMETALLIC REAGENTS TO ALDEHYDES AND KETONES

During the reaction, the C=O double bond in the reactant forms a C-O single bond in the product. The breaking of the C=O double bond allows for the formation of two single bonds in the product. One will be attached to the oxygen and one to the carbon which was originally in the carbonyl. The carbon will gain whatever R group was part of the organometallic reagent and the oxygen will gain a "H".



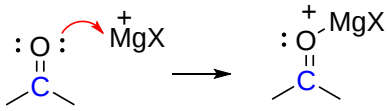
EXAMPLE 19.7.2



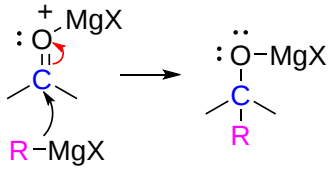
MECHANISM FOR THE ADDITION OF GRIGNARD REAGENTS TO CARBONYLS

The mechanism starts with the formation of a acid-base complex between $^{+}$MgX and the carbonyl oxygen. The $^{+}$MgBr of the Grignard reagent acts as a Lewis acid and accepts a lone pair of electrons from the carbonyl oxygen. This gives the oxygen a positive charge which correspondingly increases the partial positive charge on the carbonyl carbon increasing it susceptibility to nucleophilic attack. The carbanion nucleophile from the Grignard reagent adds to the electrophilic carbon of the acid-base complex forming a C-C bond. The two electrons of the C=O are pushed toward the carbonyl oxygen atom forming a tetrahedral magnesium alkoxide intermediate. The alkoxide intermediate is converted to an alcohol through addition of a acidic aqueous solution. The $^{+}$MgX ion is also converted to HOMgX.

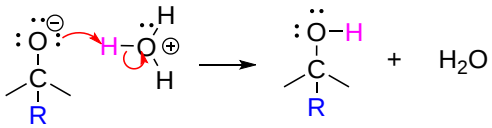
STEP 1: LEWIS ACID-BASE FORMATION



STEP 2: NUCLEOPHILIC ATTACK



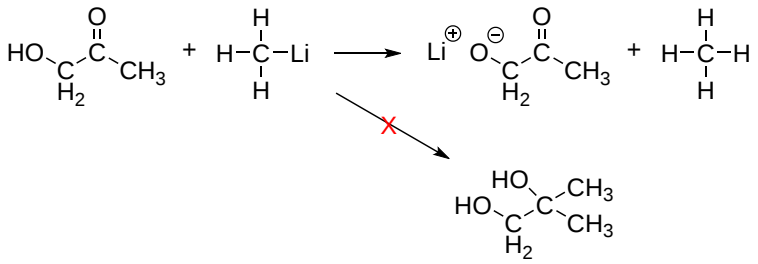
STEP 3: PROTONATION



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LIMITATION OF ORGANOMETALLIC REAGENTS

As discussed above, Grignard and organolithium reagents are powerful bases. Because of this they cannot be used as nucleophiles on compounds which contain acidic hydrogens. If they are used they will act as a base and deprotonate the acidic hydrogen rather than act as a nucleophile and attack the carbonyl. A partial list of functional groups which cannot be used with organometallic reagents includes: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

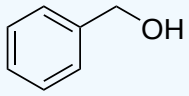


PLANNING AN ALCOHOL SYNTHESIS USING A GRIGNARD REACTION

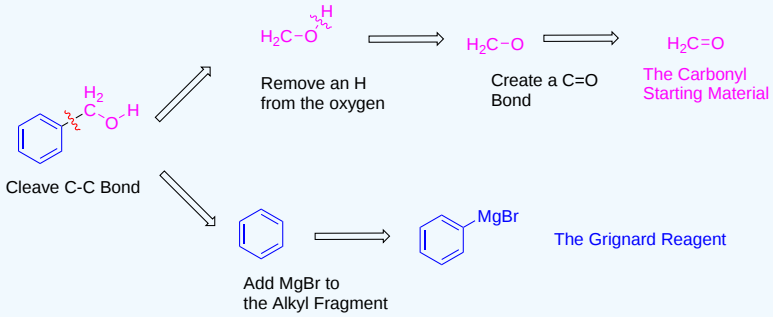
The nucleophilic addition of a Grignard reagent to a carbonyl is a powerful tool in organic synthesis because if forms a C-C bond. Also, there is often more than one way to make a given target molecule. Primary alcohols have one C-C bond which can be retrosynthetically cleaved. Secondary alcohols have two and tertiary alcohols have three.

EXAMPLE 19.7.2

What reagents are required to make the following molecule using a Grignard Reaction?

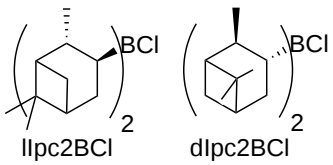


Solution



SOMETHING EXTRA

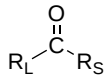
As previously mentioned, a hydride reduction using $LiAlH_4$ or $NaBH_4$ has the possibility of forming R or S stereoisomers of a chiral carbon in the product. An important area of organic synthesis is developing stereoselective methods which yield only one of the possible R and S stereocenters. Stereoselective hydride reductions can be accomplished by using the reagent **Diisopinocampheylchloroborane (Ipc_2BCl).** The two versions of this reagent, (+)-Ipc_2BCl & (−)-Ipc_2BCl, allow for either an R or S stereocenter to be created during the hydride reduction. Ipc_2BCl was first reported in 1961 by Zweifel and Brown and is considered a pioneering work in stereoselective synthesis using boranes. Herbert Charles Brown (1912-2004) was an American chemist who received the Nobel Prize in Chemistry in 1979 for his work with organoboranes.



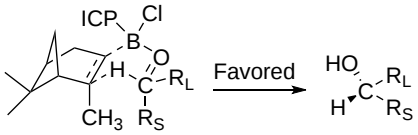
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Ipc_2BCl allows for stereoselectivity by changing the mechanism of the hydride reduction and introducing sterics to the reaction. Asymmertric carbonyls which have a sterically large substituent (R_L) and a sterically small substituent (R_S) will have a preferred orientation during this reaction causing a particular stereoisomer to be formed.

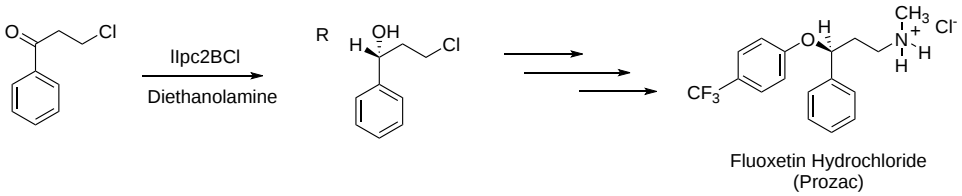
Asymmetric Carbonyl



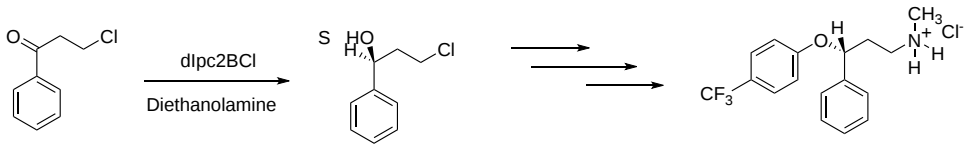
RL = Sterically Large Substituent
RS = Sterically Small Substituent



Stereochemical control during a synthesis is important because a particular stereoisomer is usually the target molecular. This is particularly true in the synthesis of pharmaceuticals were one stereoisomer often has different biological properties and another. An example of this is the drug Fluoxetine (Prozac) which was shown to have superior biological properties when the R isomer of its single chiral carbon was tested. Fluoxetine is an antidepressant given FDA approval in 1987. in 2010, over 24.4 million prescriptions for fluoxetine were filled in the United States alone. Currently, there are many different synthesis pathways to Fluoxetine. A fragment of one pathway is shown below which uses the two Ipc_2BCl versions to synthesis both the R and S enantiomers of Fluoxetine.

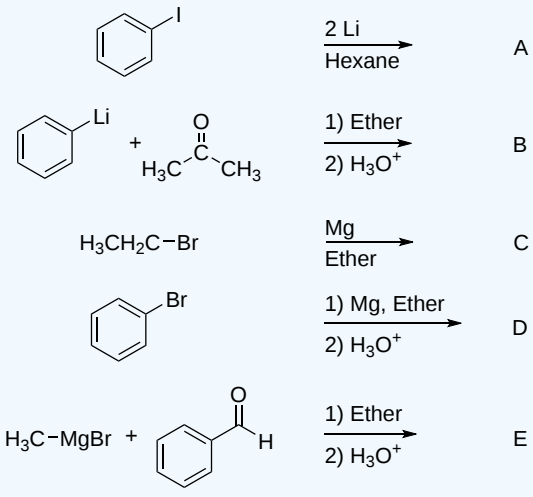


Fluoxetin Hydrochloride
(Prozac)



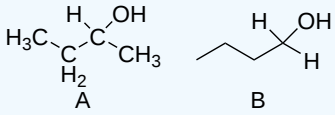
? EXERCISE 19.7.1

Please draw the products of the following reactions:



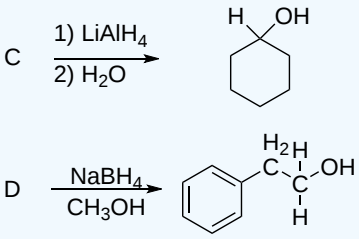
Answer

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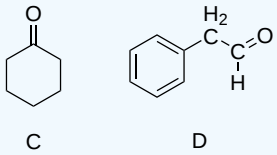


EXERCISE 19.7.2

Draw the structure of the molecule which must be reacted to produce the product.

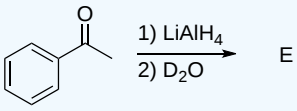


Answer

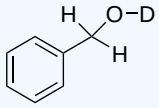


EXERCISE 19.7.3

Deuterium oxide (D_2O) is a form of water where the hydrogens have been replaced by deuteriums. For the following $LiAlH_4$ reduction the water typically used has been replaced by deuterium oxide. Please draw the product of the reaction and place the deuterium in the proper location. Hint! Look at the mechanism of the reaction.



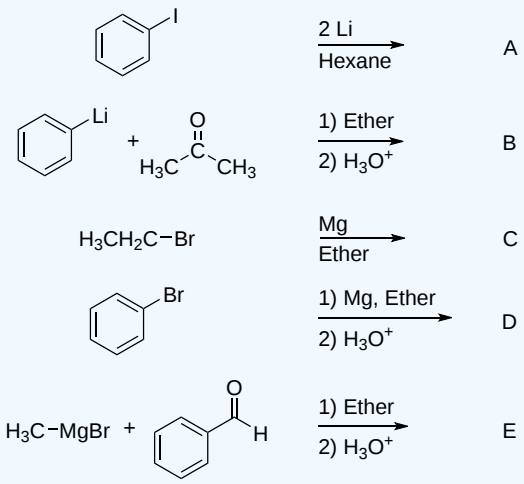
Answer



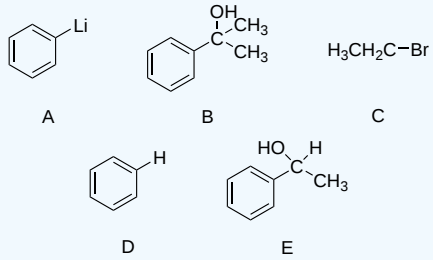
EXERCISE 19.7.4

Please write the product of the following reactions.

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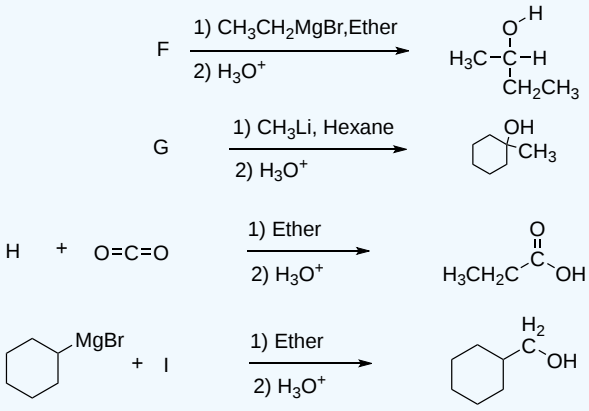


Answer

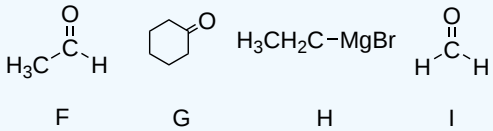


EXERCISE 19.7.5

Please indicate the starting material required to produce the product.



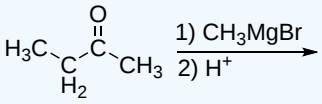
Answer



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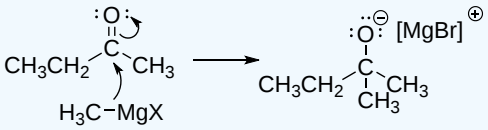
EXERCISE 19.7.6

Give a detailed mechanism and the final product of this reaction

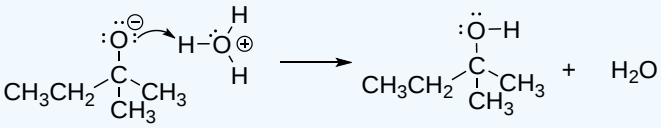


Answer

Step 1: Nucleophilic attack

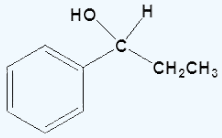


Step 2: Protonation

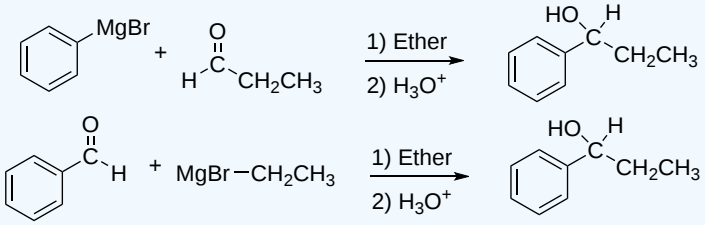


EXERCISE 19.7.7

How two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



Answer



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19.8: NUCLEOPHILIC ADDITION OF AMINES - IMINE AND ENAMINE FORMATION

OBJECTIVES

After completing this section, you should be able to

- write equations to describe the reactions that occur between aldehydes or ketones and primary or secondary amines.
- identify the product formed from the reaction of a given aldehyde or ketone with a given primary or secondary amine.
- identify the aldehyde or ketone, the amine, or both, required in the synthesis of a given imine or enamine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a primary amine.
- write the detailed mechanism for the reaction of an aldehyde or ketone with a secondary amine.
- explain why the rate of a reaction between an aldehyde or ketone and a primary or secondary amine is dependent on pH.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

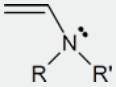
- 2,4-dinitrophenylhydrozone
- enamine
- imine

STUDY NOTES

An imine is a compound that contains the structural unit



An enamine is a compound that contains the structural unit



Both of these types of compound can be prepared through the reaction of an aldehyde or ketone with an amine.

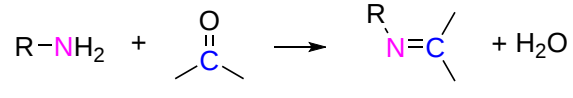
You may have the opportunity to observe the reaction of an aldehyde and ketone with 2,4-dinitrophenylhydrazine (Brady's reagent) to form a 2,4-dinitrophenylhydrozone in the laboratory. This is a classical organic chemistry test to confirm the presence of a carbonyl group. The reaction produces very colorful and bright precipitates of yellow, orange and red.

If you can understand why the two reactions of imine and enamine formation are essentially identical, and can write a detailed mechanism for each one, you are well on the way to mastering organic chemistry. If you understand how and why these reactions occur, you can keep the amount of material that you need to memorize to a minimum.

The nucleophilic addition of amines involves reacting primary or secondary amines with carbonyl compounds like aldehydes or ketones. This forms imines (with primary amines) or enamines (with secondary amines) along with water as a byproduct. These reactions are crucial in organic synthesis for building carbon-nitrogen bonds and creating various functional groups.

REACTION WITH PRIMARY AMINES TO FORM IMINES

The reaction of aldehydes and ketones with ammonia or 1°-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction.

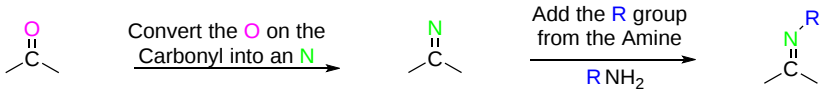


1° Amine Aldehyde or Ketone Imine

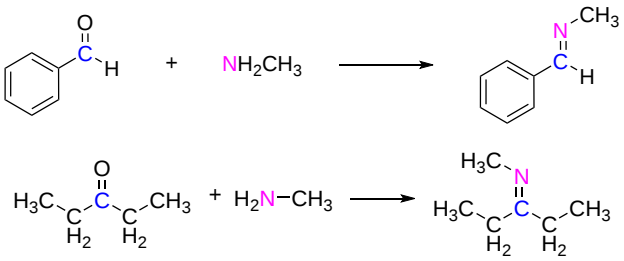
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PREDICTING THE PRODUCTS OF AN IMINE FORMING REACTION

During imine formation, the carbonyl oxygen is completely removed. The nitrogen of the 1º amine reactant replaces the carbonyl oxygen to form the imine C=N bond. During the process the nitrogen of the 1º amine loses both of its hydrogens.



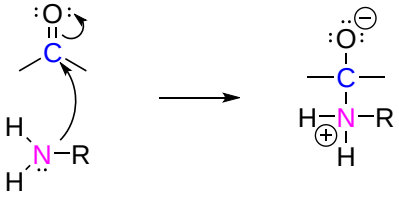
EXAMPLES OF IMINE FORMING REACTIONS



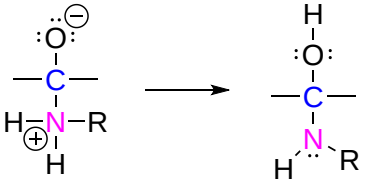
MECHANISM OF IMINE FORMATION

Imine formation is a reversible process that starts with the nucleophilic addition of a primary amine to the carbonyl group of an aldehyde or ketone. Next, a proton transfer forms a neutral amino alcohol called a carbinolamine. Acid protonation of the carbinolamine oxygen converts it into a better leaving group which is subsequently eliminated as water producing an iminium ion. Deprotonation of nitrogen gives the final imine product.

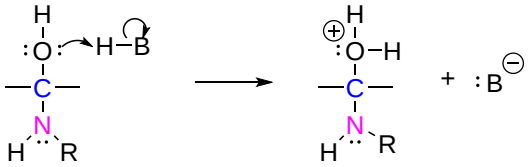
STEP 1: NUCLEOPHILIC ADDITION



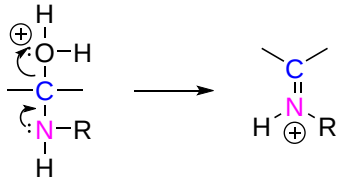
STEP 2: PROTON TRANSFER



STEP 3: PROTONATION

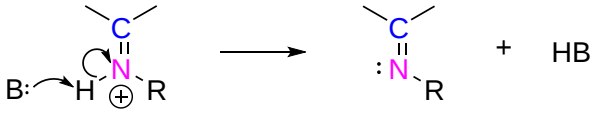


STEP 4: WATER IS ELIMINATED TO FORM AN IMINIUM ION



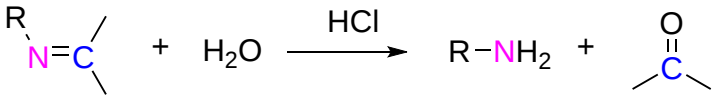
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STEP 5: DEPROTONATION



REVERSIBILITY OF IMINE FORMING REACTIONS

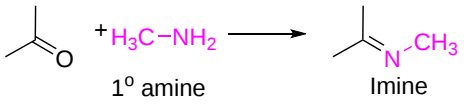
Imines can be hydrolyzed back to the corresponding 1° amine under acidic conditions.

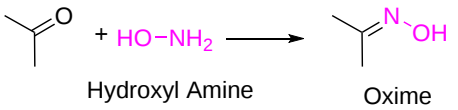


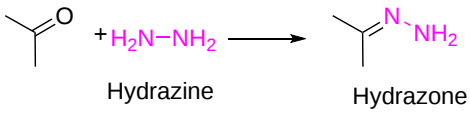
REACTIONS INVOLVING OTHER REAGENTS OF THE TYPE Y-NH_2

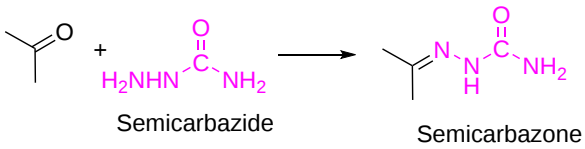
A wide variety of substances with $-NH_2$ groups can react with aldehydes and ketones by an addition-elimination sequence to yield compounds with a carbon-nitrogen double bond. Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type $Y–NH_2$ have been studied, and found to give stable products ($R_2C=N–Y$) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed below, together with the structures and names of their carbonyl reaction products. Hydrazones are used as part of the Wolff-Kishner reduction and will be discussed in more detail in Section 19.9.

With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. It should be noted that although semicarbazide has three nitrogen groups ($–NH_2$) only one of them is a reactive amine. The other two are similar to amides and are deactivated by resonance with the adjacent carbonyl group.

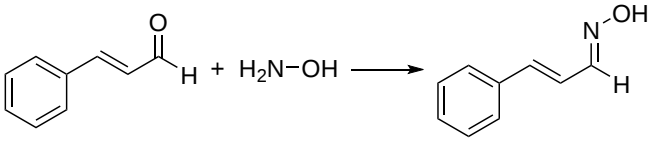




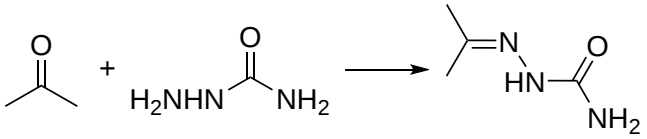




EXAMPLE



Cinnamaldehyde reacting with hydroxylamine to form cinnamaldehyde oxime

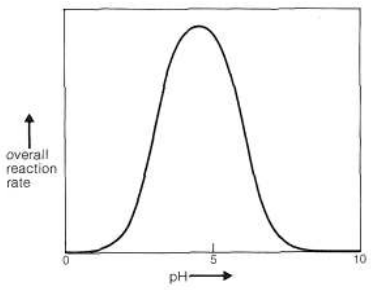


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Acetone reacting with semicarbazide to form acetone semicarbazide

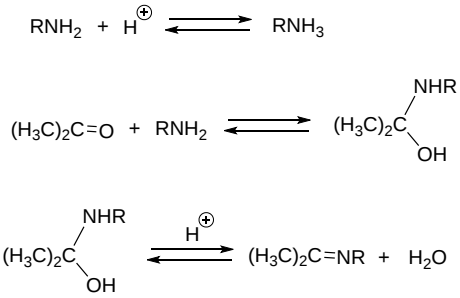
THE PH DEPENDENCE OF IMINE FORMING REACTIONS

The pH for reactions which form imine compounds must be carefully controlled. The rate at which these imine compounds are formed is generally greatest near a pH of 5, and drops at higher and lower pH's. At high pH there will not be enough acid to protonate the OH in the intermediate to allow for removal as H_2O. At low pH most of the amine reactant will be tied up as its ammonium conjugate acid and will become non-nucleophilic.



Schematic variation of the rate of condensation of RNH_2 with a carbonyl compound as a function of pH.

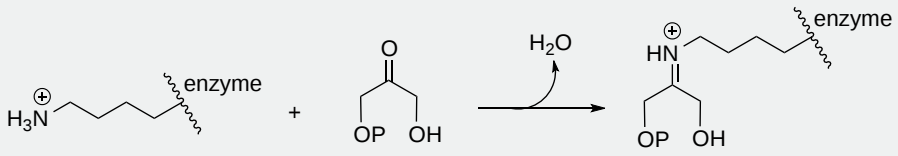
Clearly, if the unshared electron pair on the nitrogen of RNH_2 is combined with a proton it cannot attack the carbonyl carbon to give the aminoalkanol produced during the mechanism. So at high acid concentration (low pH) we expect the rate and the equilibrium for the overall reaction to be unfavorable.



Dehydration of the aminoalkanol is acid catalyzed; this reaction normally is fast at pH values smaller than 3-4. As the pH is increased above 4, the dehydration step in the mechanism decreases in rate because it requires an acid catalyst. At pH 6 dehydration is the slow step of the mechanism, and at higher pH values it finally becomes too slow to give a useful overall rate of reaction.

BIOLOGICAL IMINE FORMING REACTIONS

Imine intermediates are common in biological pathways. Carbon-carbon bond forming enzymes called aldolases often form a protonated iminium link between a carbonyl carbon on a substrate and the $-NH_3^+$ from a lysine amino acid found in the active site of the enzyme. The reaction below shows an aldolase reaction from the Calvin Cycle where the carbonyl containing substrate is dihydroxyacetone. The Calvin Cycle is involved in the biochemical processes of carbon fixation and the production of sugars in plants.

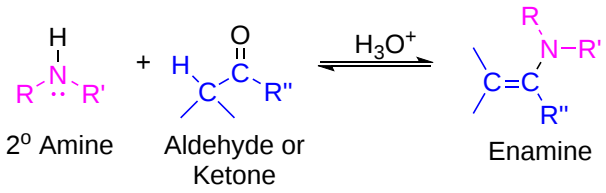


Protonated Amine From Lysine | **Dihydroxyacetone** | **A Protonated Iminium Linkage**

After the carbon-carbon bond forming part of an aldolase reaction is completed, the iminium linkage is hydrolyzed, freeing the product so that it can diffuse out of the active site and allow another catalytic cycle to begin.

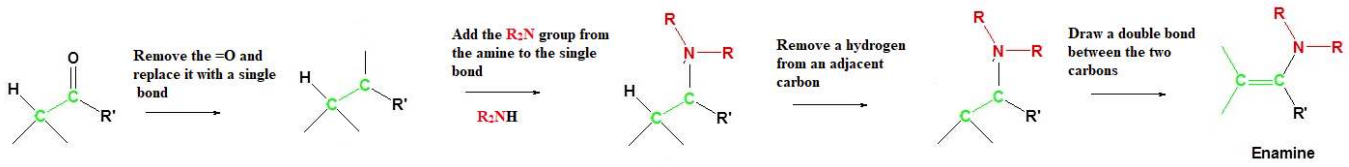
REACTION WITH SECONDARY AMINES TO FORM ENAMINES

Most aldehydes and ketones react with 2º-amines to give products known as **enamines** (alkene + amine). It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Secondary amines form a distinctly different functional group after nucleophilic addition because they lack the second hydrogen on nitrogen required for imine formation. During this reaction a hydrogen is removed from an adjacent carbon forming a C=C bond.

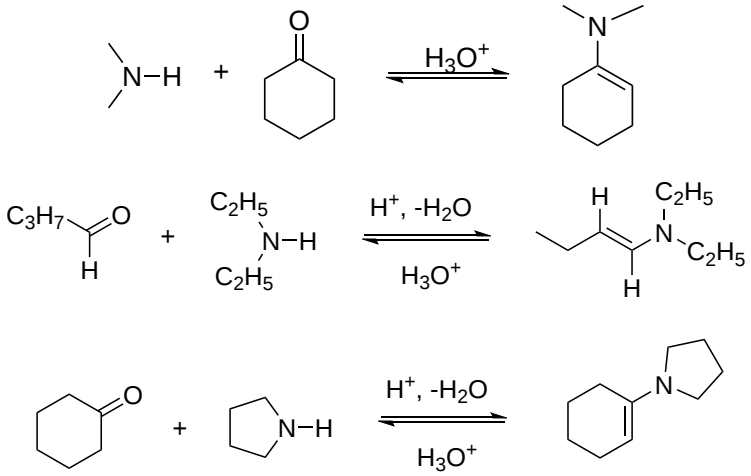


PREDICTING THE PRODUCTS OF AN ENAMINE FORMING REACTION

During enamine formation the carbonyl oxygen is completely removed. The nitrogen of the amine reactant replaces the oxygen to form a N-C bond. During the process the amine loses its lone hydrogen. A hydrogen is removed from a carbon adjacent to the original carbonyl carbon forming a C=C between them.

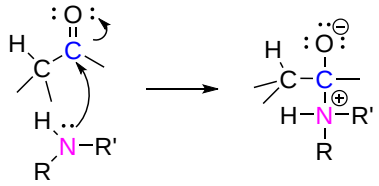


EXAMPLE



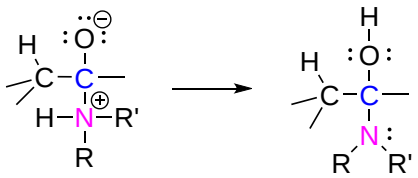
MECHANISM

STEP 1: THE SECONDARY AMINE UNDERGOES NUCLEOPHILIC ADDITION TO FORM A NEUTRAL TETRAHEDRAL INTERMEDIATE

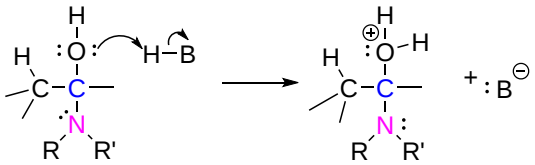


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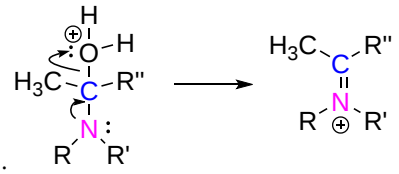
STEP 2: A PROTON IS TRANSFERRED FROM THE AMMONIUM ION MOIETY OF THE TETRAHEDRAL INTERMEDIATE TO THE ALKOXIDE ION MOIETY. THIS FORMS A NEUTRAL FUNCTIONAL GROUP CALLED A CARBINOLAMINE



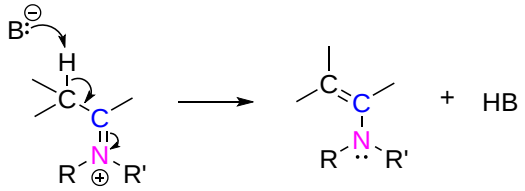
STEP 3: THE OH GROUP ON THE CARBINOLAMINE IS PROTONATED BY HYDRONIUM TURNING IT INTO A GOOD LEAVING GROUP



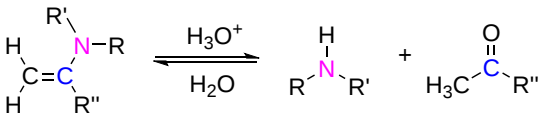
STEP 4: THE LONE PAIR ELECTRONS ON THE NITROGEN FORM THE C=N DOUBLE BOND CAUSING WATER TO BE ELIMINATED. THIS FORMS AN IMINIUM ION



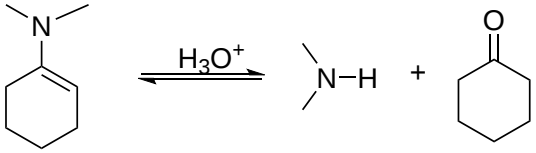
Step 5: Water (or a base) removes a hydrogen from an adjacent carbon to form an alkene bond. This pushes two electrons from the C=N double bond onto the positively charged nitrogen creating the neutral enamine product and hydronium (or BH).



REVERSIBILITY OF ENAMINES

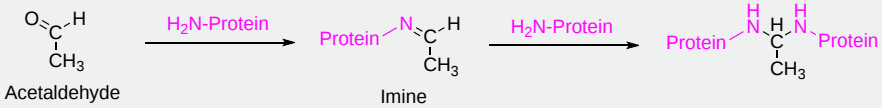


EXAMPLE



SOMETHING EXTRA: HOW DOES ALCOHOL CAUSE CIRRHOSIS AND LIVER CANCER?

One of the most insidious aspects of alcohol abuse is the fact that it will allow a user to continue, sometimes for decades, while it slowly destroys their body. Our bodies are actually designed to handle limited amounts of alcohol. Human metabolism includes enzymes that can convert alcohol into harmless metabolites in three steps. In the first step, an enzyme called alcohol dehydrogenase (ADH) acts as a catalyst for the conversion of alcohol to the toxic intermediate acetaldehyde.



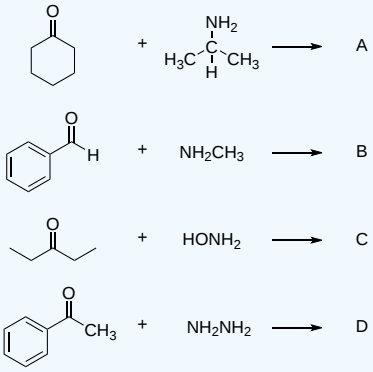
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How acetaldehyde forms a protein adduct

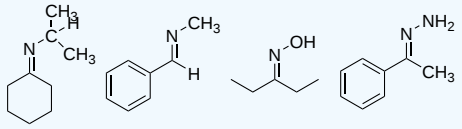
Forming adducts with DNA changes its structure and increases the chances of irregular replication, which is the starting point of cancer. Our bodies have processes that can repair or replace damaged proteins and DNA, but if enough build up they can lead to cirrhosis, liver cancer, liver failure, and death. Alcohol accounts for 28% of all liver-disease-related deaths in the U.S., and is also responsible for a little over 3% of all cancer deaths that occur globally. Hepatocellular carcinoma (liver cancer) is the fifth most common type of cancer, with an estimated 500,000 new cases being diagnosed every year worldwide. Because this type of cancer is usually discovered late, the prognosis is poor, with a median survival time of 1-2 months.

EXAMPLE 19.8.1

Please draw the products of the following reactions.

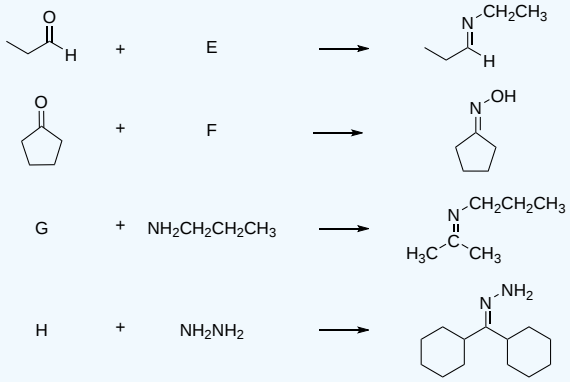


Solution

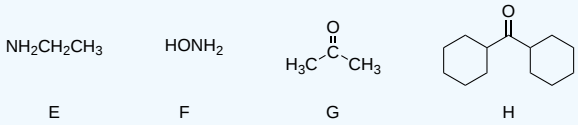


EXAMPLE 19.8.2

Please draw the structure of the reactant needed to produce the indicated product.

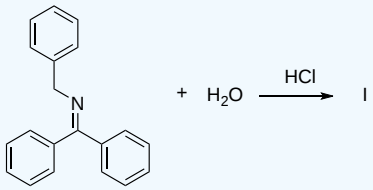


Solution

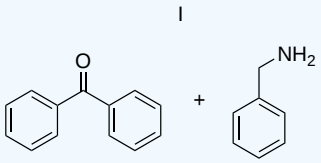


EXAMPLE 19.8.3

Please draw the products of the following reactions.

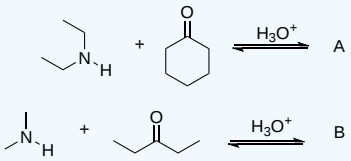


Solution

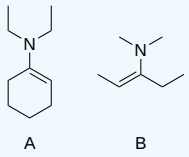


EXAMPLE 19.8.4

Please draw the products for the following reactions.

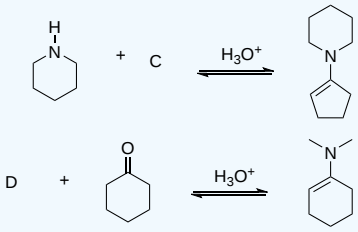


Solution

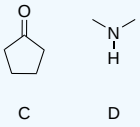


EXAMPLE 19.8.5

Please give the structure of the reactant needed to product the following product



Solution



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19.9: NUCLEOPHILIC ADDITION OF HYDRAZINE - THE WOLFF-KISHNER REACTION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the Wolff-Kishner reduction of an aldehyde or ketone.
- identify the product formed from the Wolff-Kishner reduction of a given aldehyde or ketone.

KEY TERMS

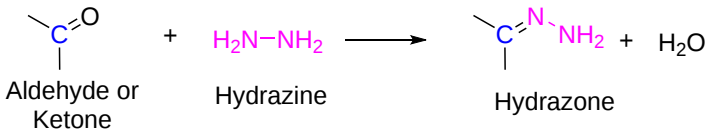
Make certain that you can define, and use in context, the key term below.

- Wolff-Kishner reduction

STUDY NOTES

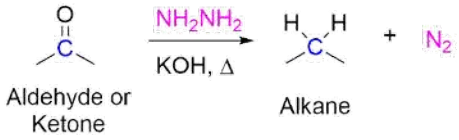
After studying this section, you can add yet another method of reducing organic compounds to your growing list of reduction reactions.

Aldehydes and ketones can be converted to a hydrazone derivative by reaction with hydrazine (H_2NNH_2). Hydrazone formation is a variation of the imine forming reaction discussed in the previous section.



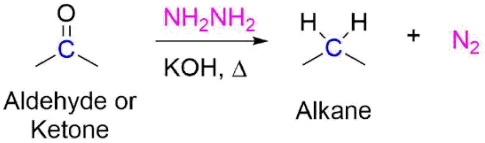
REACTION WITH A BASE AND HEAT CONVERTS A HYDRAZONE TO AN ALKANE

Hydrazones can be further converted to the corresponding alkane by reaction with a base, usually KOH, and heat. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. In the examples below the symbol "Δ" represents the addition of heat to a reaction. During this reaction nitrogen gas, which contains a very stable N-N triple bond, is produced.

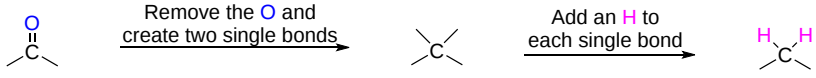


BOTH REACTIONS TOGETHER PRODUCE THE WOLFF-KISHNER REDUCTION

These two steps previously discussed can be combined to provide a general reaction for the conversion of aldehydes and ketones to alkanes called the Wolff-Kishner Reduction. Overall, the Wolff-Kishner reduction removes the carbonyl oxygen in the form of water by forming an intermediate hydrazone. The hydrazone then undergoes loss of N_2 gas along with protonation to give the alkane reaction product. Note that the Clemmensen reduction accomplishes the same transformation of a carbonyl to an alkane under acidic conditions.

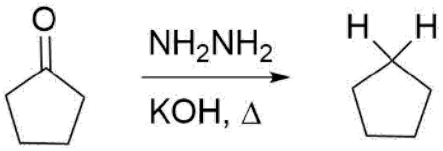


PREDICTING THE PRODUCTS OF A WOLFF-KISHNER REDUCTION

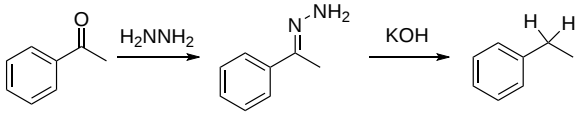


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EXAMPLES



Conversion of Cyclopentanone to cyclopentane

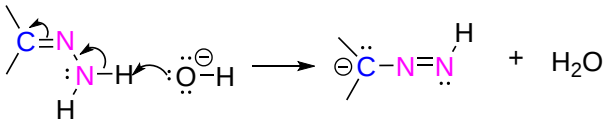


Conversation of Acetophenone to Ethylbenzne

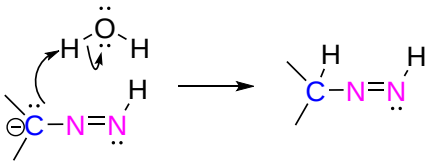
MECHANISM OF THE WOLFF-KISHNER REDUCTION

Hydrazine reacts with a carbonyl to form a hydrazone using a mechanism similar to that of an imine formation discussed in the previous section. The weakly acidic N-H bond is deprotonated to form the hydrazone anion. The hydrazone anion has a resonance structure that places a double bond between the nitrogens and a negative charge on carbon. The hydrazone anion is then protonated to form a neutral intermediate. A second weakly acidic N-H bond is deprotonated which causes the formation of N_2 gas and a carbanion. In the final step the carbanion is protonated to form an alkane product.

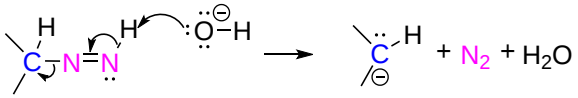
STEP 1: DEPROTONATION



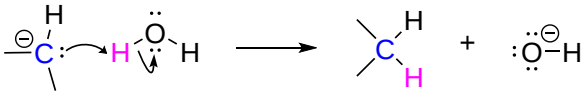
STEP 2: PROTONATION



STEP 3: SECOND DEPROTONATION

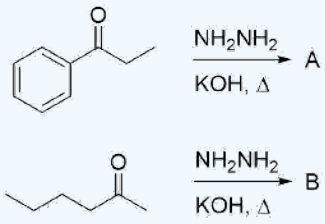


STEP 4: THE CARBANION IS PROTONATED TO FORM THE ALKANE PRODUCT.

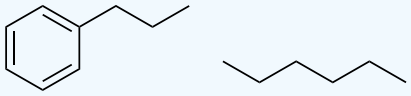


? EXERCISE 19.9.1

Please draw the products of the following reactions.



Answer



A B

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19.10: NUCLEOPHILIC ADDITION OF ALCOHOLS - ACETAL FORMATION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the formation of acetals.
- identify the acetal formed from the reaction of a given aldehyde or ketone with a given alcohol.
- identify the carbonyl compound, the alcohol, or both, needed to form a given acetal.
- write a detailed mechanism for the reaction which occurs between an aldehyde or a ketone and an alcohol.
- explain how an acid catalyst makes aldehydes and ketones more susceptible to attack by alcohols.
- illustrate how the reversibility of the reaction between an aldehyde or a ketone and an alcohol can be used to protect a carbonyl group during an organic synthesis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

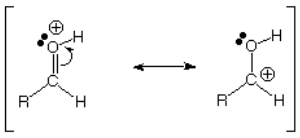
- acetal
- hemiacetal

STUDY NOTES

This section presents a second example of the use of a protecting group. [The first was in the discussion of alcohols, Section 17.8.] Because of the reactivity of hydroxy groups and carbonyl groups, we often need to protect such groups during organic syntheses. When you are designing multi-step syntheses as part of an assignment or examination question, you must always keep in mind the possibility that you may need to protect such groups to carry out the desired sequence of reactions successfully.

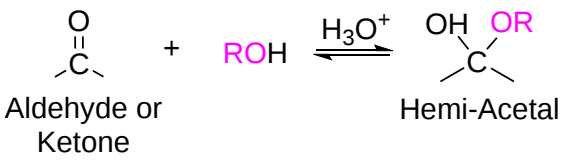
It has been demonstrated in Section 19.5 that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diols. In a similar reaction, one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (h*emi*, Greek, half). This reaction can continue by adding another equivalent of an alcohol to form a diether called an **acetal** $R_2C(OR')_2$. Hemiacetals and acetals are important functional groups because they appear in the structures of many sugars.

An acid catalyst must be used during this reaction because alcohols are weak nucleophiles and would add very slowly under neutral conditions. Under acidic conditions, the oxygen of the carbonyl becomes protonated, increasing the electrophilicity of the carbonyl carbon, speeding up the reaction.

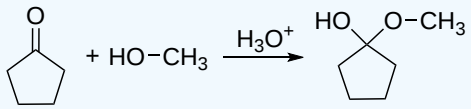


Also, it is common to actively remove the water created with the formation of an acetal by using molecular sieves or a **Dean-Stark trap**. This step is important, since acetal formation is reversible, and the removal of water pushes the equilibrium to the right by Le Chatelier's principal. Indeed, once pure hemiacetals or acetals are obtained, they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

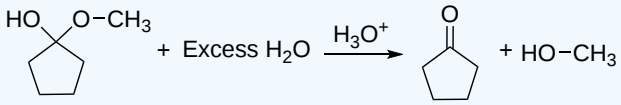
FORMATION OF HEMIACETALS



EXAMPLE 19.10.1: FORMATION OF A HEMIACETAL

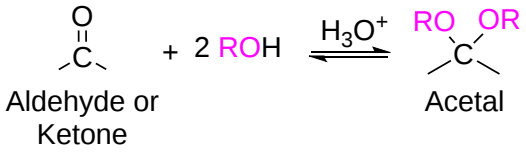


EXAMPLE 19.10.2: HEMIACETAL HYDROLYSIS REVERTING TO THE KETONE



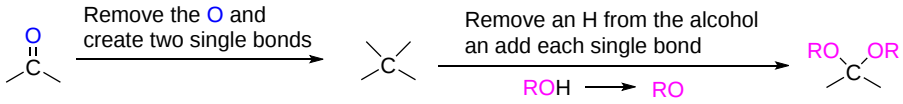
FORMATION OF ACETALS

Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.

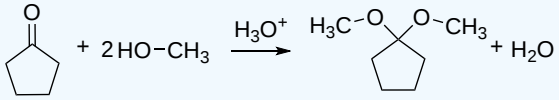


PREDICTING THE PRODUCT OF A ACETAL FORMATION

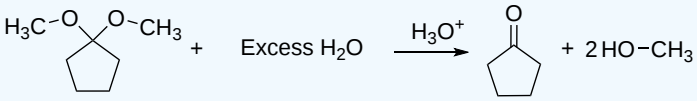
Overall, the carbonyl in the reactant is removed and replaced by two single bonds between oxygen and the original carbonyl carbon. Both of these single bonds are attached O-R groups produced after the reagent alcohol has lost a hydrogen.



EXAMPLE 19.10.3: FORMATION OF ACETALS



EXAMPLE 19.10.4: ACETAL HYDROLYSIS REVERTING TO THE KETONE

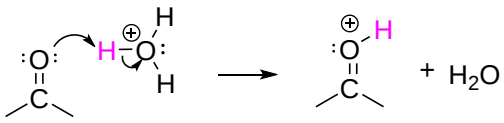


MECHANISM FOR HEMIACETAL AND ACETAL FORMATION

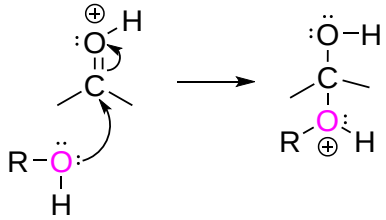
After protonation, an alcohol undergoes nucleophilic addition to the carbonyl group initially forming a hemiacetal upon deprotonation. Further protonation of the OH group in the hemiacetal allows for the elimination of water to form an oxonium ion. A second alcohol nucleophile adds to the oxonium ion to produce a protonated acetal. After deprotonation, the product acetal is formed.

The mechanism shown here applies to both acetal and hemiacetal formation.

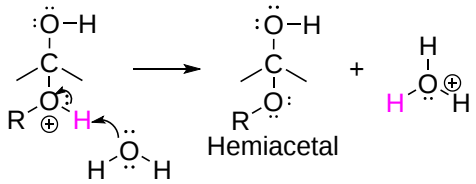
STEP 1: THE ACID CATALYST PROTONATES THE CARBONYL OXYGEN, MAKING THE CARBONYL CARBON MORE ELECTROPHILIC.



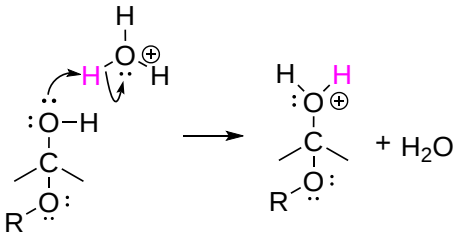
STEP 2: AN ALCOHOL UNDERGOES NUCLEOPHILIC ADDITION TO THE CARBONYL PRODUCING A PROTONATED HEMIACETAL.



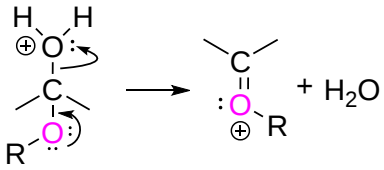
STEP 3: WATER ACTS AS BASE TO CAUSE A DEPROTONATION CREATING A HEMIACETAL AND HYDRONIUM.



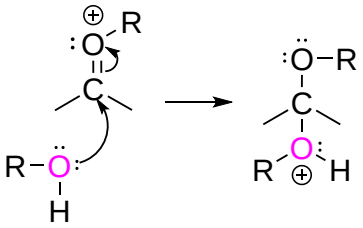
STEP 4: THE OH GROUP OF THE HEMIACETAL IS PROTONATED MAKING IT INTO A GOOD LEAVING GROUP.



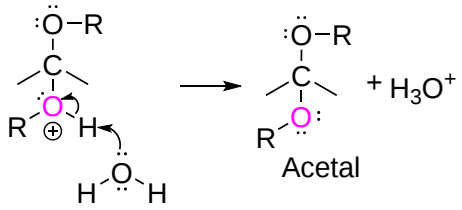
STEP 5: LONE PAIR ELECTRONS ON THE ETHER OXYGEN REFORMS THE C=O BOND CAUSING THE ELIMINATION OF WATER AND PRODUCING AN OXONIUM ION.



STEP 6: A SECOND ALCOHOL UNDERGOES NUCLEOPHILIC ADDITION TO OXONIUM ION PRODUCING A PROTONATED ACETAL.

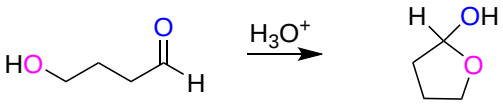


STEP 7: WATER ACTS AS A BASE AND CAUSES A DEPROTONATION, CREATING THE PRODUCT ACETAL AND HYDRONIUM.

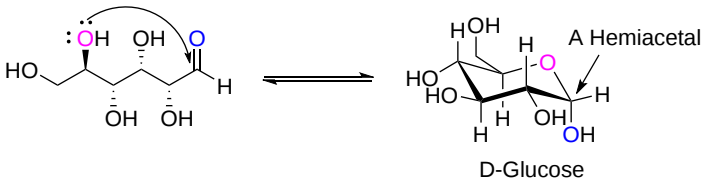


BIOLOGICAL ACETAL AND HEMIACETAL FORMATION

Molecules which have both an alcohol and a carbonyl can undergo an intramolecular reaction to form a cyclic hemiacetal.



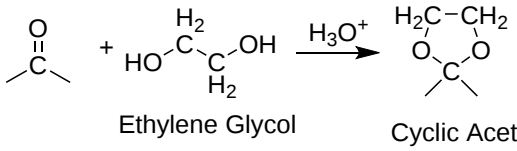
Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry as we will see in Section 25.7. For example, the common sugar glucose exists in the cylcic manner more than 99% of the time in a mixture of aqueous solution.



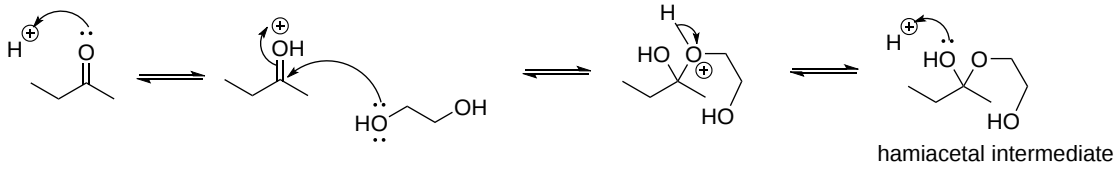
Conversion of D-Glucose to Beta-D-Glucopyranose (Cyclic Hemiacetal)

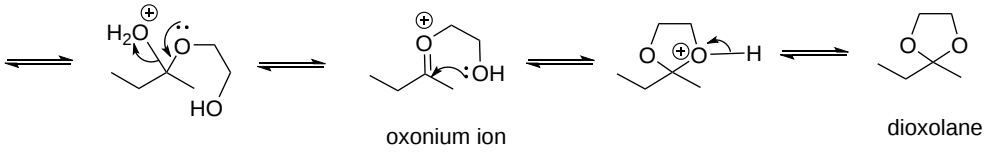
ACETALS AS PROTECTING GROUPS

The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride reagents ($LiAlH_4$ & $NaBH_4$), and organometallic reagents (RMgX & RLi). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented. To accomplish this, it is common to use a diol such as ethylene glycol(rather than two equivalents of a simple alcohol) to form a cyclic acetal ring commonly called a dioxolane.

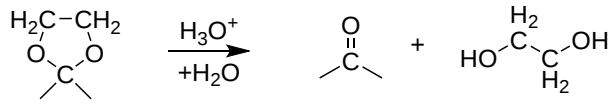


Because both OH groups are part of the same molecule, the second nucleophilic addtion in the formation of the acetal is intramolecular and forms a ring. Cyclic acetals are more stable towards hydrolysis than acyclic ones and are also kinetically favored because the intramolecular ring-closing reaction is fast.

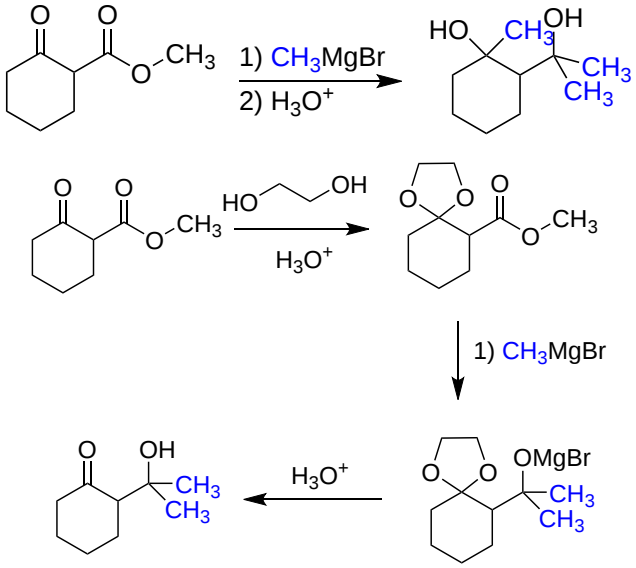




Once the addition reaction is accomplished (or whatever reaction required protecting the carbonyl), the reversibility of acetal formation can be used to reform the original carbonyl.

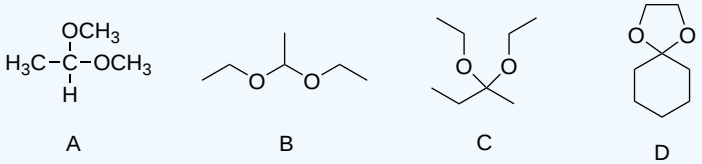


In the following example we would like a Grignard reagent to react with the ester and not the ketone. This cannot be done without a protecting group because Grignard reagents react with both esters and ketones with the ketone typically more reactive than the ester. This reaction sequence uses ethylene glycol to form the cyclic acetal protecting group for the ketone followed by reaction of the ester with a Grignard reagent. Once this reaction is complete, the acetal is hydrolyzed back to the ketone in the same step that reprotonates the alcohol (while eliminating the MgBr).

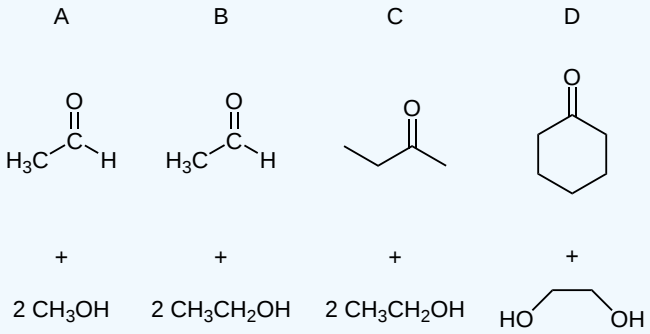


EXERCISE 19.10.1

For each acetal/ketal A-D in the figure below, specify the required aldehyde/ketone and alcohol starting materials.

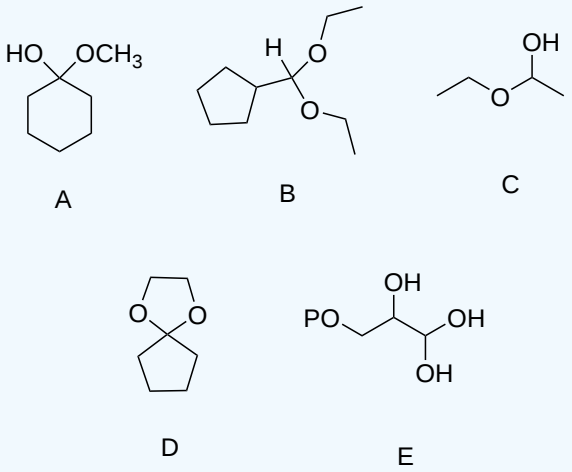


Answer



EXERCISE 19.10.2

Categorize each of the following molecules as a hemiacetal, acetal, hydrate of an aldehyde, or hydrate of a ketone.



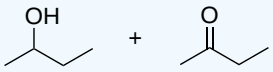
Answer

A - hemiacetal, B - acetal, C - hemiacetal, D - acetal, E - hydrate of an aldehyde

EXERCISE 19.10.3

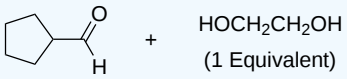
Specify the acetal that would form from a reaction between the given starting compounds.

a.



(2 Equivalents)

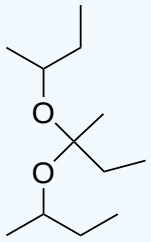
b.



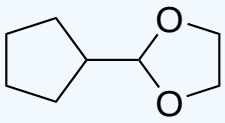
Answer

a.

https://chem.libretexts.org/@go/page/36390



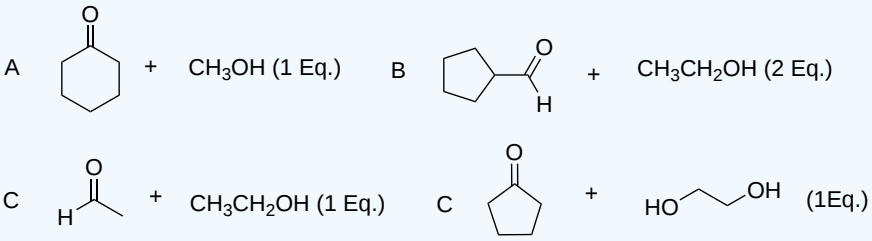
b.



EXERCISE 19.10.4

Specify the aldehyde/ketone and alcohol combination that would be required to form the compounds in exercise 2.

Answer



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19.11: NUCLEOPHILIC ADDITION OF PHOSPHORUS YLIDES - THE WITTIG REACTION

OBJECTIVES

After completing this section, you should be able to

- write an equation to illustrate the formation of an ylide (phosphorane).
- write an equation to illustrate the reaction that takes place between an ylide and an aldehyde or ketone.
- identify the alkene which results from the reaction of a given ylide with a given aldehyde or ketone.
- identify the aldehyde or ketone, the ylide, or both, needed to prepare a given alkene by a Wittig reaction.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- betaine
- Wittig reaction
- ylide (phosphorane)

STUDY NOTES

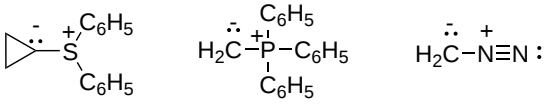
The name triphenylphosphine is derived as follows: the compound PH_3 is called phosphine; replacing the three hydrogen atoms with phenyl groups therefore gives us triphenylphosphine.

Note the following series of IUPAC-accepted trivial names:

- NH_3—ammonia
- PH_3—phosphine
- AsH_3—arsine

PHOSPHORUS YLIDES

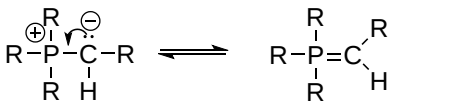
An **ylide,** is defined as a compound with positive and negative charges on adjacent atoms and an overall neutral charge. There are multiple types of ylides but for the Wittig reaction an **organophosphorus ylide**, also called a **Wittig Reagent**, will be used.



Sulfur Ylide Phosphorus Ylide Nitrogen Ylide

Although many Wittig reagents are commercially available, it is often necessary to create them synthetically. Wittig reagents can be synthesized from an **alkylphosphonium salt** created using an S_N2 reaction between an alkyl halide and a nucleophilic trialkyl phosphine. Because trialkyl phosphines typically make good nucleophiles, the S_N2 reactions usually occur with high yields. The subsequent alkylphosphonium salt has an increased acidity (pKa ~22) and can be deprotonated using strong bases, such as *n*-butyllithium, sodium amide, sodium hydride, and alkoxides to create the neutral Wittig reagent. The increased acidity of the alkylphosphonium salt is due to the stabilizing inductive and resonance effects provided by the phosphorus adjacent to the carbanion conjugate base.

The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure call a **phosphorane**. Although Wittig reagents are commonly drawn in the phosphorane form, the ylide form is often used because it shows the nucleophilic carbanion.

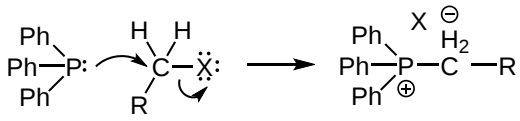


Ylide Form Phosphorane Form

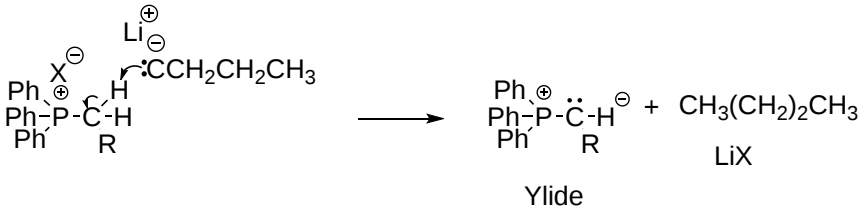
MECHANISM OF YLIDE FORMATION

The lone pair electrons on the phosphine attack the electrophilic carbon of an alkyl halide as part of a S_N2 reaction. This forms a P-C bond while ejecting the halogen leaving group to create an alkylphosphonium salt. A strong base, such as *n*-butyllithium, deprotonates the acidic hydrogen of the alkylphosphonium salt to create an ylide Wittig reagent.

STEP 1: S_N2 REACTION

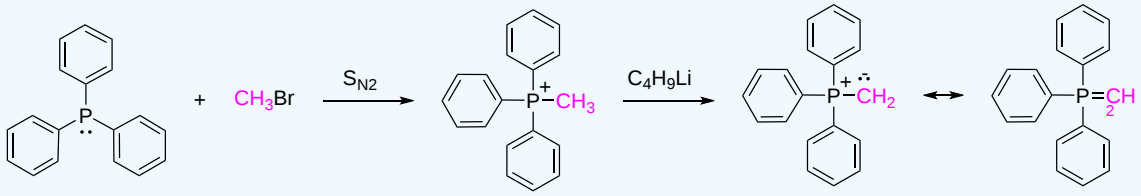


STEP 2: DEPROTONATION



EXAMPLE 19.11.1

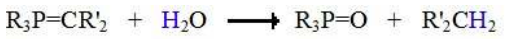
A common Wittig reagent is **methylenetriphenylphosphorane** ($Ph_3P{=}CH_2$) which is synthesized by reacting **Triphenyl phosphine** with methylbromide followed by deprotonation with *n*-butyllithium.



YLIDES IN SYNTHESIS

Because an S_N2 reaction is used in the synthesis of ylides, methyl and primary halides perform the best. Secondary halides can also be used but the yields are generally lower. This should be considered when planning out a synthetic pathway which involves a synthesized Wittig reagent.

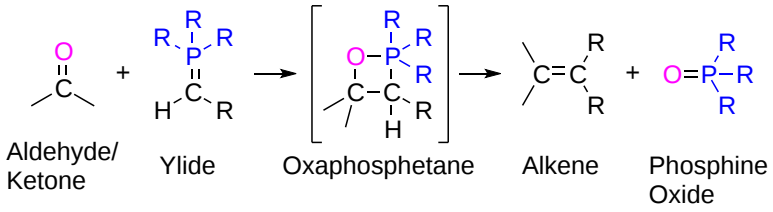
The ylides are typically strong bases and are protonated by water, alcohols, and other acidic hydrogens. Contact with water causes phosphorous ylides to decompose in to hydrocarbons and phosphine oxides, as shown below.



THE WITTIG REACTION

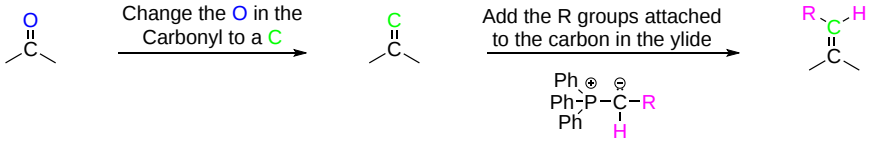
Alkylidenephosphorane ylides (Wittig Reagents) react with aldehydes or ketones through nucleophilic addition, to give substituted alkenes in a reaction called the **Wittig reaction**. This reaction was developed in 1954 by George Wittig who was awarded the Nobel Prize for this work in 1979. Because of its reliability and wide applicability, the Wittig reaction has become a standard tool used in organic synthesis for the preparation of alkenes.

In the Wittig reaction, an **ylide** (typically triphenylphosphorus ylide), adds to an aldehyde or ketone to yield a four-membered heterocyclic intermediate called an **oxaphosphetane**. The oxaphosphetane intermediate spontaneously decomposes to produce an alkene plus a **phosphine oxide**. Cleavage of the oxaphosphetane to alkene and phosphine oxide products is exothermic and irreversible.

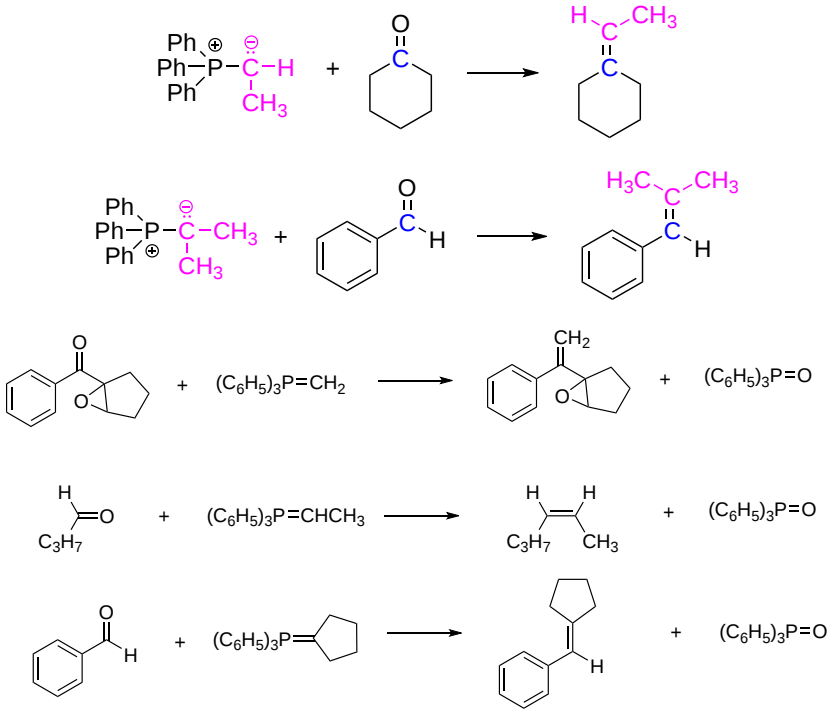


PREDICTING THE PRODUCT OF A WITTIG REACTION

Overall the carbonyl oxygen of an aldehyde or ketone is replaced by the nucleophilic, carbanion present in the ylide while still maintaining the double bond. First, convert the oxygen in the starting material into a carbon while maintaining the double bond. This carbon represents the nucleophilic carbon in the ylide. Then look at the ylide reactant and observe the two groups attached to the nucleophilic carbon. Then transfer these to the bare carbon in the double bond. There may be some possibility of creating E/Z isomers and this will be discussed later.



EXAMPLES OF THE WITTIG REACTION

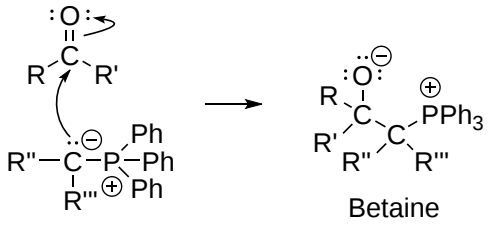


MECHANISM OF THE WITTIG REACTION

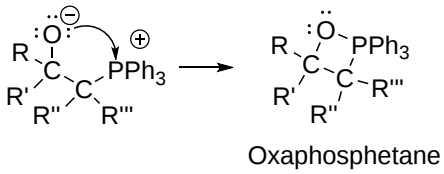
The initial mechanistic step to form the oxaphosphetane intermediate appears to take place by different pathways which is dependent on the structure of the reactants and the exact experimental conditions. One pathway involves a [2+2] cycloaddition between the ylide and carbonyl to directly form the oxaphosphetane. Cyloadditions, such as this, will be discussed in more detail in section 30.5.

In another postulated mechanism, the ylide undergoes nucleophilic addition to the carbonyl group, forming the initial carbon-carbon bond and creating a dipolar charge-separated intermediate species called a **betaine**. The betaine subsequently undergoes ring closure to form the four-membered oxaphosphetane structure. In the final step of the mechanism, the oxaphosphetane undergoes intramolecular elimination to give an alkene and a triphenylphosphine oxide.

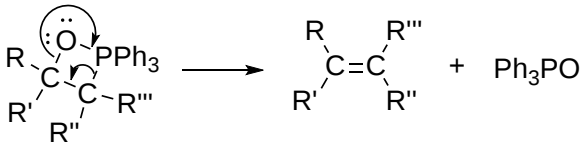
STEP 1: NUCLEOPHILLIC ATTACK ON THE CARBONYL DOUBLE BOND



STEP 2: FORMATION OF THE 4-MEMBERED OXAPHOSPHETANE RING

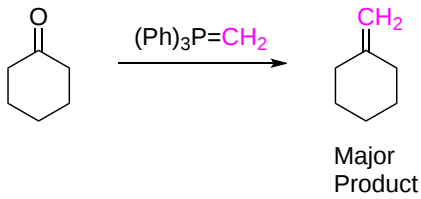


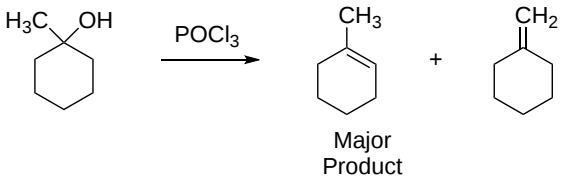
STEP 3: INTRAMOLECULAR ELIMINATION



BENEFITS OF THE WITTIG REACTION

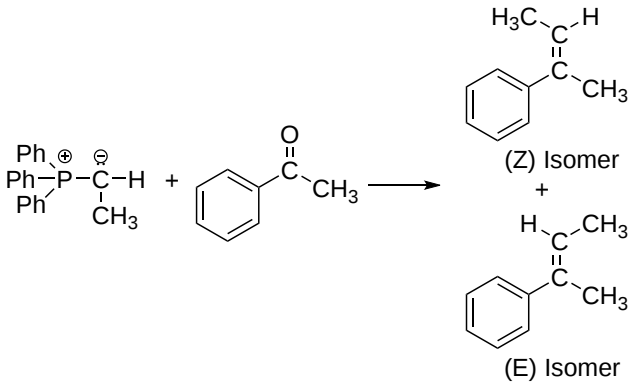
A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration or other elimination reactions.





LIMITATIONS OF THE WITTIG REACTION

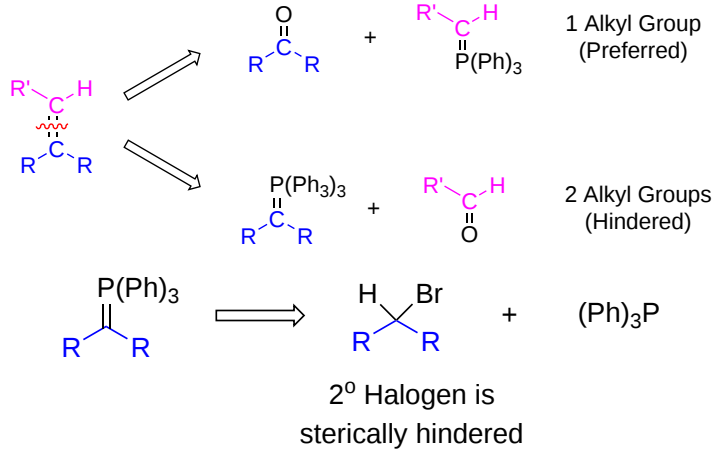
One limitation of the Wittig reaction is possibility of E and Z isomers of the alkene forming. With simple ylides, the product formed is usually primarily the Z-isomer, although a lesser amount of the E-isomer is often also formed. If the E-isomer is the desired product, variations of the Wittig reaction, such as the **Schlosser modification** which uses a stabilized ylide, may be used. It is common to avoid the possibility of forming E/Z isomer by either using symmetrical ketones or symmetrical ylides.



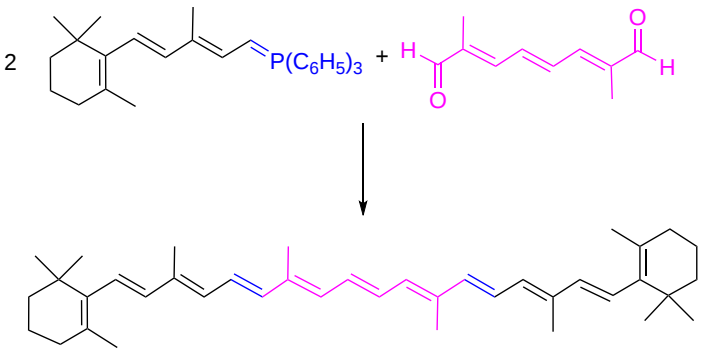
As mentioned above, the Wittig reagent itself is usually derived from an S_N2 reaction with an alkyl halide. Ylide formation with most secondary halides is inefficient. For this reason, Wittig reagents are rarely used to prepare tetrasubstituted alkenes. However, the Wittig reaction is robust and can tolerate the presence of many other functional groups including alkenes, aromatic rings, ethers, alcohols, and ester groups. Bis-ylides (containing two P=C bonds) have also been made and used successfully.

SYNTHESIS OF ALKENES USING THE WITTIG REACTION

When using retrosynthetic analysis to determine the preferred route to synthesize an alkene, it is important to remember that Wittig reagents are commonly prepared by using an S_N2 reaction. To find the possible reactants of a Wittig reaction, cleave the C=C bond in the target molecule to create two pieces. Place an oxygen on one piece to create a carbonyl and place a $(Ph_3)P$ on the other piece to create the Wittig reagent. There are two possible combinations of this separation. The one whose Wittig reagent has the fewest number of alkyl groups will be easier to prepare by the required S_N2 reaction and will represent the preferred route.

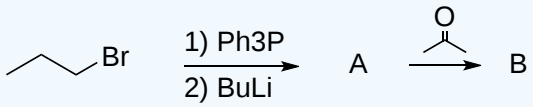


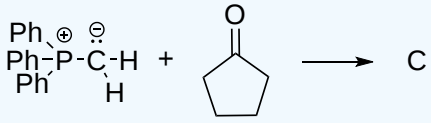
The Wittig reaction is commonly used in the preparations of pharmaceuticals and other commercial chemicals. The dietary source of **vitamin A (β-Carotene)** can be synthesized by a Wittig reaction using two equivalents of the ylide, **β-ionylideneacetaldehyde**.

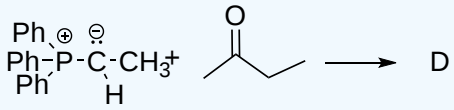


EXERCISE 19.11.1

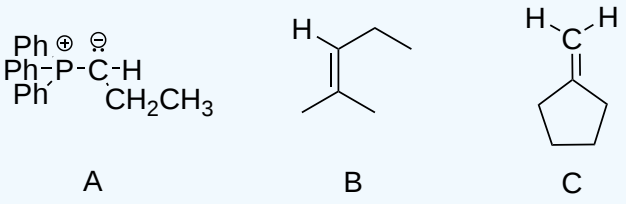
Draw the product of the following reactions.

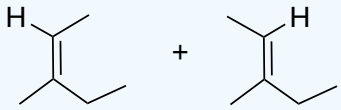






Answer

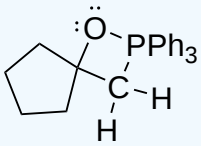




EXERCISE 19.11.2

Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

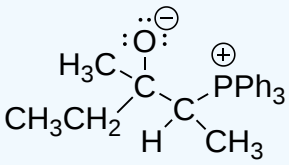
Answer



EXERCISE 19.11.3

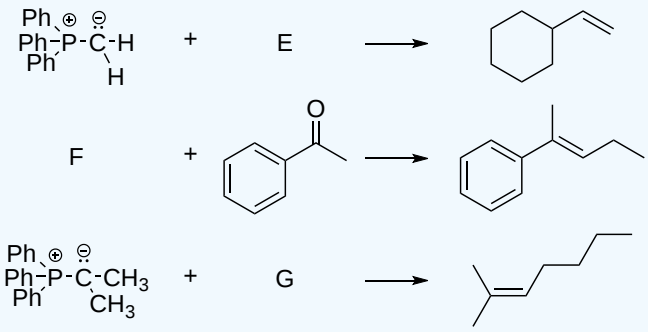
Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

Answer

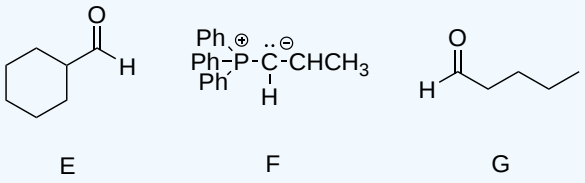


EXERCISE 19.11.4

Indicate the starting material required to produce the product in each reaction.



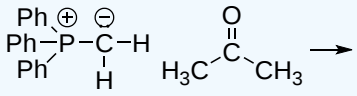
Answer



E F G

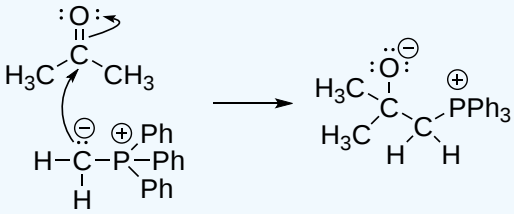
EXERCISE 19.11.6

Give a detailed mechanism and the final product of this reaction

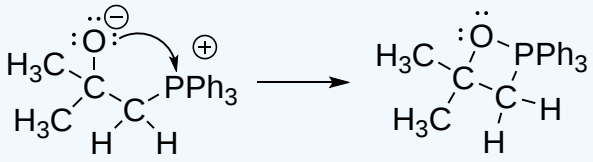


Answer

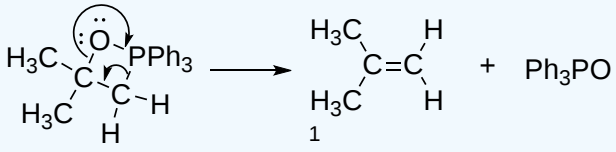
Step 1: Nucleophilic attack on the carbonyl



Step 2: Formation of a 4 membered ring



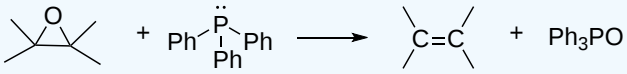
Step 3: Formation of the alkene



1

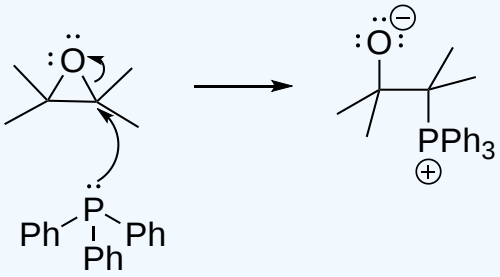
EXERCISE 19.11.7

It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Please propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.

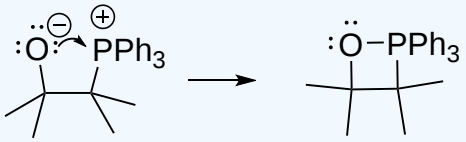


Answer

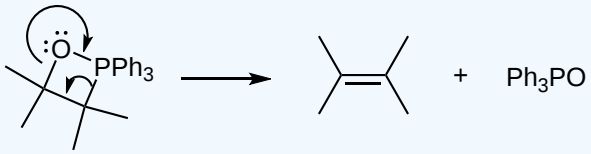
Nucleophillic attack on the epoxide



Formation of a 4 membered ring



Formation of the alkene



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19.12: BIOLOGICAL REDUCTIONS

OBJECTIVES

After completing this section, you should be able to

- determine whether or not a given aldehyde will undergo the Cannizzaro reaction.
- write an equation to illustrate the Cannizzaro reaction.
- identify the products formed when a given aldehyde undergoes a Cannizzaro reaction.
- write the detailed mechanism of the Cannizzaro reaction.

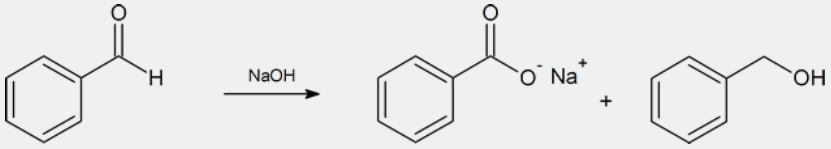
KEY TERMS

Make certain that you can define, and use in context, the key term below.

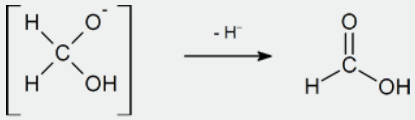
- Cannizzaro reaction

STUDY NOTES

In 1853 Stanislao Cannizzaro discovered that the base-induced disproportionation of an aldehyde resulted in a carboxylic acid (oxidation product) and an alcohol (reduction product).



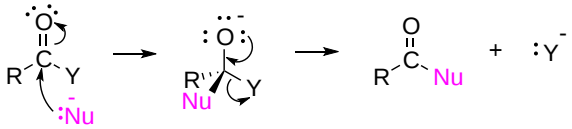
Note that in the mechanism shown in the reading has an intermediate generated from methanal (formaldehyde) that effectively becomes a hydride (H^-) donor, which reduces a second molecule of methanal to methanol.



hydride donor

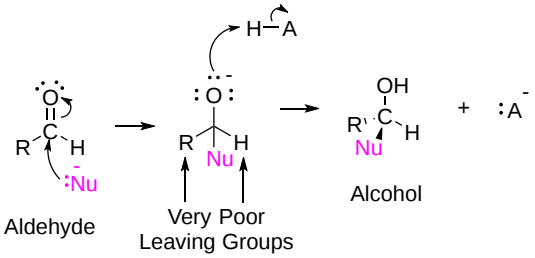
Carbonyl reductions are a part of important biological pathways in living organisms. Recall in Section 17.4 that NADH can donate H^- to reduce aldehydes and ketones. You may wish to review this section.

As seen in Section 18.11, nucleophilic addition reactions usually do not occur in many carboxylic acid derivatives due to the presence of a leaving group. Following nucleophilic addition, the tetrahedral alkoxide intermediate can reform the carbonyl by eliminating the leaving group as part of a reaction called **nucleophilic acyl substitution**. The nucleophilic acyl substitution reaction will be discussed in greater detail in Chapter 21.



Y = -Br, -Cl, -OR, $-NR_2$, $-O_2R$

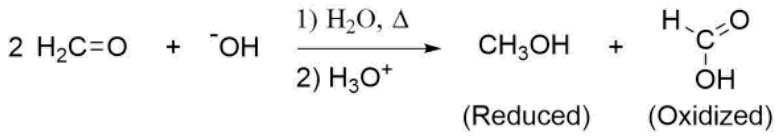
This reaction does not occur in aldehydes or ketones because alkyl or hydrogen substituents make very poor leaving groups. After nucleophilic addition, the negative charge on the tetrahedral alkoxide intermediate remains on the oxygen and is subsequently protonated to form a hydroxyl group (OH). This represents the 1,2 nucleophilc addition reaction discussed in most of this chapter.



THE CANNIZZARO REACTION

An important exception to the idea of hydrogen making a poor leaving group is seen in the **Cannizzaro reaction**, discovered in 1853 by Stanislao Cannizzaro. A characteristic reaction of aldehydes without α hydrogens is the self oxidation-reduction they undergo in the presence of strong base. If the aldehyde has α hydrogens, other reactions usually occur more rapidly. The Cannizzaro reaction, combines many features of other reactions studied in this chapter. During this reaction, nucleophilic addition of a hydroxide ($^{-}$OH) to an aldehyde gives a tetrahedral alkoxide intermediate. The alkoxide subsequently reforms the carbonyl, eliminating a hydride ion ($^{-}$:H) as a leaving group, and creating an oxidized carboxylic acid product. The eliminated hydride ion reduces a second aldehyde molecule, in a similar fashion as hydride containing reagents $LiAlH_4$ and $NaBH_4$, to create a reduced alcohol product. For example, methanal creates methanol (reduced) and methanoic acid (oxidized) when heated with aqueous NaOH.

EXAMPLE

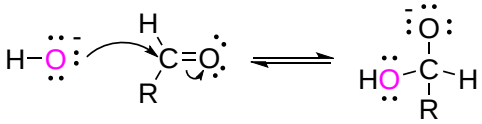


Methanal Undergoing a Cannizzaro Reaction to form Methanol and Methanoic Acid

MECHANISM OF THE CANNIZZARO REACTION

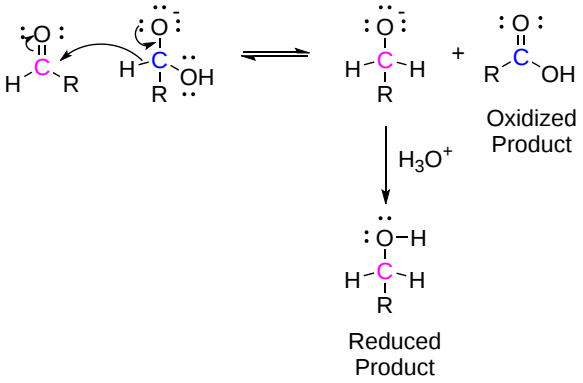
The first step of the mechanism is the reversible nucleophilic addition of a hydroxide ion to the carbonyl group of an aldehyde. This is analogous to the first mechanistic step in the formation of a hydrate under basic conditions. The hydroxide nucleophile attacks the electrophilic carbonyl carbon forming a C-O single bond. The two electrons from the carbonyl pi bond are pushed onto the electronegative oxygen to form a tetrahedral alkoxide intermediate. In the second step of the mechanism, the alkoxide intermediate reforms the carbonyl, eliminating a hydride ion as the leaving group, and forms a carboxylic acid functional group as an oxidized product. The hydride ion acts as a nucleophile and attacks the carbonyl carbon of a second aldehyde forming a C-H bond. The two electrons from the second pi bond are pushed onto the electronegative oxygen to form a different alkoxide intermediate. This alkoxide intermediate is quickly protonated to form an alcohol functional group as a reduced product.

STEP 1: NUCLEOPHILIC ATTACK



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STEP 2: HYDRIDE TRANSFER

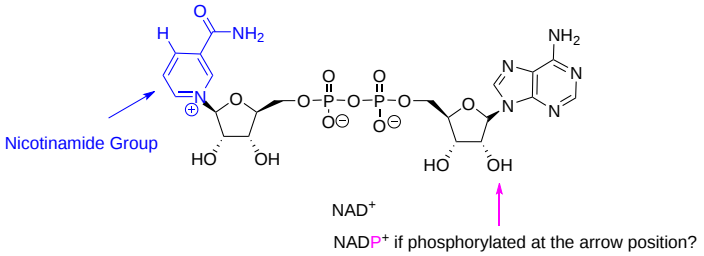


BIOLOGICAL REDUCTIONS USING HYDRIDE TRANSFER TO A CARBONYLS

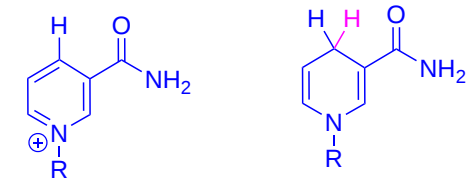
The Cannizzaro reaction is interesting because its mechanism is analogous to the hydride reductions of carbonyls which occur in the biological pathway of many living organisms. One of the most important biological reducing agents is NADH (the reduced form of nicotinamide adenine dinucleotide) which can act as a source of the hydride ion. NADH donates a hydride to carbonyls in an analogous fashion to the alkoxide ion intermediate of the Cannizzaro reaction. A set of lone pair electrons on a NADH nitrogen atom pushes the hydride off as a leaving group forming NAD+ (the oxidized form of nicotinamide adenine dinucleotide). The ejected hydride adds as a nucleophile to a wide variety of carbonyl containing biological molecules. Some examples of this addition are described below.

NICOTINAMIDE ADENINE DINUCLEOTIDE - A HYDRIDE TRANSFER COENZYME

Although we are talking about hydrides acting as nucleophiles and leaving groups in this section, you already know that discreet hydride ions are far too unstable to exist as actual intermediates in the organic reactions of living cells. Biochemical redox reactions involving hydride transfer require the participation of a hydride transfer coenzyme. In reactions involving carbonyl compounds, a molecule called nicotinamide adenine dinucleotide generally plays this role. The full structure of the oxidized form of this coenzyme, abbreviated NAD+, is shown below, with the active nicotinamide group colored blue.



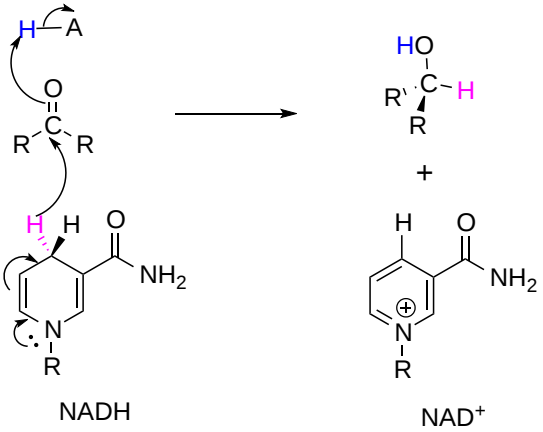
Because the redox chemistry occurs specifically at the nicotinamide part of the molecule, typically the rest of the molecule is simply designated as an 'R' group. NAD^+ and $NADP^+$ both function in biochemical redox reactions as hydride acceptors: that is, as oxidizing agents. The other forms of the coenzyme, NADH and NADPH, serve as hydride donors: that is, as reducing agents.



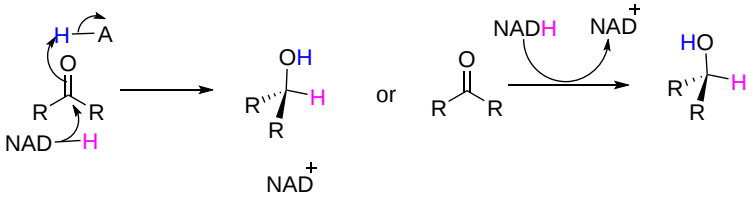
NAD+
NADP+
(Hydride Acceptor)

NADH
NADPH
(Hydride Donor)

The phosphate on the nucleotide pentose group of NADP+ and NADPH is located far from the nicotinamide ring, and does not participate directly in the hydride transfer function of the cofactor.

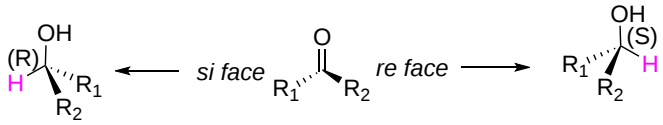


This reaction can be simplified in the following way:

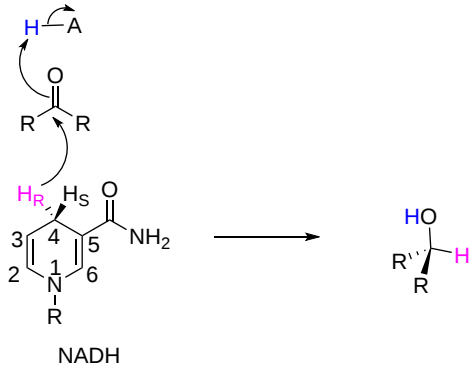


STEREOCHEMISTRY OF HYDRIDE TRANSFER REACTIONS

Ketone/aldehyde hydrogenase reactions are stereospecific in two distinct ways. In the hydrogenase direction, attack by the hydride can occur from either the *re* or the *si* face of an asymmetrical carbonyl, leading to the *S* or *R* alcohol depending on the priorities of R_1 and R_2 (in the example R_1 has higher priority than R_2).

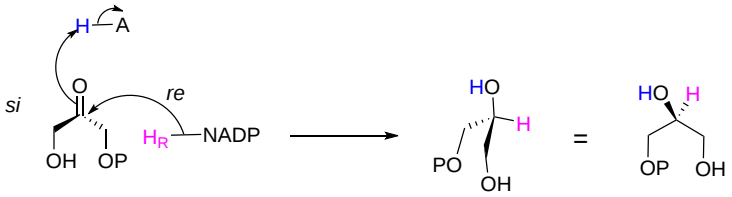


The specificity is determined by which side of the ketone or aldehyde substrate the NAD(P)H cofactor is bound to in the active site. In addition, hydrogenases specifically catalyze the transfer of either the *pro-R* or the *pro-S* hydrogen at C_4 of the nicotinamide ring. In the example below, the *pro-R* hydrogen of NADH is transferred to reduce the ketone.



EXAMPLES OF BIOLOGICAL HYDRIDE TRANSFER REACTIONS

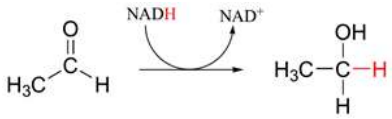
1. In 1997, an enzyme was discovered in a class of microbes known as ‘archaea’ that catalyzes the same reaction with the opposite substrate stereochemistry (J. Biochem 1997, 122, 572). The primary metabolic role of the enzyme is apparently to catalyze the reduction of dihydroxyacetone phosphate to (S)-glycerol phosphate, with transfer of the pro-R hydrogen atom from NADPH to the *re* face of dihydroxyacetone phosphate.



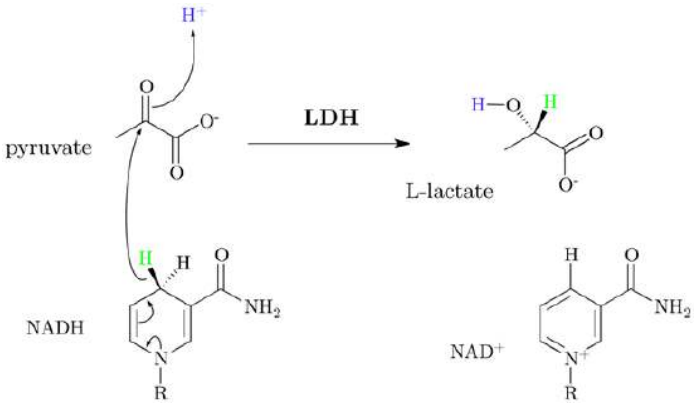
dihydroxyacetone phosphate

(S)-glycerol phosphate

2. In a reaction that is very important to people in the wine and beer-making industry, an NADH-dependent enzyme in yeast produces ethanol by reducing acetaldehyde. The acetaldehyde is derived from the thiamine diphosphate-dependent decarboxylation of pyruvate.

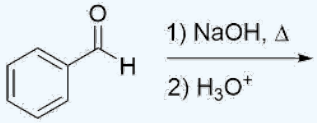


3. Lactic acid fermentation occurs by converting pyruvate into lactate through hydride addition using the enzyme lactate dehydrogenase and producing NAD+ in the process. This process takes place in oxygen depleted muscle and some bacteria. It is responsible for the sour taste of sauerkraut and yogurt.

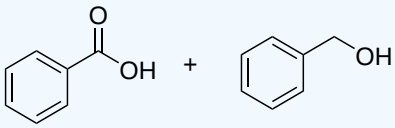


EXERCISE 19.12.1

Please draw the expected products of the following reaction:



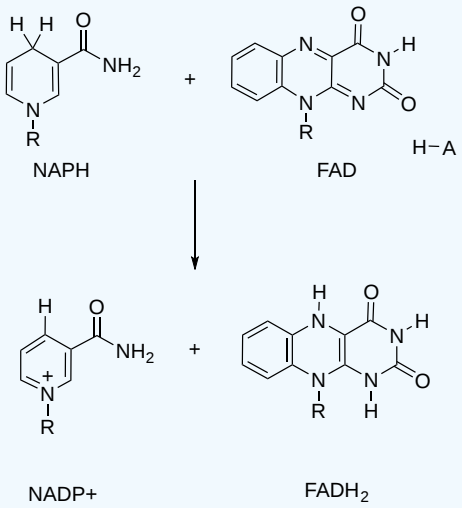
Answer



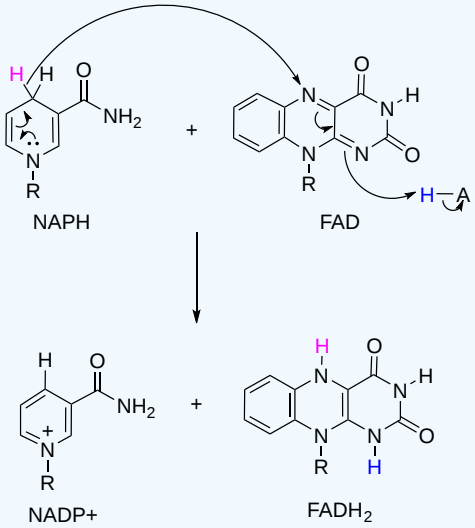
EXERCISE 19.12.2

Please draw the mechanism for the following hydride transfer reaction:

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Answer



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19.13: CONJUGATE NUCLEOPHILIC ADDITION TO A, B-UNSATURATED ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

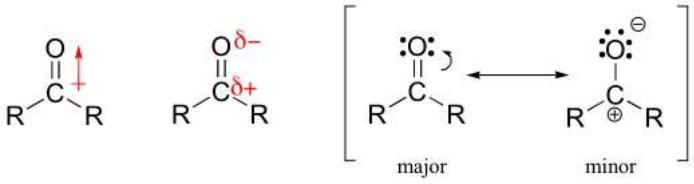
- explain how the carbonyl group which is present in α, β-unsaturated aldehydes and ketones activates the carbon-carbon double bond so that it is susceptible to attack by nucleophiles.
- write equations to illustrate the addition of amines, water and lithium diorganocopper reagents to α, β-unsaturated aldehydes and ketones.
- identify the product formed from the reaction of a given primary or secondary amine with a given α, β-unsaturated aldehyde or ketone.
- identify the aldehyde or ketone, the primary or secondary amine, or both, needed to prepare a given β-amino aldehyde or ketone.
- identify the product formed from the reaction of an α, β-unsaturated aldehyde or ketone with water.
- identify the product formed from the reaction of a given α, β-unsaturated aldehyde or ketone with a given lithium diorganocopper reagent.
- identify the α, β-unsaturated aldehyde or ketone, the lithium diorganocopper reagent, or both, needed to prepare a given product through a conjugate addition reaction.

STUDY NOTES

At first this section may appear to contain a considerable amount of information, but you should realize that much of the material presented is really repetition. Essentially we see how three different nucleophilic reagents, primary and secondary amines, water and lithium diorganocoppers can add across a carbon-carbon double bond when the latter is conjugated to the carbonyl group of an aldehyde or ketone. Note that the first reagent can also react directly with the carbonyl group of an aldehyde or ketone when there is no conjugated carbon-carbon double bond present, but that the third reagent, lithium dialkylcopper, cannot do so.

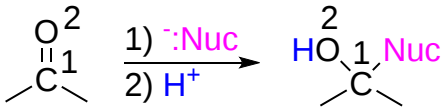
You may be confused about the designation of the product from the conjugate addition to an α, β-unsaturated aldehyde or ketone as a 1,4 adduct. You can more clearly understand this name if you recognize that the proton added in the second step of the reaction first adds to the oxygen of the enolate ion to produce an enol. The latter then tautomerizes to the more stable keto form.

One of the largest and most diverse classes of reactions involves nucleophilic additions to a carbonyl group. As discussed in Section 19.4, carbonyl carbons are electrophilic due to bond polarity created by resonance.

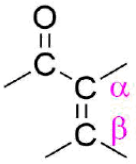


Previously in this chapter, we have discussed a nucleophilic addition to carbonyl carbons called a **1,2 addition**. During 1,2 addition the nucleophile adds to the carbonyl carbon which is defined as the one position. Subsequently, hydrogen adds to the carbonyl oxygen which considered the two position. Overall an atom is added in both the 1 and 2 position justifying the reaction name, 1,2 addition.

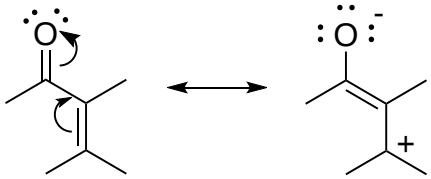
BASIC REACTION OF 1,2 ADDITION



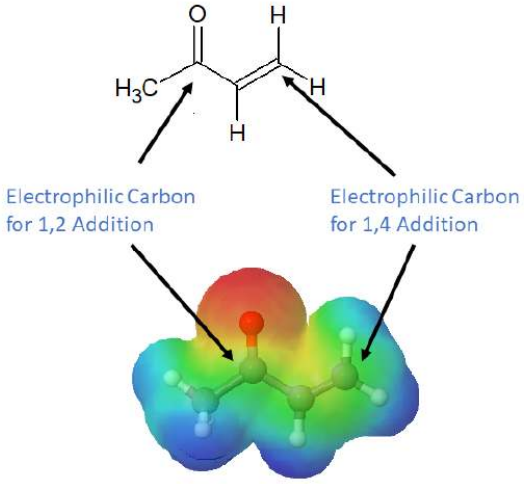
An important functional group is created when an alkene is placed in conjugation with a carbonyl. These conjugated carbonyl are called enones or **α, β-unsaturated carbonyls**. The term α commonly refers to the carbon adjacent to a carbonyl and β referrers to the next carbon in the chain.



Conjugation transmits the electrophilic character of the carbonyl carbon to the β-carbon of the **α, β-unsaturated carbonyl** double bond. The resonance structure shown below shows that the electronegative oxygen atom in α, β-unsaturated carbonyls pulls electrons away from the β carbon making it more electrophilic than a typical alkene carbon.

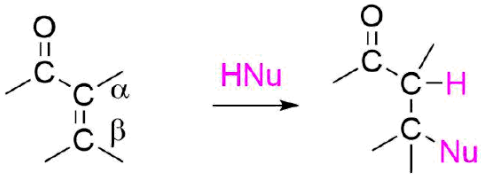


From this resonance form, it should be clear that nucleophiles may attack either at the carbonyl carbon or at the β-alkene carbon. These two modes of reaction are referred to as 1,2-addition and **1,4-addition** respectively. A 1,4-addition is also called a **conjugate addition**.



BASIC REACTION OF 1,4 CONJUGATE ADDITION

In 1,4 addition, a nucleophile is added to the carbon β to the carbonyl while a hydrogen is added to the carbon α to the carbonyl. Overall, the carbonyl is unaffected by the nucleophilic addition. It is important to note that this reaction only occurs because the alkene is conjugated with a carbonyl. The utility of 1,4 conjugate addition is shown by the wide variety of nucleophiles which can be added to a α, β unsaturated carbonyls.

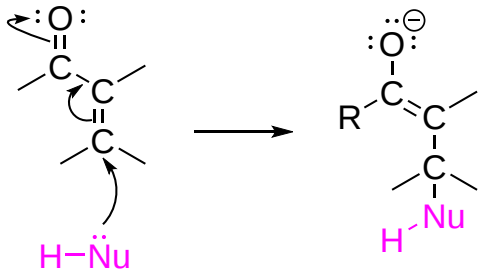


GENERAL MECHANISM FOR 1,4 CONJUGATE ADDITION

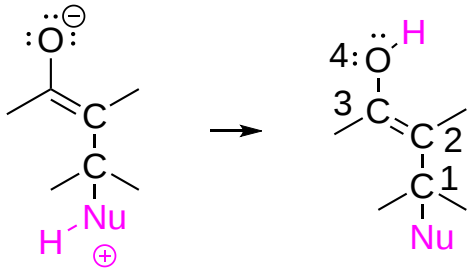
The mechanism starts with the nucleophile attacking the electrophilic β carbon forming a single bond. The two electrons from the alkene pi bond are pushed onto the electronegative carbonyl oxygen creating an enolate. In the next step the the enolate is protonated to form an enol. If the original nucleophile was neutral, this addition will cause it to become positively charge. A proton transfer will occur making the nucleophile neutral and turning the enolate into an enol. If the original nucleophile was negatively charged this protonation is accomplished by the subsequent addition of a proton source. The product of the second step of the mechanism shows why the reaction is called a 1,4 addition. The nucleophile bonds to the β alkene carbon which is considered the one position and the hydrogen adds to the carbonyl oxygen

which is in the four position. Overall, addition occurs in the one and four position. In the final step of the mechanism, the enol undergoes a rearranges to form a carbonyl during a process called tautomerization. Tautomerization causes the hydrogen to move from the oxygen to the β-carbon. The tautomerization process will be discussed in greater detail in Section 22.3.

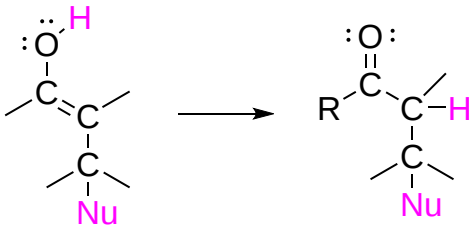
STEP 1: NUCLEOPHILIC ATTACK



STEP 2: PROTONATION

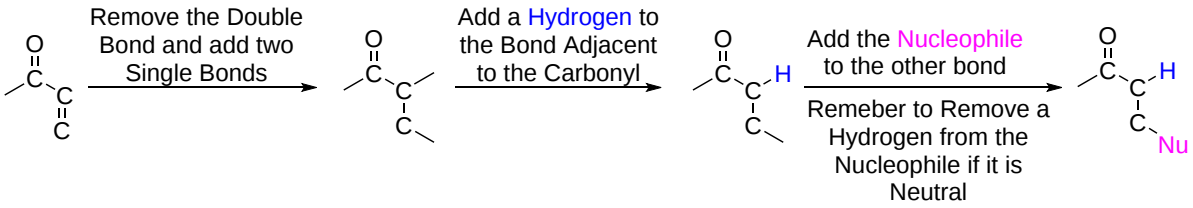


STEP 3: TAUTOMERIZATION



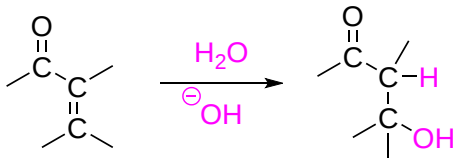
PREDICTING THE PRODUCTS OF A 1,4 CONJUGATE ADDITION

In total, 1,4 addition occurs across the alkene bond of the α, β unsaturated carbonyl. The alkene pi bonds is broken to form two single bonds, one on the α-carbon and one on the β-carbon. During 1,4 addition, the α-carbon of the α, β unsaturated carbonyl forms a bond with a hydrogen while the β-carbon forms a bond to the nucleophile. Remember that neutral nucleophiles typically lose a hydrogen during 1,4 addition.

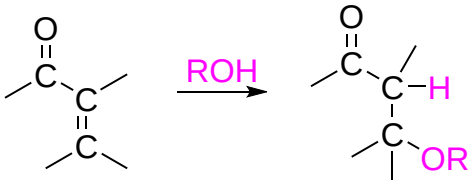


NUCLEOPHILES WHICH ADD 1,4 TO A, B UNSATURATED CARBONYLS

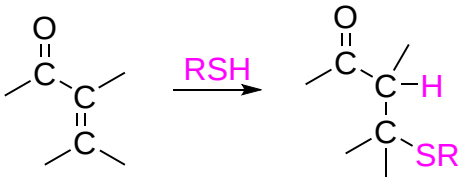
HYDROXIDE



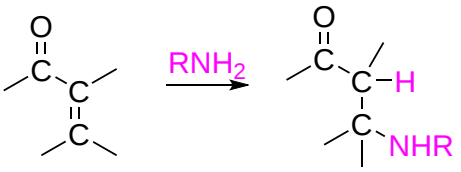
ALCOHOLS



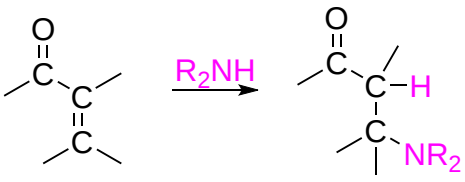
THIOLS



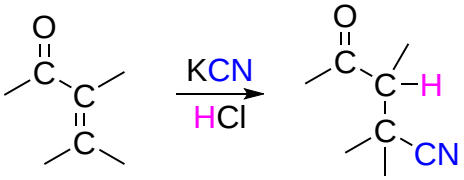
1^{O} AMINES



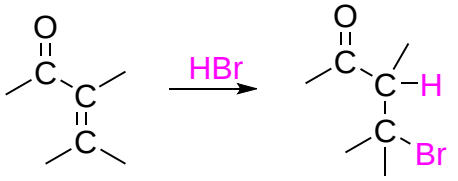
2^{O} AMINES



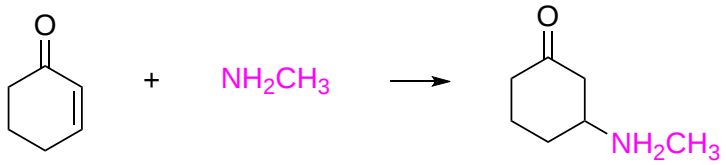
CYANIDES



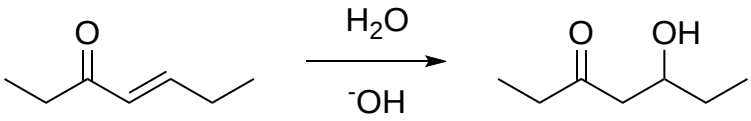
HBR



EXAMPLES



The synthesis of 3-(*N*-Methylamino)cyclohexanone



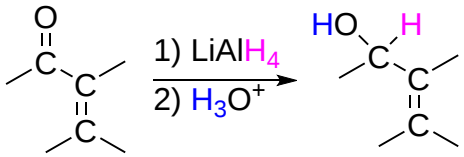
The Synthesis of 5-Hydroxy-3-heptenone

1,2 VS. 1,4 ADDITION

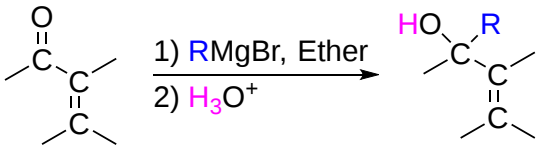
Whether 1,2 or 1,4-addition occurs to a α, β unsaturated carbonyl depends on multiple variables but is mostly determined by the nature of the nucleophile. During the addition of a nucleophile there is a competition between the formation 1,2 and 1,4 addition products. If the nucleophile is a strong base, such as Grignard reagents or metal hydrides, both the 1,2 and 1,4 reactions are irreversible and therefor are under kinetic control. Since 1,2-additions to the carbonyl group are fast, we would expect to find a predominance of 1,2-products from these reactions. If the nucleophile is a weak base, such as, water, alcohols or amines, then the possible 1,2 addition is usually reversible. This means the competition between 1,2 and 1,4 addition is under thermodynamic control. In this most cases, the 1,4-addition product dominates because the stable carbonyl group is retained.

NUCLEOPHILES WHICH ADD 1,2 TO A, B-UNSATURATED CARBONYLS

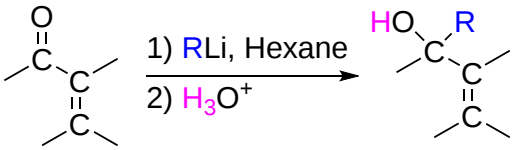
METAL HYDRIDES ($LiAlH_4$)



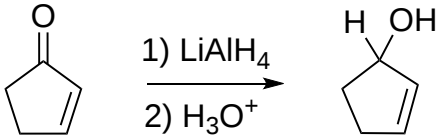
GRIGNARD REAGENTS



ORGANOLITHIUM REAGENTS



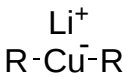
EXAMPLE



GILMAN REAGENTS

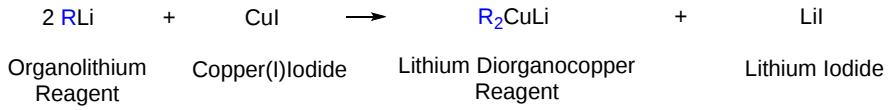
Another important reaction exhibited by organometallic reagents is metal exchange. Organolithium reagents react with cuprous iodide to give a **lithium diorganocopper reagent**, which often is referred to as a **Gilman reagent**. Remember that organolithium reagents are

formed by a reaction of lithium metal with an organohalide. Lithium diorganocopper reagents are considered a source of carbanion like nucleophiles similar to Grignard and Organolithium reagents. However, the reactivity of lithium diorganocuprate reagents is slightly different and this difference will be exploited in different situations. Diorganocuprate reagents are made from the reaction of two equivalents of an organolithium reagent and copper (I) iodide (CuI). The created lithium diorganocuprate reagent acts as a source of $R:^-$

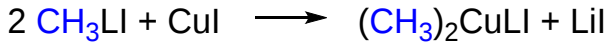


Lithium Diorganocopper (Gilman Reagent)

GENERAL REACTION



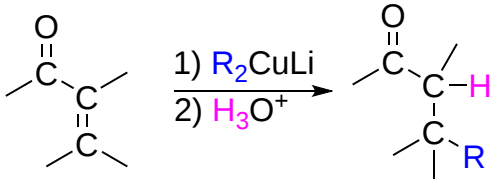
EXAMPLE



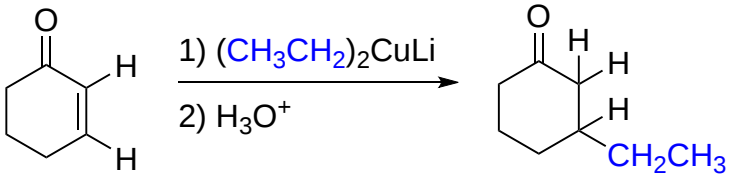
Formation of Lithium Dimethylcopper

REACTION OF 1,4 CONJUGATE ADDITION OF GILMAN REAGENTS TO A, B UNSATURATED KETONES

Lithium diorganocopper reagents, R_2CuLi, undergo 1,4 conjugate addition when reacted with α, β Unsaturated ketones. Using lithium diorganocopper reagents allows for a wide range of organic groups to undergo this 1,4 conjugate addition including alkyl, aryl, and alkenyl groups. Because a C-C single bond is formed this reaction is an excellent method for adding to the carbon framework of a ketone.

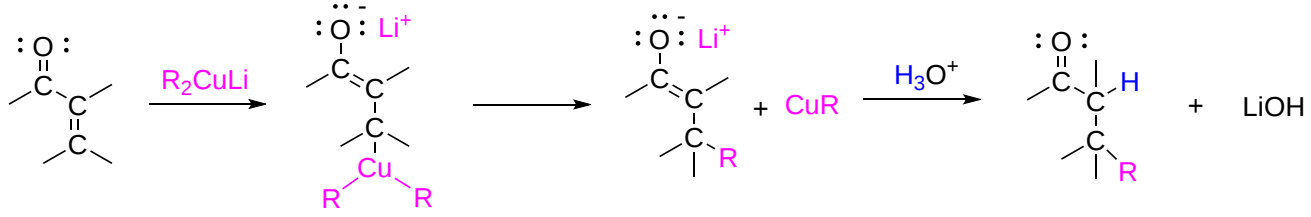


EXAMPLE



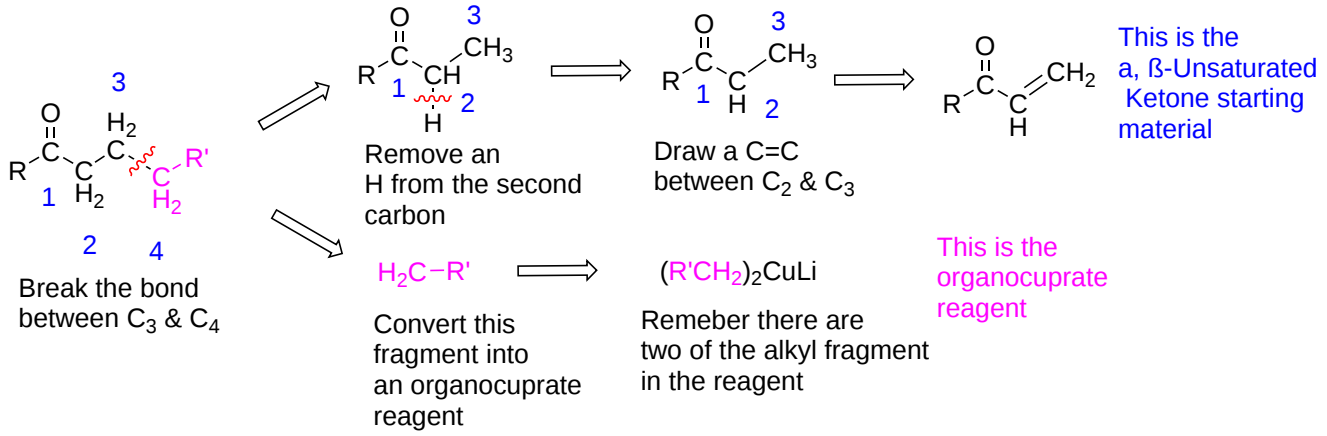
MECHANISM FOR THE 1,4 CONJUGATE ADDITION OF LITHIUM DIORGANOCOPPER REAGENTS TO A, B-UNSATURATED KETONE

This mechanism is only slightly different than the general mechanism for 1,4 conjugate addition described above. The mechanism starts with the nucleophilc diorganocopper anion (R_2Cu^-) adding to the electrophilc β alkene carbon forming a Cu-C bond. The R group from the diorganocopper is then transferred to the β alkene carbon with elimination of a neutral organocopper species (RCu). Protonation of the enolate ion followed by tautomerization creates the final 1,4 addition product.



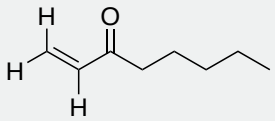
SYNTHESIS OF KETONES USING 1,4 CONJUGATE ADDITION OF LITHIUM DIORGANOCOPPER REAGENTS TO A, B UNSATURATED KETONES

When using retrosynthetic analysis to plan the synthesis of a ketone, remember this reaction allows for the formation of a C-C bond between third and fourth carbon away from a ketone. The carbonyl group in the target molecule will become a α, β unsaturated carbonyl in the probable reactant. To determine the structure of a possible reactant, start by cleaving the C-C between the third and fourth carbon away from the carbonyl to create two fragments. The take the fragment which retains the carbonyl and remove a hydrogen from the second carbon and connect the second and third carbon with a double bond. The creates the required α, β unsaturated carbonyl reactant. The other fragment will become the lithium diorganocopper reagent. Remember the lithium diorganocopper reagent contains two of the required R group. Note! If the fourth carbon away from the ketone in the target molecule is tertiary or quarternary there may be multiple bonds which could be retrosynthetically cleaved.



SOMETHING EXTRA: WHY DO METALS HAVE A SMELL WHEN THEY ARE NONVOLATILE?

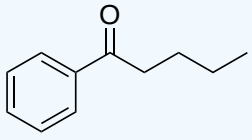
If you have ever encountered a metallic scent when counting coins or handling metals, especially copper, you were probably being fooled. The metallic smell could not have come from the metal because metals are non-volatile and do not evaporate. This means the odor molecules associated with metal scent must come from a different source. The volatile molecules that create the metallic smell are produced by a chemical reaction between skin oils and the metal itself. These volatile molecules, primarily aldehydes and ketones, create a sensory illusion that the metal is producing the smell, even though metals have no natural odor. The main molecule is the α, β Unsaturated Ketone, 1-Octen-3-one, which is described as smelling like mushrooms or metal. This is an illusion because the molecule doesn't smell like metals; metals smells like this molecule. Because we have smelled 1-Octen-3-one coming from metals for so long, we mistake its smell with the metal itself. This kind of chemical reaction also explain why blood produces a metallic smell when it comes into contact with skin. Blood contains iron in hemoglobin, and the same chemical reaction produces odor molecules when blood touches skin.



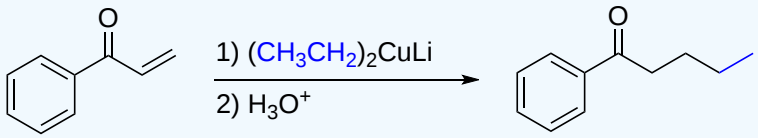
Structure of 1-Octen-3-one

EXERCISE 19.13.1

How would you make the following molecule using a 1,4 Conjugate Addition of a Gilman Reagent to a α, β Unsaturated Ketone?



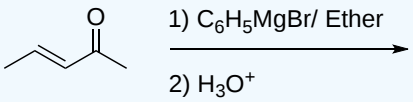
Answer



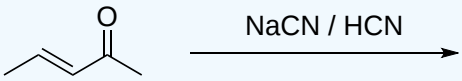
EXERCISE 19.13.2

Draw the bond-line structures for the products of the reactions below.

a)

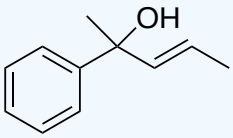


b)

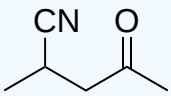


Answer

A

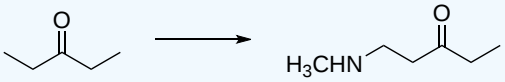


b)

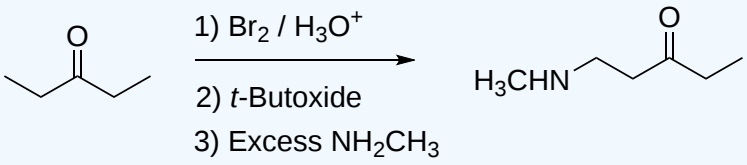


EXERCISE 19.13.3

Specify the reagents needed to perform the following chemical transformation.



Answer



This page titled 19.13: Conjugate Nucleophilic Addition to α, β-unsaturated Aldehydes and Ketones is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Steven Farmer, Dietmar Kennepohl, Layne Morsch, & Layne Morsch.

19.14: SPECTROSCOPY OF ALDEHYDES AND KETONES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which the carbonyl absorption of aldehydes and ketones is found.
2. identify the region of the infrared spectrum in which the two characteristic C$\ce{-}$H absorptions of aldehydes are found.
3. use a table of characteristic absorption frequencies to assist in the determination of the structure of an unknown aldehyde or ketone, given its infrared spectrum and other spectral or experimental data.
4. identify the region of a proton NMR spectrum in which absorptions caused by the presence of aldehydic protons and protons attached to the α-carbon atoms of aldehydes and ketones occur.
5. identify two important fragmentations that occur when aliphatic aldehydes and ketones are subjected to analysis by mass spectrometry.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- McLafferty rearrangement

STUDY NOTES

The appearance of a strong absorption at 1660–1770 cm^{-1} in the infrared spectrum of a compound is a clear indication of the presence of a carbonyl group. Although you need not remember the detailed absorptions it is important that you realize that the precise wavenumber of the infrared absorption can often provide some quite specific information about the environment of the carbonyl group in a compound. Notice how conjugation between a carbonyl group and a double bond (α, β-unsaturated aldehyde or ketone or aromatic ring) lowers the absorption by about 25–30 cm^{-1}.

You may wish to review the McLafferty rearrangement and the alpha cleavage in Section 12.3.

IR SPECTRA

Ketones

The carbonyl (C=O) stretching vibration band of saturated aliphatic ketones appears at:

- Aliphatic ketones 1715 cm^{-1}
- α, β-unsaturated (enone) 1685-1666 cm^{-1}

Figure 8. shows the spectrum of 2-butanone. This is a saturated ketone, and the C=O band appears at 1715.

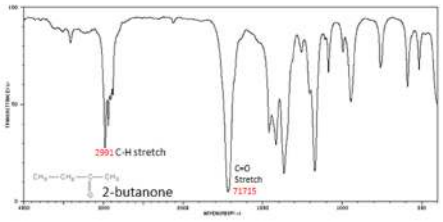


Figure 8. Infrared Spectrum of 2-Butanone

Aldehyde

In the IR spectra of an aldehyde, a peak usually appears around 2720 cm^{-1} and often appears as a shoulder-type peak just to the right of the alkyl C–H stretches.

H–C=O stretch 2830-2695 cm^{-1}

C=O stretch

- Aliphatic aldehydes 1740-1720 cm^{-1}
- α, β-unsaturated aldehydes (enones) 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

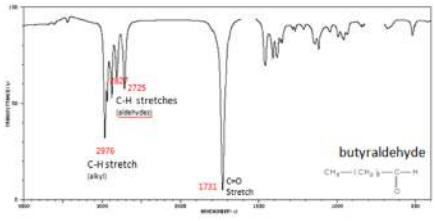
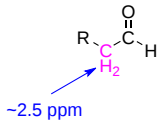


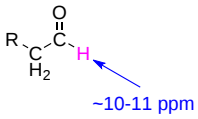
Figure 9. Infrared Spectrum of Butyraldehyde

^{1}H NMR SPECTRA

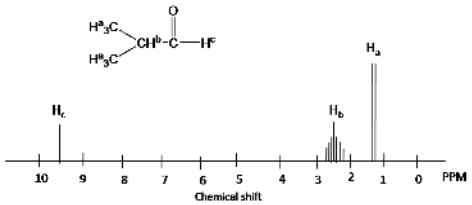
Hydrogens attached to a carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones are deshielded due the anisotropy created by the C=O bond and usually show up at 2.0-2.5 ppm.



Aldehyde hydrogens are highly deshielded, appearing far downfield at 9-10 ppm, due the anisotropy created by the pi electrons of the C=O bond, and induction caused by the highly electronegative oxygen atom.

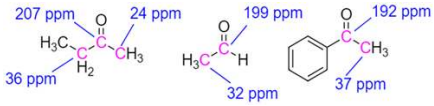


The ^{1}H NMR spectra of 2-methylpropanal is shown below. The methyl groups, (H_b), show up at 1.1 ppm. The -CH- group is moved downfield due to effect an adjacent aldehyde group (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm). Splitting pattern is determined by (N+1) rule: H_a is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak. (Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)



^{13}C NMR SPECTRA

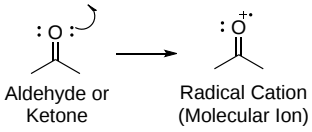
Aldehydes and ketones have distinctive ^{13}C NMR peaks which appear in the range 190 to 215 ppm range. Very few types of carbons absorb in this range so the presence of ^{13}C peak around 200 ppm is considered evidence for a carbonyl group.



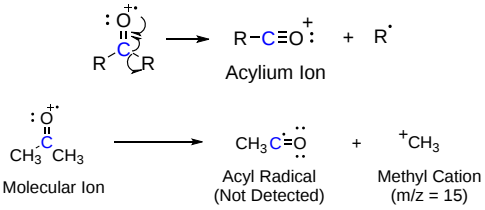
MASS SPECTRA

Aldehydes and ketones generally give moderately intense signals due to their molecular ions, $\mathbf{M^+}$. Thus the determination of the molecular weight of a ketone by mass spectroscopy usually is not difficult. Furthermore, there are some characteristic fragmentation patterns that aid in structural identification. These are:

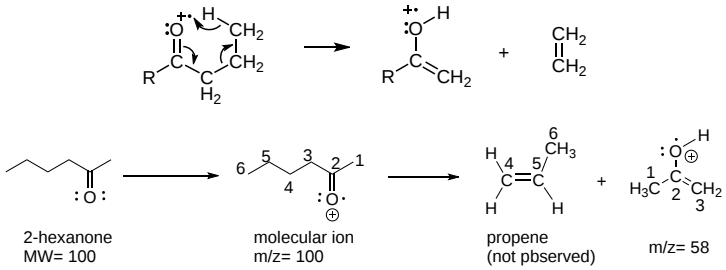
- Formation of the molecular ion:



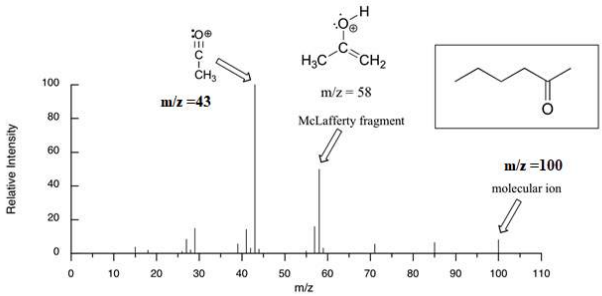
- *α cleavage to form an acylium ion. This is usually the base peak in the mass spectra.*



- *A common fragmentation pattern for larger carbonyl compounds is a transfer of γ hydrogen with β cleavage* called the **McLafferty rearrangement:**



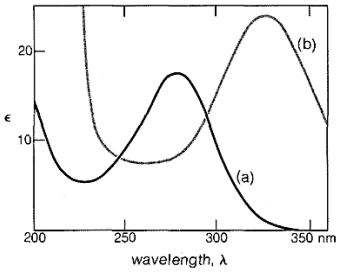
The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is an acylium ion formed after alpha cleavage is at m/z = 43. The molecular ion peak is at m/z =100.





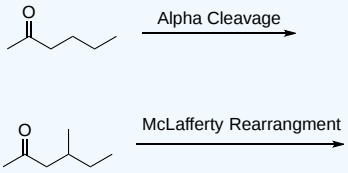
2-Butanone 3-Buten-2-one

The absorption at 277 nm for 2-butanone is an n → pi* transition, and with 3-buten-2-one, this absorption shifts to longer wavelengths (324 nm). There is also an intense absorption band for 3-buten-2-one at 219 nm, which is a pi →pi* transition. With 2-butanone a corresponding absorption occurs at 185 nm, which is out of the range of the spectrometer used to take the spectra.

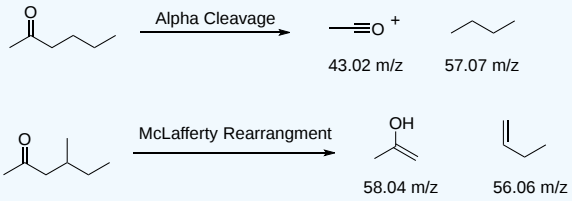


? EXERCISE 19.14.1

What are the masses of all the components in the following fragmentations?

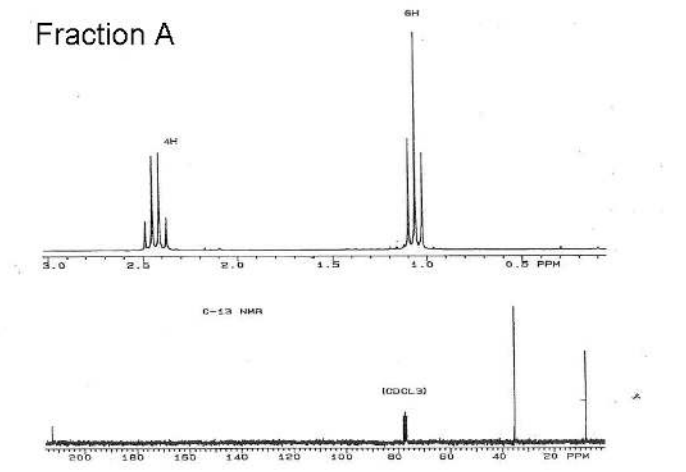


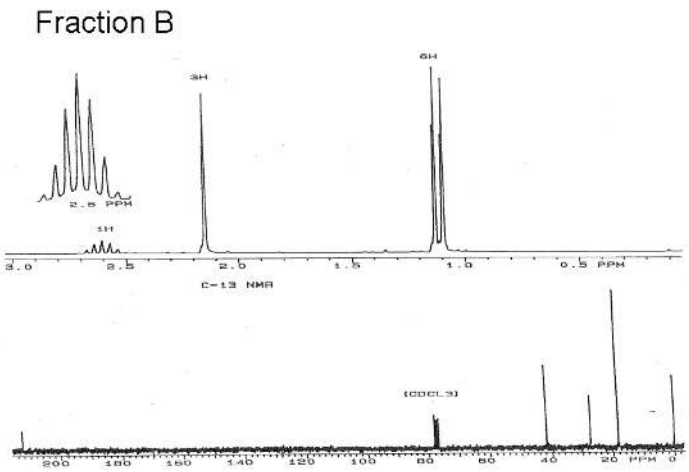
Answer

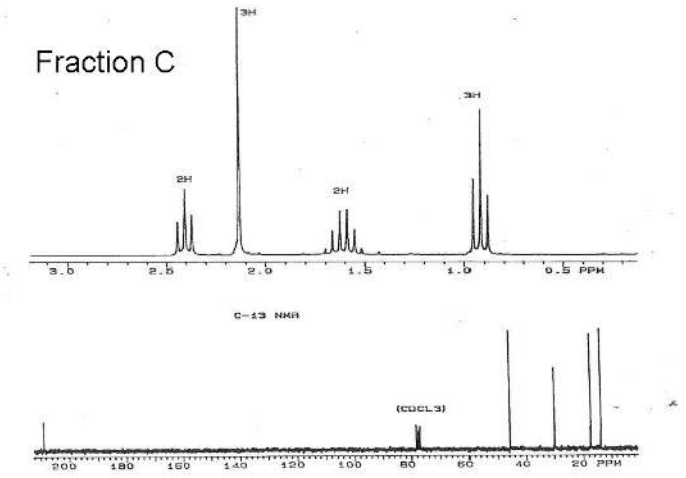


? EXERCISE 19.14.2

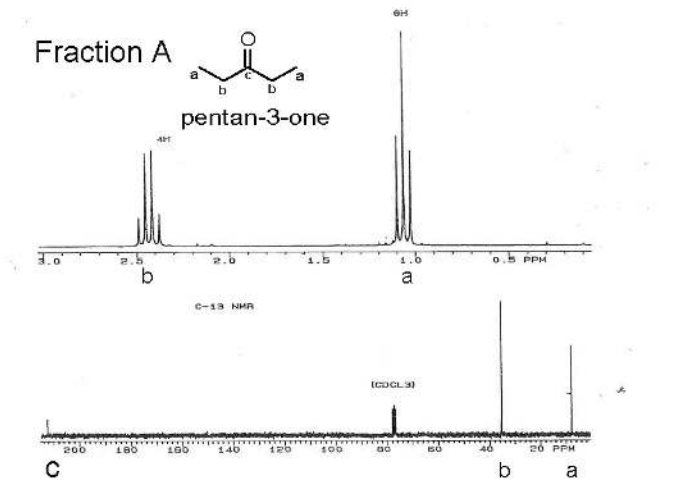
A mixture was separated into three fractions: A, B, and C. Elemental analysis reveals that the fractions are structural isomers with the following composition: 69.72% C, 11.70% H, and 18.58% O. The IR spectra for all fractions show several moderate bands around 2950 cm^{-1}, and a strong band near 1700 cm^{-1}. The proton and ^{13}C NMR spectra for each fraction are shown below. Give the common name and draw the bond-line structure for each fraction and correlate the NMR signals with their respective atoms.

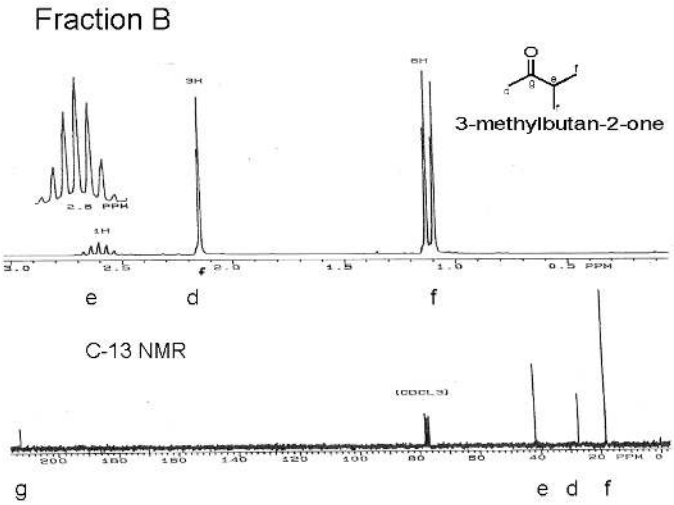

Fraction A
6H
4H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM

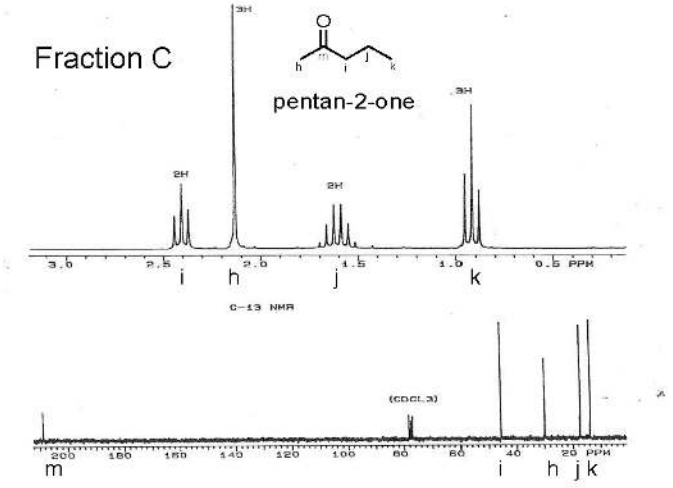

Fraction B
6H
3H
2.8 PPM
1H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM


Fraction C
3H
3H
2H
2H
3.0
2.5
2.0
1.5
1.0
0.5 PPM
C-13 NMR
(CDCL3)
200
180
150
140
120
100
80
60
40
20 PPM

Answer







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19.S: ALDEHYDES AND KETONES (SUMMARY)

CONCEPTS & VOCABULARY

19.0 Chapter Objectives and Preview of Carbonyl Chemistry

- Aldehydes are carbonyl compounds with an R group and a hydrogen attached to the carbonyl carbon.
- Ketones are carbonyl compounds with two R groups attached to the carbonyl carbon.

19.1 Naming Aldehydes and Ketones

- Aldehydes are named following IUPAC rules with the standard ending -al.
- Ketones are named following IUPAC rules with the standard ending -one.
- Aldehydes have priority over ketones when both appear in the same molecule.

19.2 Preparing Aldehydes and Ketones

- Primary alcohols can be oxidized to aldehydes with PCC (pyridinium chlorochromate) or DMP (Dess-Martin Periodinane).
- Terminal alkynes can be hydrated to form aldehydes through hydroboration-oxidation reactions.
- Esters can be reduced to aldehydes with DIBAL-H.
- Acid chlorides can be reduced to aldehydes with hydrides.
- Nitriles can be reduced to aldehydes with DIBAL-H.
- Secondary alcohols can be oxidized to ketones with chromic acid/Jones reagent.
- Alkynes can be hydrated to form ketones.
- Aryl ketones can be formed by Friedel-Crafts acylation of aromatic rings.
- Nitriles can be reacted with Grignard reagents to form ketones.
- Alkenes can be cleaved with ozone to form aldehydes or ketones.
- Acid halides can be converted to ketones by reacting with Gilman reagents.

19.3 Oxidation of Aldehydes and Ketones

- Aldehydes can be oxidized more easily than ketones due to the aldehyde hydrogen.
- Jones reagent is a mixture of CrO_3 and aqueous acid.
- Aldehydes can be oxidized to carboxylic acids with chromium trioxide/Jones reagent.
- Ketones can undergo oxidative cleavage with very strong oxidizing agents such as potassium permanganate.
- Ketones can be oxidized to esters by peroxycarboxylic acids in a reaction known as Baeyer-Villiger oxidation.

19.4 Nucleophilic Addition Reactions of Aldehydes and Ketones

- Carbonyl bonds are polarized with a partial positive charge on the carbon making it an electrophile and a target for attack by nucleophiles.
- Neither aldehydes nor ketones have a good leaving group causing both to undergo nucleophilic addition reactions.
- Aldehydes are more reactive than ketones to nucleophilic addition reactions.

19.5 Nucleophilic Addition Reactions of Water: Hydration

- Gem-diols are molecules that have two hydroxide groups attached to the same carbon.
- Aldehydes and ketones can react with water under either acidic or basic conditions to form gem-diols.

19.6 Nucleophilic Addition Reactions of HCN: Cyanohydrin Formation

- Cyanohydrins are molecules with a cyanide and a hydroxide attached to the same carbon.
- Cyanohydrins can be formed from aldehydes or ketones by reacting with cyanide ion and a weak acid.

19.7 Nucleophilic Addition Reactions of Hydride and Grignard Reagents: Alcohol Formation

- Metal hydrides can reduce aldehydes and ketones to alcohols.
- Organometallic reagents include carbon bonds to metals which react similarly to carbanions.
- Grignard reagents (R-Mg-X) and organolithium compounds add to aldehydes and ketones to form alcohols.

19.8 Nucleophilic Addition of Amines: Imine and Enamine

- Imines are characterized by a carbon-nitrogen double bond.
- Reaction of aldehydes and ketones with primary amines can form imines.
- Reaction of aldehydes and ketones with secondary amines can form enamines.

19.9 Nucleophilic Addition of Hydrazine - The Wolff-Kishner Reaction

- Hydrazine will react with aldehydes and ketones to form hydrazones (similar to imine formation). Heating of the hydrazone with base converts it to an alkane.
- The combination of hydrazone formation and reduction (of aldehydes and ketones) is called the Wolff-Kishner reaction.

19.10 Nucleophilic Addition of Alcohols: Acetal Formation

- Hemiacetals have one hydroxide and one ether attached to a carbon.
- Acetals have two ethers attached to a carbon.
- Reaction of an aldehyde or ketone with an alcohol under acidic conditions forms a hemi-acetal. Continuation of the same reaction results in an acetal.
- Acetals can reform the aldehyde or ketone by reacting with acid.
- Acetals are useful as protecting groups due to the reversible nature of acetal formation.

19.11 Nucleophilic Addition of Phosphorun Ylides: The Wittig Reaction

- A molecule with positive and negative charges on adjacent atoms is called an ylide.
- Wittig reagents are organophosphorus ylides which can be drawn as a double bonded structure called a phosphorane.
- The Wittig reaction is used to convert an aldehyde or ketone into an alkene by reacting with an organophosphrous ylide.
- Oxaphosphetane intermediates containing a 4 membered ring including one oxygen and one phosphorus atom occur during the Wittig reaction.

19.12 Biological Reductions

- The Cannizzaro reaction allows an aldehyde to react with another like molecule in strong base to form one oxidized molecule (carboxylic acid) and one reduced molecule (alcohol).
- NADH, one of the most important biological reducing agents, uses a similar mechanism to the Cannizzaro reaction while reducing ketones in biological systems to alcohols while being converted to NAD^+.

19.13 Conjugate Nucleophilic Addition of alpha, beta-Unsaturated Aldehydes and Ketones

- α, β-unsaturated carbonyls have an alkene attached to the carbonyl carbon.
- Due to resonance delocalization, the β-carbon of an α, β-unsaturated carbonyl is electrophilic and will react with nucleophiles.
- α, β-unsaturated carbonyls can undergo 1,2 or 1,4 addition.
- 1,4 addition is also called conjugate addition.
- Lithium diorganocopper reagents are called Gilman reagents.
- Gilman reagents typically react with α, β-unsaturated carbonyls via conjugate addition.

19.14 Spectroscopy of Aldehydes and Ketones

- IR of aldehydes and ketones is defined strongly by the carbonyl stretching vibration.
- ^1H NMR of aldehydes show the aldehyde proton between 10 and 11 ppm as well as the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^1H NMR of ketones show the protons on carbon adjacent to the carbonyl at about 2.5 ppm.
- ^{13}C NMR of aldehydes and ketones show the carbonyl carbon at about 200 ppm.
- Mass spectra of aldehydes and ketones typically yield moderately intense molecular ions, M^+. They also can undergo some rearrangements that yield common fragmentation patterns.

SKILLS TO MASTER

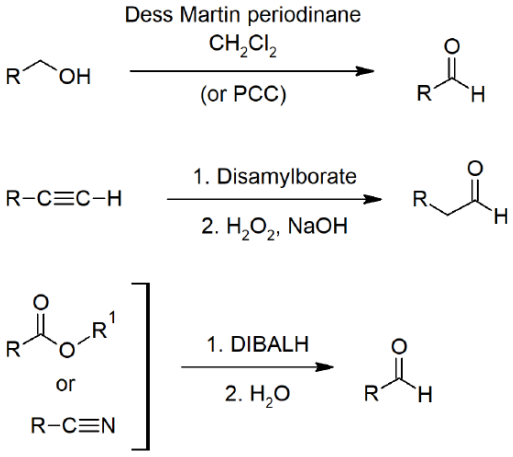
- Skill 19.1 Explain the relative reactivity of aldehydes vs. ketones to nucleophiles, based on carbonyl bond polarity.
- Skill 19.2 Name aldehydes and ketones using IUPAC rules.
- Skill 19.3 Draw the structure of an aldehyde or ketone from the IUPAC name.
- Skill 19.4 Interpret common names of aldehydes and ketones.
- Skill 19.5 Describe methods for preparing aldehydes and ketones.
- Skill 19.6 Draw mechanisms for oxidations of aldehydes and ketones.
- Skill 19.7 Explain general reactivity of aldehydes and ketones through the nucleophilic addition mechanism.
- Skill 19.8 Draw mechanisms for nucleophilic addition reactions to aldehydes and ketones including
  - Hydration
  - Cyanohydrin formation
  - Hydride Reduction

- Organometallic reactions
- Addition of amines
- Wolff-Kishner reaction
- Acetal formation
- Wittig reaction
- Cannizzaro reaction
- Conjugate addition

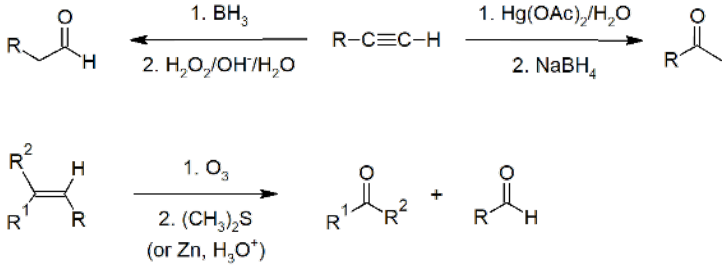
- Skill 19.9 Use IR, NMR and MS to identify aldehydes and ketones.

SUMMARY OF REACTIONS

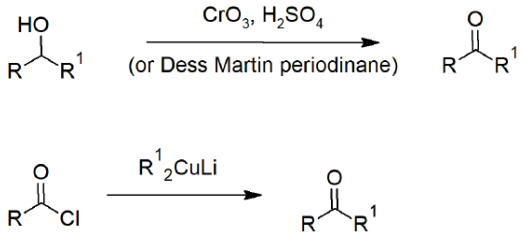
ALDEHYDE PREPARATION



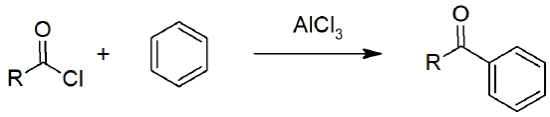
ALDEHYDE AND KETONE PREPARATION

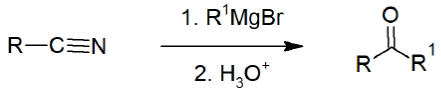


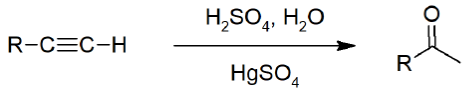
KETONE PREPARATION



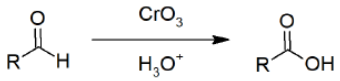
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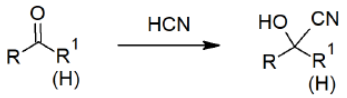


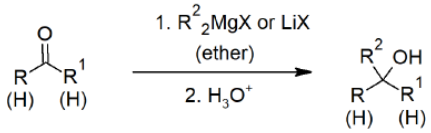


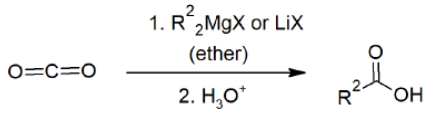


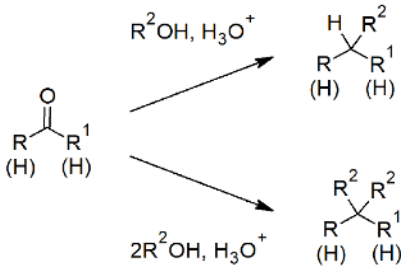
ALDEHYDE AND KETONE REACTIONS



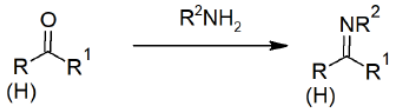


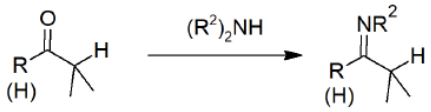


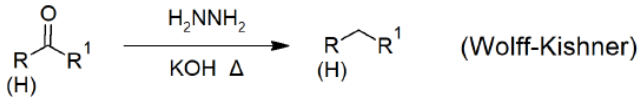


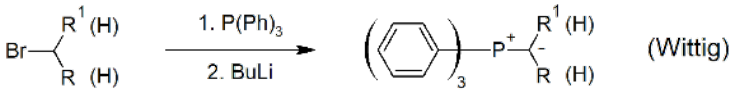


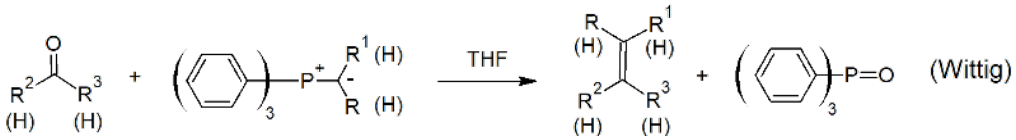
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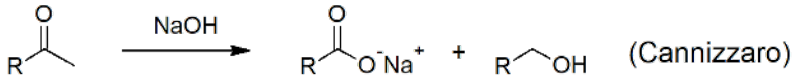




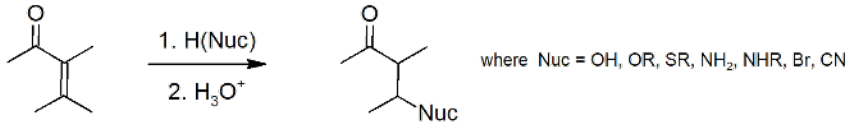


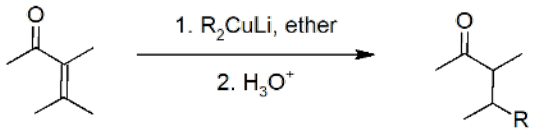






CONJUGATED ADDITION REACTIONS





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CHAPTER OVERVIEW

20: CARBOXYLIC ACIDS AND NITRILES

This chapter presents a straightforward discussion of the chemistry of carboxylic acids (formerly called “fatty acids”) and nitriles. As usual, we begin with a description of how the compounds are named. We then consider the subtleties of their structure, and how these structural features influence physical properties, such as boiling point. We place considerable emphasis on the dissociation of carboxylic acids and the effect of substituents on acid strength.

We have already encountered a number of methods for preparing carboxylic acids. We shall review these methods, and learn about two additional procedures. The only reactions of carboxylic acids that we study in detail in this chapter are reduction and decarboxylation, although two other common reactions of carboxylic acids, alpha substitution and nucleophilic acyl substitution, will be described in later chapters.

We will then look at the formation of nitriles and their chemical reactivity; and our discussion of carboxylic acid and nitrile chemistry concludes with a look at the infrared and NMR spectra of these compounds, with emphasis on the characterization of carboxylic acids.

20.0: Chapter Objectives and Introduction to Carboxylic Acids

20.1: Naming Carboxylic Acids and Nitriles

20.2: Structure and Properties of Carboxylic Acids

20.3: Biological Acids and the Henderson-Hasselbalch Equation

20.4: Substituent Effects on Acidity

20.5: Preparing Carboxylic Acids

20.6: Reactions of Carboxylic Acids - An Overview

20.7: Chemistry of Nitriles

20.8: Spectroscopy of Carboxylic Acids and Nitriles

20.S: Carboxylic Acids and Nitriles (Summary)

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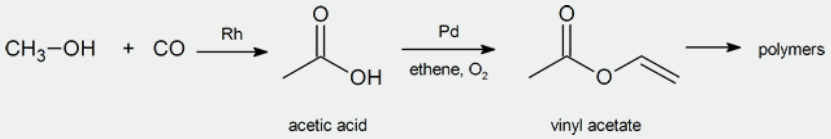
20.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBOXYLIC ACIDS

OBJECTIVES

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
- solve road-map problems which require a knowledge of the chemistry of carboxylic acids.
- define, and use in context, the key terms introduced in this chapter.

STUDY NOTES

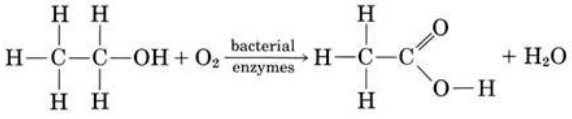
The global demand for acetic acid is about 6.5 million tonnes per year. A common industrial preparation of acetic acid is the catalytic oxidation of methanol with carbon monoxide. Much of the acetic acid produced is converted to vinyl acetate polymer and used in adhesives and paints.



Not only are carboxylic acids valuable, but they and their derivatives are useful starting materials for many synthetic products. Finally, carboxylic acids and their derivatives are also found in a variety of natural systems and important biological pathways.

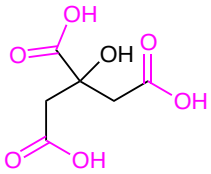
CARBOXYLIC ACIDS

Carboxylic acids have been known throughout human history. Prehistoric people likely made acetic acid when their fermentation reactions went awry and produced vinegar instead of wine. The Sumerians (2900–1800 BCE) used vinegar as a condiment, a preservative, an antibiotic, and a detergent. Vinegar contains 4 to 5 percent acetic acid. Acetic acid gives vinegar its sour taste and pungent odor and can do the same thing to wine. Acetic acid, CH_3COOH, is an example of the class of compounds called **carboxylic acids**, each of which contains one or more carboxyl groups, COOH. The general formula of a carboxylic acid is RCOOH.



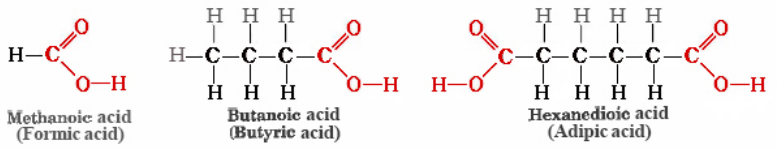
Ethanol **Ethanoic Acid (Acetic Acid)**

Citric acid was discovered by an Islamic alchemist, Jabir Ibn Hayyan (also known as Geber), in the 8th century, and crystalline citric acid was first isolated from lemon juice in 1784 by the Swedish chemist Carl Wilhelm Scheele. Medieval scholars in Europe were aware that the crisp, tart flavor of citrus fruits is caused by citric acid.



Citric acid

Naturalists of the 17th century knew that the sting of a red ant's bite was due to an organic acid that the ant injected into the wound. Formic acid (the name comes from Latin word *formica* meaning "ant") is present in ants and bees and is responsible for the burning pain of their bites and stings. Butyric acid, a component of rancid butter and Limburger cheese, has a vile odor. Adipic acid is an example of a dicarboxylic acid—it has two functional groups—and is used to make nylon



NATURALLY OCCURRING CARBOXYLIC ACIDS

Carboxylic acids are widespread in nature, often combined with other functional groups. Simple alkyl carboxylic acids, composed of four to ten carbon atoms, are liquids or low melting solids having very unpleasant odors. The **fatty acids** are important components of the biomolecules known as lipids, especially fats and oils. As shown in the following table, these long-chain carboxylic acids are usually referred to by their common names, which in most cases reflect their sources. A mnemonic phrase for the C_{10} to C_{20} natural fatty acids capric, lauric, myristic, palmitic, stearic and arachidic is: "**C**urly, **L**arry & **M**oe **P**erform **S**illy **A**ntics" (note that the names of the three stooges are in alphabetical order).

Table 17.4.1: Common Saturated Fatty Acids

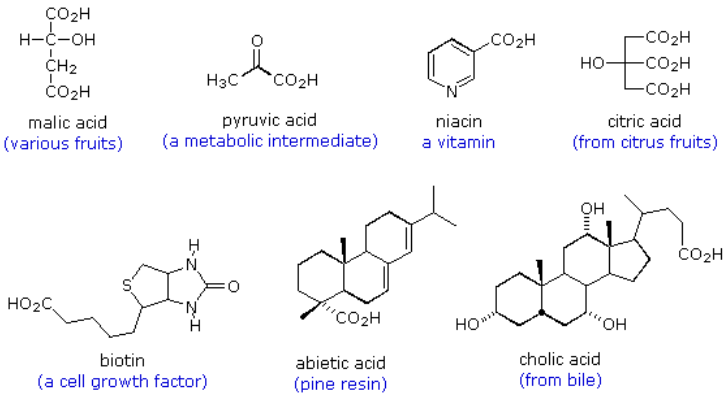
Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC

Interestingly, the molecules of most natural fatty acids have an *even number of carbon atoms*. Since nature makes these long-chain acids by linking together acetate units, it is not surprising that the carbon atoms composing the natural products are multiples of two. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. All the double bonds in the unsaturated compounds listed on the table have *cis* (or Z) stereochemistry.

Table 17.4.2: Common Unsaturated Fatty Acids

Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The following formulas are examples of other naturally occurring carboxylic acids. The molecular structures range from simple to complex, often incorporate a variety of other functional groups, and many are chiral.

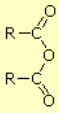
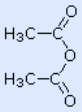
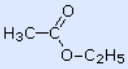
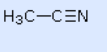


Naturally occurring carboxylic acids

CARBOXYLIC ACID DERIVATIVES

Other functional group combinations with the carbonyl group can be prepared from carboxylic acids, and are usually treated as related derivatives. The chemistry behind the conversion of carboxylic acids to carboxylic acid derivatives will be discussed in then next chapter.

Five common classes of these **carboxylic acid derivatives** are listed in the following table. Although nitriles do not have a carbonyl group, they are included here because the functional carbon atoms all have the same oxidation state. The top row shows the general formula for each class, and the bottom row gives a specific example of each. As in the case of amines, amides are classified as 1º, 2º or 3º, depending on the number of alkyl groups bonded to the nitrogen.

acyl halide	anhydride	ester	amide	nitrile
 X = F, Cl, Br or I			 R′ = H or alkyl	
 propanoyl chloride	 acetic anhydride	 ethyl acetate	 formamide	 acetonitrile

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20.1: NAMING CARBOXYLIC ACIDS AND NITRILES

OBJECTIVES

After completing this section, you should be able to

1. write the IUPAC name of a carboxylic acid, given its Kekulé, condensed or shorthand structure.
2. draw the condensed or shorthand structure of a carboxylic acid, given its IUPAC name.
3. draw the structure of the following carboxylic acids, given their trivial names: formic acid and acetic acid.
4. provide an acceptable name for a nitrile of given structure.
5. draw the condensed or shorthand structure of a nitrile, give either its trivial or IUPAC name.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- carboxylic acid
- nitrile

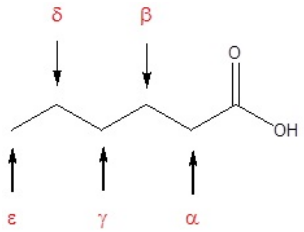
STUDY NOTES

You need not memorize all the trivial names listed in the table, just remember the two names identified in Objective 3, above.

CARBOXYLIC ACIDS, RCO_2H

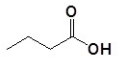
The IUPAC system of nomenclature assigns a characteristic suffix to these classes. The **–e** ending is removed from the name of the parent chain and is replaced **-oic acid**. Since a carboxylic acid group must always lie at the end of a carbon chain, it is always is given the #1 location position in numbering and it is not necessary to include it in the name.

Many carboxylic acids are called by the common names. These names were chosen by chemists to usually describe a source of where the compound is found. In common names of carboxylic acids, carbon atoms near the carboxyl group are often designated by Greek letters. The atom adjacent to the carbonyl function is alpha, the next removed is beta and so on.

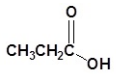


Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

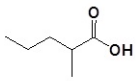
Example (Common Names Are in Red)



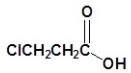
Butanoic acid
(Butyric Acid)



Propanoic acid
(Propionic Acid)



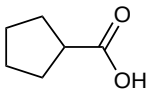
2-Methylpentanoic acid
(β-Methylvaleric acid)



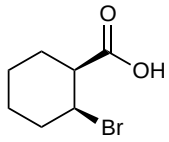
3-Chloropropanoic acid
(γ-Chloropropionic acid)

NAMING CARBOXYL GROUPS ADDED TO A RING

When a carboxyl group is added to a ring, the suffix **-carboxylic acid** is added to the name of the cyclic compound. The ring carbon attached to the carboxyl group is given the #1 location number.

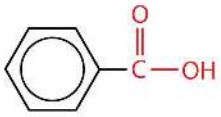


cyclopentanecarboxylic acid



(1S,2S)-2-bromocyclohexanecarboxylic acid

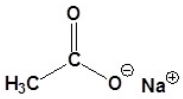
The acid with the carboxyl group attached directly to a benzene ring is called benzoic acid (C_6H_5COOH).



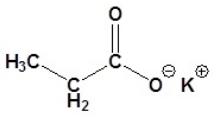
Benzoic acid

NAMING CARBOXYLATES

Salts of carboxylic acids are named by writing the name of the cation followed by the name of the carboxylic acid with the **–ic acid** ending replaced by an **–ate** ending. This is true for both the IUPAC and Common nomenclature systems.



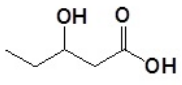
Sodium ethanoate
(Sodium Acetate)



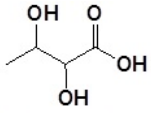
Potassium Propanoate
(Potassium propionate)

NAMING CARBOXYLIC ACIDS WHICH CONTAIN OTHER FUNCTIONAL GROUPS

Carboxylic acids are given the highest nomenclature priority by the IUPAC system. This means that the carboxyl group is given the lowest possible location number and the appropriate nomenclature suffix is included. In the case of molecules containing carboxylic acid and alcohol functional groups, the OH is named as a hydroxyl substituent. However, the **l** in hydroxyl is generally removed.

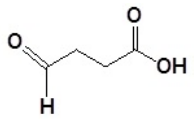


3-Hydroxypentanoic acid

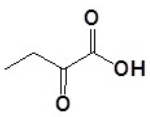


2,3-Dihydroxybutanoic acid

In the case of molecules containing a carboxylic acid and aldehydes and/or ketones functional groups, the carbonyl is named as an "Oxo" substituent.

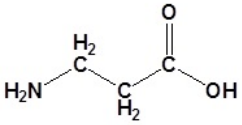


4-Oxobutanoic acid

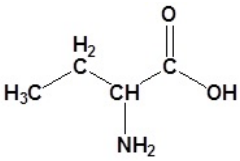


2-Oxobutanoic acid

In the case of molecules containing a carboxylic acid an amine functional group, the amine is named as an "amino" substituent.



3-Aminopropanoic acid

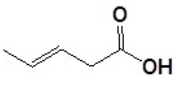


2-Aminobutanoic acid

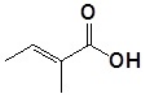
When carboxylic acids are included with an alkene the following order is followed:

(Location number of the alkene)-(Prefix name for the longest carbon chain minus the -ane ending)-(an –enoic acid ending to indicate the presence of an alkene and carboxylic acid)

Remember that the carboxylic acid has priority so it should get the lowest possible location number. Also, remember that *cis/tran* or E/Z nomenclature for the alkene needs to be included if necessary.



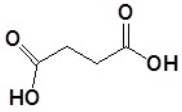
Trans-3-pentenoic acid



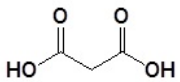
(E)-2-Methyl-2-butenoic acid

NAMING DICARBOXYLIC ACIDS

For dicarboxylic acids the location numbers for both carboxyl groups are omitted because both functional groups are expected to occupy the ends of the parent chain. The ending **–dioic acid** is added to the end of the parent chain name.



Butanedioic acid



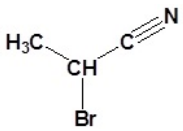
Propanedioic acid

NAMING NITRILES, R−C≡N

A **nitrile** is any organic compound with a −C≡N functional group. In literature the prefix **cyano-** is used interchangeably with the term nitrile to refer to the functional group. Nitriles used to be known as cyanides; the smallest organic nitrile is ethanenitrile, CH_3CN, (old name: methyl cyanide or acetonitrile).

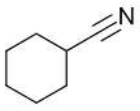
Open chain nitriles are named with the word **-nitrile** after the name of the parent alkane name. Remmber to include the carbon atom of the nitrile as part of the parent chain. For example, CH_3CN has two carbons including the nitrile carbon, therefore it is ethanenitrile. The carbon in the nitrile is given the #1 location position. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

Butane nitrile

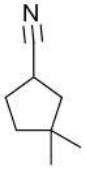


2-Bromopropane nitrile

When a nitrile is the highest priority functional group attached to a cycloalkane, the name of the parent cycloalkane is followed by the word **-carbonitrile**. The ring carbon attached to the nitrile is numbered C1 and the nitrile is not given a number in the name.

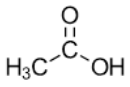


Cyclohexanecarbonitrile

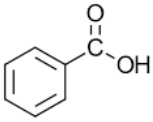


3,3-Dimethylcyclopentanecarbonitrile

Nitriles are often named based off the common name of the corresponding carboxylic acid. This is done by replacing the -ic acid or -oic acid ending with **-onitrile**. In these cases the nitrile carbon is numbered C1 but the nitrile itself is not given a number in the name.

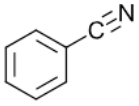


Acetic Acid



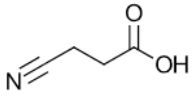
Benzoic Acid

Acetonitrile



Benzonitrile

In the case of molecules containing a carboxylic acid and nitrile functional group, the nitrile is named as a "cyano" substituent. Note! The carbon in the nitrile is not counted as part of the parent chain when named as a cyano substituent.



3-Cyanopropanoic Acid

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20.2: STRUCTURE AND PROPERTIES OF CARBOXYLIC ACIDS

OBJECTIVES

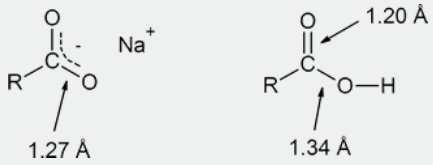
After completing this section, you should be able to

1. describe the geometry and electronic structure of a simple carboxylic acid; for example, acetic acid.
2. describe the hydrogen bonding that occurs between carboxylic acid molecules, and hence account for the relatively high boiling points of these compounds.
3. write an expression for the dissociation constant of a given carboxylic acid, and use it to calculate dissociation constants, percentage dissociation, etc.
4. identify carboxylic acids as being weaker acids than mineral acids, such as hydrochloric acid, but stronger acids than alcohols.
5. use the concept of resonance to explain why carboxylic acids are stronger acids than alcohols.
6. draw an orbital picture of a carboxylate anion to show the equivalence of the two oxygen atoms.
7. explain why the two carbon-oxygen bond lengths are identical in sodium carboxylate, but different in carboxylic acid.
8. write an equation for the reaction of a carboxylic acid with a base, such as sodium hydroxide.

STUDY NOTES

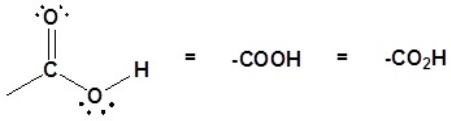
You might wish to review Sections 2.7, “Acids and Bases: The Brønsted-Lowry Definition” and 6.7, “Describing a Reaction: Equilibria, Rates, and Energy Changes” in conjunction with this section.

In the reading, the discussion of the role of resonance in the acidity of a carboxylic acid explains that the two carbon-oxygen bonds in the delocalized carboxylate anion are identical (both 1.27 Å). However, in the structure of a carboxylic acid the **C–O** bond (1.20 Å) is shorter than the **C–OH** bond (1.34 Å).



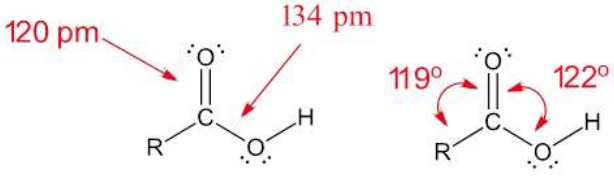
STRUCTURE OF THE CARBOXYL ACID GROUP

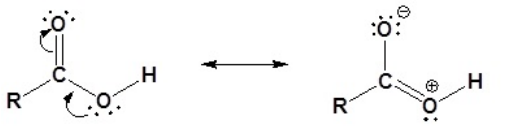
Carboxylic acids are organic compounds which incorporate a carboxyl functional group, CO_2H. The name carboxyl comes from the fact that a carbonyl and a hydroxyl group are attached to the same carbon.



Carboxyl Group

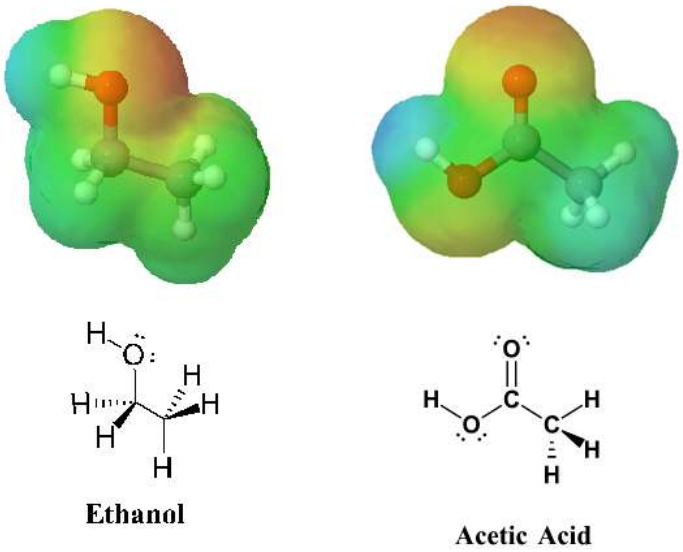
The carbon and oxygen in the carbonyl are both sp^2 hybridized which gives a carboxylic acid a trigonal planar shape (around the carbonyl carbon) making the bond angles roughly 120°. A resonance structure exists where one of the lone pairs of the hydroxyl oxygen (OH) is conjugated with the pi bond system of the carbonyl group. The conjugation can be represented by the resonance structure shown below which holds all the atoms in the carboxylic acid in a co-planar arrangement.





Major Contributor Minor Contributor

The effects of conjugation in a carboxylic acid can be seen when comparing the electrostatic potential maps of ethanol and acetic acid. Conjugation creates a greater polarization in the O-H bond in acetic acid, as shown by its darker blue color, which subsequently leads to a greater acidity in carboxylic acids.



Ethanol Acetic Acid

ACIDITY OF CARBOXYLIC ACIDS

Carboxylic acids are named such because they tend to be more acidic than other functional groups in organic chemistry. In dilute aqueous solutions, they act as Brønsted–Lowry acids and partially dissociate to produce the corresponding carboxylate ion and hydronium (H_3O^+).



Carboxylic acid Carboxylate ion

The extent of this dissociation is described by the K_a value of the carboxylic acid. In a 0.1 M solution of acetic acid ($K_a = 1.75 \times 10^{-5}$ @ 25 °C) only about 0.1% of the molecules are dissociated.

$$\begin{aligned} K_{eq} &= K_a \\ &= \frac{[\mathrm{RCOO^-}][\mathrm{H_3O^+}]}{[\mathrm{RCOOH}]} \\ &= 1.75 \times 10^{-5} \end{aligned}$$

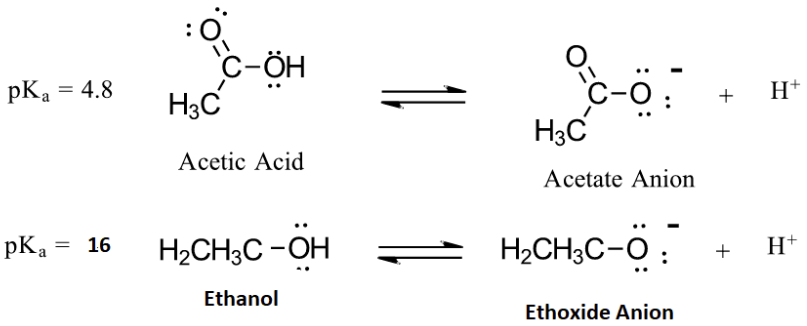
with $pK_a = -\log K_a$.

The pK_a's of some typical carboxylic acids are listed in Table **20.2.1**. The factors which affect the acidity of different carboxylic acids will be discussed in the next section of this text.

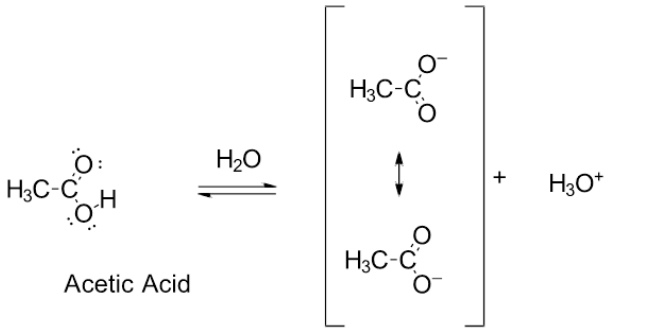
Table **20.2.1**: Acidity of example carboxylic acids

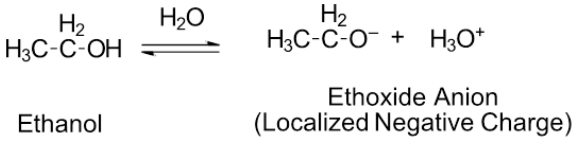
Compound	K_a	pK_a
F_3CCO_2H	0.59	0.23
Cl_3CCO_2H	0.22	0.66
p-$O_2NC_6H_4CO_2H$	3.39 X 10^{-4}	3.47
HCO_2H	1.78 X 10^{-4}	3.75
$C_6H_5CO_2H$	6.31 X 10^{-5}	4.20
p-$CH_3OC_6H_4CO_2H$	3.55 X 10^{-5}	4.45
CH_3CO_2H	1.75 X 10^{-5}	4.76
$CH_3CH_2CH_2CO_2H$	1.51 X 10^{-5}	4.82

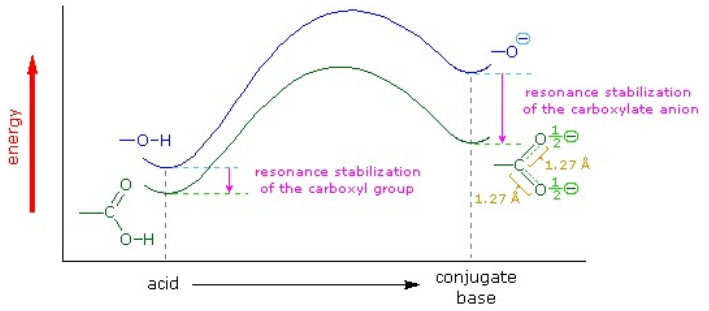
The acidity of carboxylic acids comes about, in part, due to resonance stabilization of the carboxylate conjugate base. A classic example compares the relative acidity of ethanol and acetic acid, but the conclusions we reach will be equally valid for all alcohol and carboxylic acid groups. Despite the fact that they are both oxygen acids, the pK_a values of ethanol and acetic acid are very different (acetic acid is more than 10^{11} times more acidic than ethanol). In both species, the negative charge on the conjugate base is held by an oxygen so electronegativity does not explain the difference in acidity.



For acetic acid, however, there is a key difference: a resonance contributor can be drawn in which the negative charge is localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy allowing for the the negative charge on the acetate ion to be equally shared between two oxygens. In the ethoxide anion, by contrast, the negative charge is 'locked' on the single oxygen. This stabilization leads to a marked increase in stability of the acetate anion, as illustrated by the energy diagram shown below. The increased stabilization of the acetate anion conjugate base promotes the acidity of acetic acid.

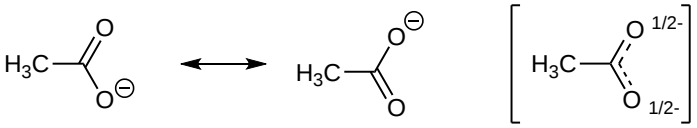






The delocalization of charge by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the difference of over 11 pK_a units between ethanol and acetic acid (and remember, pK_a is a log expression, so this represents a difference of over 10^{11} between the acidity constants for the two molecules). The acetate anion is that much more stable than the ethoxide anion, all due to the effects of resonance delocalization.

X-ray crystallographic studies provide experimental evidence of the acetate anion resonance hybrid. Both C-O bonds in acetate are 126 pm which is roughly the average of C=O double bond (123 pm) and the C-O single bond (132 pm) of acetic acid. Both of the C-O bonds in the acetate anion are considered to have a bond order of 1 1/2. The negative charge is equally spread between the two oxygens giving them each a charge of -1/2.



Resonance structures and resonance hybrid of acetate ion.

PHYSICAL PROPERTIES OF SOME CARBOXYLIC ACIDS

Carboxylic acids tend to have higher boiling points when compared to ethers, alcohols, aldehydes, or ketones with a similar molecular weight. For example acetic acid and ethanol have boiling points of 117.9 ^oC and 78.3 ^oC respectively despite the fact that they both contain two carbons. Because carboxylic acids and alcohols both contain an O-H bond they are strongly associated by a hydrogen-bonding intermolecular force. The difference is that for carboxylic acids, two molecules of a carboxylic acid form two hydrogen bonds with each other to create a cyclic dimer (pair of molecules). Two alcohol molecules can only form one hydrogen bond between each other. Thus, carboxylic acids have stronger intermolecular forces and higher boiling points than their corresponding alcohols.

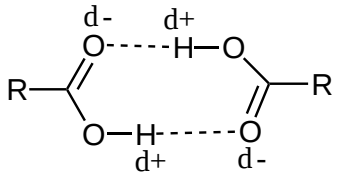
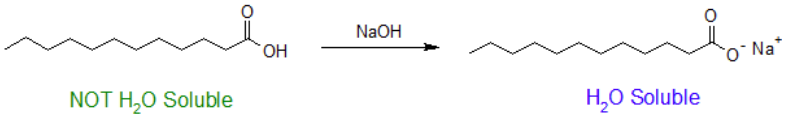


Table **20.2.2**: Intermolecular hydrogen bonding in carboxylic acids.

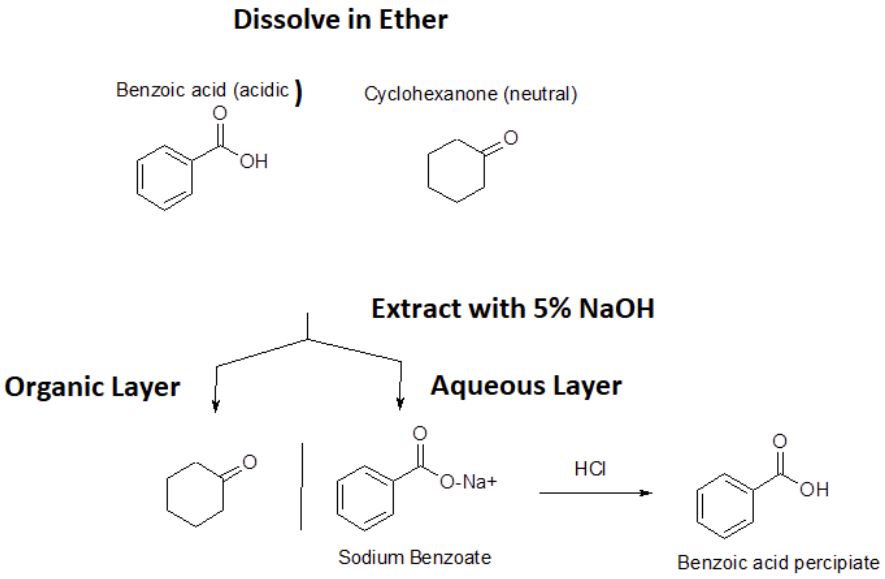
Formula	Common Name	Source	IUPAC Name	Melting Point	Boiling Point
HCO_2H	formic acid	ants (L. formica)	methanoic acid	8.4 ºC	101 ºC
CH_3CO_2H	acetic acid	vinegar (L. acetum)	ethanoic acid	16.6 ºC	118 ºC
$CH_3CH_2CO_2H$	propionic acid	milk (Gk. protus prion)	propanoic acid	-20.8 ºC	141 ºC
$CH_3(CH_2)_2CO_2H$	butyric acid	butter (L. butyrum)	butanoic acid	-5.5 ºC	164 ºC
$CH_3(CH_2)_3CO_2H$	valeric acid	valerian root	pentanoic acid	-34.5 ºC	186 ºC
$CH_3(CH_2)_4CO_2H$	caproic acid	goats (L. caper)	hexanoic acid	-4.0 ºC	205 ºC
$CH_3(CH_2)_5CO_2H$	enanthic acid	vines (Gk. oenanthe)	heptanoic acid	-7.5 ºC	223 ºC
$CH_3(CH_2)_6CO_2H$	caprylic acid	goats (L. caper)	octanoic acid	16.3 ºC	239 ºC
$CH_3(CH_2)_7CO_2H$	pelargonic acid	pelargonium (an herb)	nonanoic acid	12.0 ºC	253 ºC
$CH_3(CH_2)_8CO_2H$	capric acid	goats (L. caper)	decanoic acid	31.0 ºC	219 ºC

WATER SOLUBILITY OF CARBOXYLIC ACIDS

The ability to form hydrogen bonds gives carboxylic acids with low molecular weights some measure of solubility in water. Carboxylic acids with six or more carbons tend to only be slightly soluble in water. However, conversion to the corresponding carboxylate anion tends to immensely increase water solubility due to the creation of an ion-dipole intermolecular force. Typically a strong base is used to deprotonate a carboxylic acid and drive this reaction to completion as shown below.



This property of carboxylic acids allows many carboxylic acids to be purified by a technique called acid/base extraction. The figure below shows how a carboxylic acid (benzoic acid) can easily be separated from non-acidic water insoluble compounds (cyclohexanone) using an acid/base extraction. First, the two compounds are dissolved in an organic solvent immiscible with water (ether). Then a basic aqueous solution (5% NaOH) is added and two liquid layers are formed. As the layers are mixed, benzoic acid reacts with the basic solution to become sodium benzoate. Because sodium benzoate is soluble in water it is extracted into the aqueous layer while the non-acidic cyclohexanone remains in the organic layer. The two layers can be separated using a separatory funnel effectually removing the cyclohexanone. The aqueous layer can then be acidified with a strong acid causing sodium benzoate to become protonated, reforming benzoic acid. Because benzoic acid is insoluble in water it will form a precipitate which can easily be filtered off.

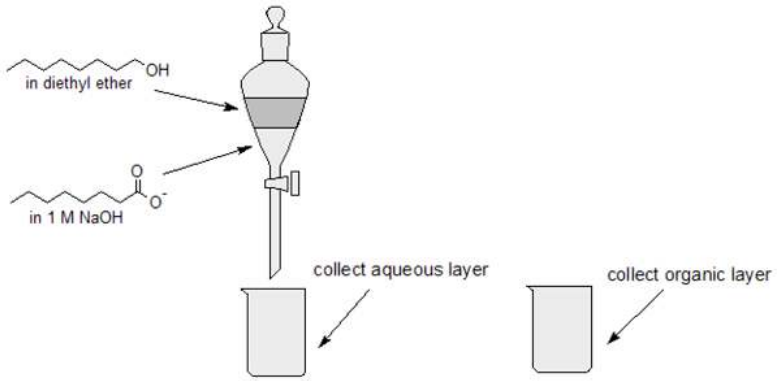


EXERCISE 20.2.1

Use acid-base chemistry and differences in water solubility to separate 1-octanol from octanoic acid using the following solutions: 1 M NaOH, ether, and 6 M HCl and any lab equipment.

Answer

Step 1: Dissolve both compounds in ether and add to a separatory funnel.
Step 2: Add 1 M NaOH to the separatory funnel.
Step 3: Mix well to deprotonate the carboxylic acid to a water soluble carboxylate ion.
Step 4: Collect the aqueous and organic layers.



Step 5: Acidify the aqueous layer using 6 M HCl to reprotonate the carboxylate to octanoic acid.
Step 6 Isolate the octanoic acid by vacuum filtration and allow sample to dry.
Step 7: Isolate the 1-octanol by removing the ether by evaporation using a warm water bath & a gentle flow of nitrogen gas.

? EXERCISE 20.2.2

What percentage of propanoic acid (CH_3CH_2COOH) is dissociated into its conjugate base in a 0.20 M aqueous solution? $K_a = 1.32 \times 10^{-5}$

Answer

From the acid equilibrium expression we get that:

$[CH_3CH_2COO^-][H_3O^+]/[CH_3CH_2COOH] = K_a = 1.32 \times 10^{-5}$

$[X][X]/[0.20\ M - X] = 1.32 \times 10^{-5}$

Assume X is small compared to 0.20 M

$[X]^2/[0.20\ M] = 1.32 \times 10^{-5}$

$X = [CH_3CH_2COO^-] = 1.62 \times 10^{-3}$ M

$[CH_3CH_2COO^-] / [CH_3CH_2COOH] \times 100 = \%Disassociation$

1.62×10^{-3} M / 0.20 M X 100 = **0.812%**

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20.3: BIOLOGICAL ACIDS AND THE HENDERSON-HASSELBALCH EQUATION

OBJECTIVES

After completing this section, you should be able to

1. identify the form that carboxylic acids take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentages of dissociated and undissociated acids [A^-] and [HA] in a solution, given the pK_a value of the acid and the pH of the solution.
3. explain why cellular carboxylic acids are always referred to by the name of their anion.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- Henderson-Hasselbalch equation
- physiological pH

CARBOXYLIC ACIDS IN BUFFERED SOLUTIONS

Due to the acidic nature of carboxylic acids, their level of dissociation is directly related to the pH of the solution. Under acidic conditions (low pH), carboxylic acids are almost completely undissociated and exist primarily in their protonated form (**RCOOH**). Under, basic conditions (high pH), carboxylic acids become nearly completely dissociated into their deprotonated carboxylate form (**$RCOO^-$**). Because the environment inside a living cell is an aqueous buffer with a nearly neutral pH = 7.3 (sometimes referred to as the **physiological pH**), then in what form do carboxylic acids exist? An important part of answering this question lies in the **Henderson-Hasselbalch equation**:

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right) \tag{20.3.1}$$

This equation shows that the amount of dissociation in a carboxylic acid is related to the pH of the solution and the pK_a of the acid. In particular, the Henderson-Hasselbalch equation shows that when the concentration of a carboxylic acid is equal to the concentration of carboxylate then the pH of the solution equals the pK_a of the acid. Also, the Henderson-Hasselbalch allows for the pH of the solution to be calculated when the pK_a of the acid is known along with the concentrations of the carboxylic acid and carboxylate are known.

EXAMPLE 20.3.1

What is the pH of an aqueous buffer solution that is 30 mM in acetic acid and 40 mM in sodium acetate? The pK_a of acetic acid is 4.8.

Solution

This is a direct application of the Henderson-Hasselbalch equation (Equation 20.3.1).

$$pH = pK_a + \log\left(\frac{[\text{ concentration of conjugate base }]}{[\text{ concentration of weak acid }]}\right)$$

The ratio of base to acid is 40/30, or 1.33. Therefore, substituting these values and the pK_a results in

$$\begin{aligned} pH &= 4.8 + \log\left(\frac{40}{30}\right) \\ &= 4.8 + \log 1.33 \\ &= 4.8 + 0.125 \\ &= 4.9 \end{aligned}$$

The Henderson-Hasselbalch equation is particularly useful when determining the protonation state of different biomolecule functional groups under physiological pH conditions. This is done under the assumption that the concentration of the biomolecule is small compared to the concentration of the buffer components. (The actual composition of a physiological buffer is complex, but it is primarily based on phosphoric and carbonic acids.).

Aspartic acid is an amino acid with a carboxylic acid functional group as part of its side chain. When aspartic acid comprises an amino acid residue of a protein in a human cell, it's side chain is in full contact with the physiological buffer. In what state is the side chain functional

group: the protonated state (a carboxylic acid) or the deprotonated state (a carboxylate ion)?

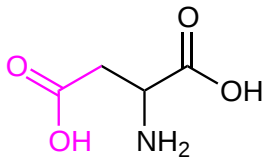


Figure **20.3.1**: Aspartic acid with the carboxylic acid side-chain highlighted. (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the buffer pH of 7.3 and a rough approximation of $pK_a = 5$ for the carboxylic acid side chain, we find that the ratio of carboxylate to carboxylic acid is about 200 to 1. The carboxylic acid is almost completely ionized to the carboxylate inside the cell. This result extends to all other carboxylic acid groups you might find on natural biomolecules or drug molecules. In the physiological environment, carboxylic acids are almost completely deprotonated. Indeed, cellular carboxylic acids are often referred to by the name of their anion. So rather than pyruvic acid, or acetic acid or lactic acid, they are discussed as pyruvate, acetate or lactate.

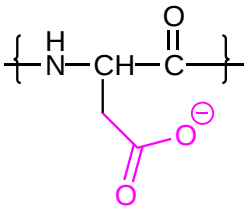


Figure **20.3.2**: Aspartate (as part of a protein or polypeptide). (CC BY-SA 4.0; Layne Morsch via LibreTexts)

Using the same process, the Henderson-Hasselbalch equation (Equation 20.3.1) can also be used to determine the protonation state of carboxylic acids in solutions buffered to other pH levels.

$$pH = pK_a + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$7.3 = 5 + \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$2.3 = \log\left(\frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}\right)$$

$$199 = \frac{[\text{carboxylate}]}{[\text{carboxylic acid}]}$$

Therefore at physiological pH, the carboxylate anion is found with a 199-fold higher concentration than the protonated carboxylic acid. Naturally, changing the pH will alter this ratio.

? EXERCISE 20.3.1

What is the ratio of acetate ion to neutral acetic acid when a small amount of acetic acid ($pK_a = 4.8$) is dissolved in a buffer of pH 2.8? pH 3.8? pH 4.8? pH 5.8? pH 6.8?

Answer

We use the Henderson-Hasselbalch equation (Equation 20.3.1) and let the base to acid ratio be x.

For pH = 2.8:

$$2.8 = 4.8 + \log x$$

$x = 0.01 to 1$

- pH 3.8, the ratio is 0.10 to 1
- pH 4.8, the ratio is 1.0 to 1
- pH 5.8, the ratio is 10 to 1
- pH 6.8, the ratio is 100 to 1

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20.4: SUBSTITUENT EFFECTS ON ACIDITY

OBJECTIVES

After completing this section, you should be able to

1. list a given series of carboxylic acids in order of increasing or decreasing acidity.
2. explain the difference in acidity between two or more given carboxylic acids.
3. arrange a series of substituted benzoic acids in order of increasing or decreasing acidity.
4. determine whether a given substituted benzoic acid will be more or less acidic than benzoic acid.
5. decide which of two or more substituted benzoic acids is the most acidic, and explain your decision on the basis of the electron-withdrawing or electron-releasing ability of the substituent.
6. use the K_a (or pK_a) of a substituted benzoic acid to predict the effect that the substituent has on the susceptibility of the benzene ring to electrophilic attack.

STUDY NOTES

You have already seen how the presence of an electron-withdrawing or electron-releasing group affects the stability of a positively charged carbocation. Now you see how these groups affect the stability of carboxylate anions, and in turn, determine the dissociation constant of a carboxylic acid.

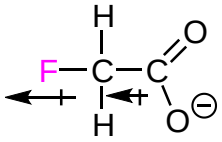
THE INDUCTIVE EFFECT

As seen in **Section 20.2**, there can be substantial range in the acidities of carboxylic acids. From the table in **Section 20.2**, we see that trifluoroacetic acid (K_a = 0.59) is almost than 60,000 times more acidic than butanoic acid (K_a = 1.51 X 10^{-5}). These vast differences in acidity can be almost exclusively explained by the inductive effect of substituents attached to the carboxylic acids.

The **inductive effect** is an experimentally observed effect of the transmission of charge through a chain of atoms in a molecule, resulting in a permanent dipole in a bond. In a carboxylic acid group the presence of halogens (such as fluorine) on adjacent carbons increases the acidity of the carboxylic acid group by stabilizing the carboxylate conjugate base.

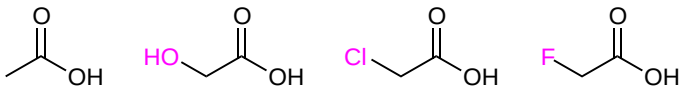
WITHDRAWING INDUCTIVE EFFECTS

A fluorine atom is more electronegative than a hydrogen atom, and thus it is able to ‘induce’, or ‘pull’ the electron density of covalent bonds towards itself. In the fluoroacetate anion, the electrons in the C-F covalent bond are pulled toward the fluorine giving the carbon a partial positive charge. The positively charged carbon, in turn, draws electron density away from the carboxylate anion, dispersing the charge, and creating a stabilizing effect. Stabilizing the carboxylate anion increases the acidity of the corresponding carboxylic acid. In this context, the fluorine substituent is acting as an **electron-withdrawing group**.



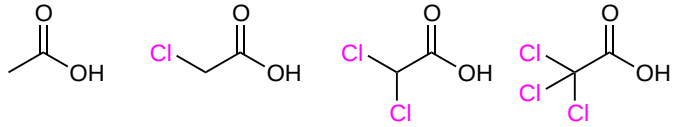
Fluoroacetate anion stabilized by electron withdrawing inductive effect of fluorine

A similar effect is seen when other electron-withdrawing groups are attached to -CH_2CO_2H. As the power of the electron-withdrawing group becomes stronger there is a corresponding drop in the pK_a of the carboxylic acid.



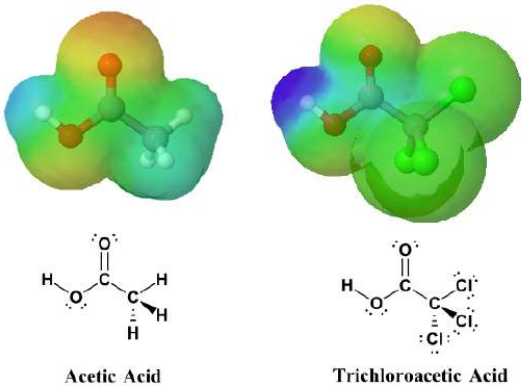
pK_a = 4.8 pK_a = 3.9 pK_a = 2.8 pK_a = 2.6

The presence of multiple electron-withdrawing groups compounds the inductive effect and continues to increase the acidity of the carboxylic acid. Dichloroacetic is a stronger acid than chloroacetic acid, and trichloroacetic acid is even stronger.



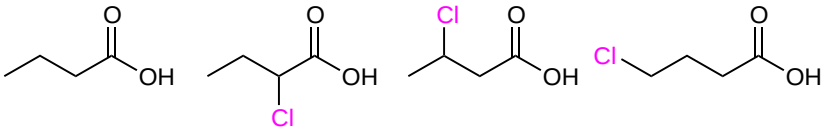
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 1.3$ $pK_a = 0.64$

The inductive effects of chlorine be clearly seen when looking at the electrostatic potential maps of acetic acid (Left) and trichloroacetic acid (Right). The O-H bond in trichloroacetic acid is highly polarized, as shown by the dark blue color making it a much stronger acid than acetic acid.



Acetic Acid Trichloroacetic Acid

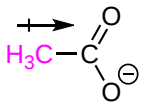
Because inductive effects are not transmitted effectively through covalent bonds, the acid-strengthening effect falls off rapidly as the number of sigma bonds between the carboxylic acid and the electron-withdrawing group increases. A distance of three sigma bonds almost completely eliminates chlorine's inductive effect in 4-chlorobutanoic acid, giving it a similar pK_a value to unsubstituted butanoic acid.



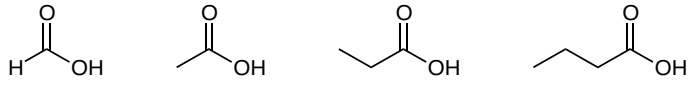
$pK_a = 4.8$ $pK_a = 2.8$ $pK_a = 4.0$ $pK_a = 4.5$

DONATING INDUCTIVE EFFECTS

Alkyl groups (hydrocarbons) are inductively electron-donating. In this case, the inductive effects pushes electron density onto the carboxylate anion, producing a destabilizing effect, decreasing the acidity of the carboxylic acid.



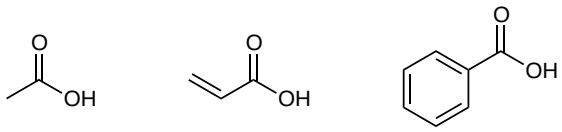
Lengthening the alkyl chain of a carboxylic acid can increase this inductive effect but it no longer decreases the acidity further after the chain is about three carbons long.



$pK_a = 3.75$ $pK_a = 4.76$ $pK_a = 4.87$ $pK_a = 4.82$

THE ACIDITY OF SUBSTITUTED BENZOIC ACIDS

Extensive research has been performed on the acidity of substituted benzoic acids. Benzoic acid itself is a somewhat stronger acid than acetic acid. The carboxyl group of benzoic acid is attached to an sp^2-hybridized carbon which is more electronegative and electron-withdrawing than the sp^3-hybridized carbon attached to the carboxyl group of acetic acid. In **Section 2.9** it was discussed that carbon becomes more electron-withdrawing as the s character of its hybrid orbitals increases. The same effect is seen in acrylic acid which is also more acidic than acetic acid.



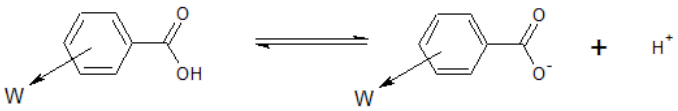
acetic acid
$pK_a = 4.8$

acrylic acid
$pK_a = 4.3$

benzoic acid
$pK_a = 4.2$

In **Section 16.4** it was discussed that substituents had a marked effect on the electron density of an aromatic ring and on the rate of electrophilic aromatic substitutions. Electron-donating substituents increase the electron density of the aromatic ring, activating it, and increasing the rate of electrophilic substitutions. Electron-withdrawing groups decreased electron density, deactivating the aromatic ring, and reduced the rate of electrophilic substitution.

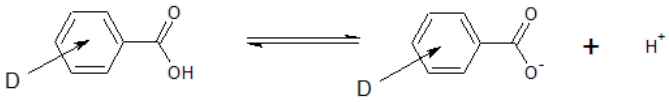
In a similar fashion, substituents have an effect on the acidity of benzoic acids. Benzoic acids with deactivating substituents, such a nitro group ($-NO_2$), in the *meta or para* position tend to be more acidic. The deactivating substituents remove electron density, stabilizes the negative charge of the carboxylate anion, and increasing the acidity of the carboxylic acid.



W = electron Withdrawing group

The carboxylate anion is stabilized by the electron withdrawing group increasing the acidity of the conjugate acid.

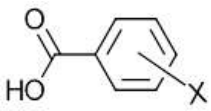
The opposite effect occurs with electron donating substituents. Electron-donating substituents in the meta or para position destabilize the carboxylate anion making the benzoic acid less acidic.



D = electron Donating group

The carboxylate anion is destabilized by the electron withdrawing group decreasing the acidity of the conjugate acid.

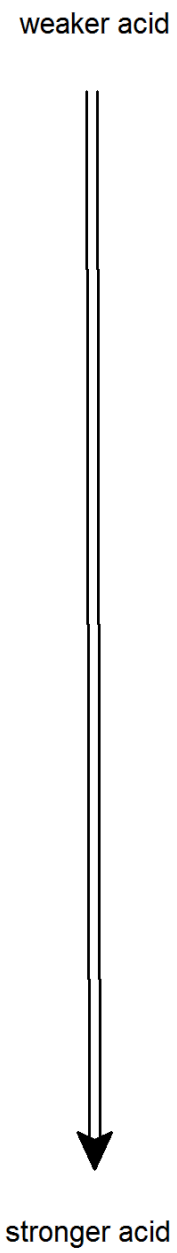
A closer look at the effects of electron-withdrawing and electron-donating substituents in the meta or para position can be seen in the pK_a values of various benzoic acids as shown in the table below. Notice the trend in the following table where electron donating substituents (X) at the meta or para positions lead to weaker acids while those having more electron withdrawing substituents generate stronger acids.



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Dissociation Constants of *m* & *p*-Substituted Benzoic Acid

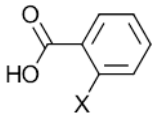
X	pK_a-*Para*	pK_a-*Meta*	Substituent Type
—NH_2	4.8	4.7	Donating
—OH	4.6	4.1	Donating
—OCH_3	4.50	4.1	Donating
—CH_3	4.4	4.3	Donating
—H	4.20	4.20	
—Cl	4.00	3.8	Withdrawing
—Br	4.0	3.8	Withdrawing
—NO_2	3.4	3.5	Withdrawing



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THE *ORTHO*-EFFECT

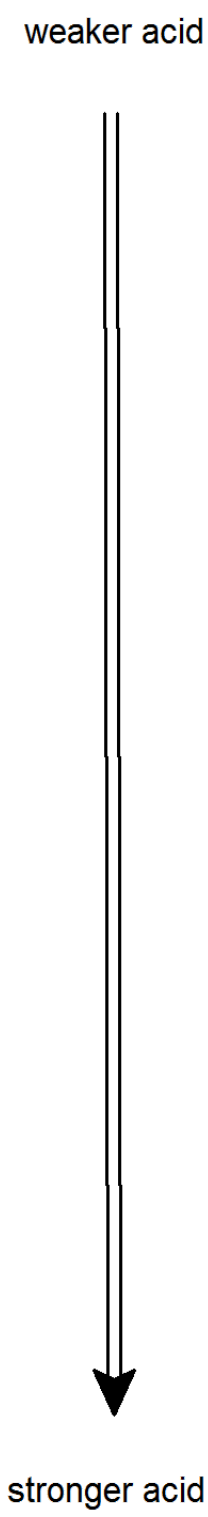
Almost all ortho-substituents increase the acid strength of a benzoic acid regardless of whether they are electron-donating or electron-withdrawing. This is called the *ortho*-effect and its cause is not completely understood. It is theorized to be a combination of both steric and electronic factors. There are exceptions of the ortho-effect, such as an amino substituent which still causes the benzoic acid to be less acidic.



Dissociation Constants of *o*-Substituted Benzoic Acid

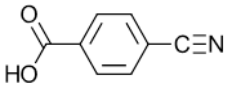
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X	pK_a-*Ortho*	Substituent Type
—NH_2	4.7	Donating
—H	4.20	
—OCH_3	4.1	Donating
—CH_3	3.9	Donating
—OH	3.0	Donating
—Cl	2.9	Withdrawing
—Br	2.9	Withdrawing
—NO_2	2.2	Withdrawing



EXAMPLE

The following molecule, *p*-cyanobenzoic acid, has a pK_a of 3.55. Does the cyano substituent activate or deactivate the aromatic ring towards electrophilic aromatic substitution?



p-cyanobenzoic acid

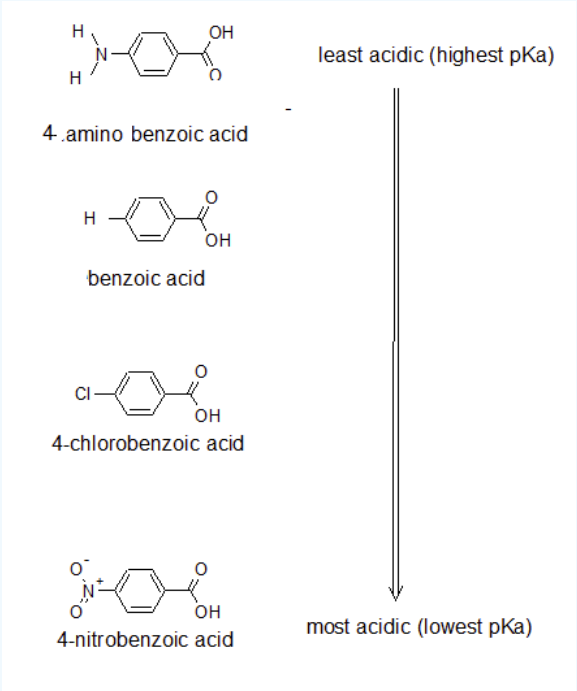
The pK_a of benzoic acid is 4.2 which means it is a weaker acid than *p*-cyanobenzoic acid. This this means that the cyano substituent is deactivating the ring.

EXAMPLE

1. Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-aminobenzoic acid; 4-chlorobenzoic acid; and benzoic acid. Try to use the expected inductive effects of the substituents to determine the acidity rather than looking at the pK_a table.

Answer

1.



EXERCISES

1) For the following pairs, which is expected to be the stronger acid? Explain your answer.

(a) $(CH_3)_3CCH_2CO_2H$ or $(CH_3)_3\overset{+}{N}CH_2CO_2H$

(b) $CH_3CH_2CO_2H$ or $CH_3\underset{OH}{\underset{|}{C}}HCO_2H$

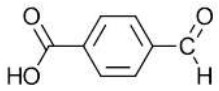
(c) $CH_3\overset{O}{\overset{\|}{C}}CO_2H$ or $CH_2{=}CHCO_2H$

d) acrylic aid vs. propiolic acid (image)

2) Oxalic acid is a dicarboxylic acid with two acidic protons. The first proton is much more acidic (pK_a = 1.20) than a typical carboxylic acid. However, Heptanedioic acid's first acidic proton has a pK_a much closer to that of a typical carboxylic acid. Explain these differences.

(image)

3) The carboxylic acid of 4-formylbenzoic acid has a pK_a of 3.75. Is this molecule likely to be more reactive or less reactive than benzene toward electrophilic aromatic substitution?



4-formylbenzoic

SOLUTIONS

1)

a) Consider the inductive effects of the substituents attached to the carboxylic acid. The *tert*-butyl group is electron-donating which should decrease the acidity of the carboxylic acid. The trimethylammonium substituent is positively charged and can be a powerful electron-withdrawing substituent. This should increase the acidity of the carboxylic acid. The compound $(CH_3)_3NCH_2CO_2H$ is expected to be a stronger acid than $(CH_3)_3CCH_2CO_2H$. The acidity constants for these two compounds match the predictions.

(image)

b) Having an electron-withdrawing hydroxyl group at the C-2 stabilizes the carboxylate ion of lactic acid through inductive effects.

(image)

This should make lactic acid more acidic than propanoic acid.

c) Due to the presence of a highly electronegative oxygen, the carbonyl group is expected to be more strongly electron-withdrawing than a carbon–carbon double bond. Thus, pyruvic acid should be a stronger acid than acrylic acid.

(image pyruvic and acrylic acid)

d) The main difference between the two compounds is the hybridization of the carbon attached to the carboxylic acid. The alkyne substituent has an sp hybridized carbon which should make it more electron-withdrawing than the alkene's sp^2 hybridized carbon.

2) With oxalic acid one carboxyl group acts as an inductive electron-withdrawing group which increases the acidity of the other carboxylic acid. This inductive effect is only relevant with the two carboxyl groups are separated by only a few bonds. In heptanedioic acid, the carboxyl groups are separated by five carbon which effectively negates the inductive effect.

3) Benzoic acid (pK_a = 4.2) has a higher pK_a and is more acidic than 4-formylbenzoic acid (pK_a = 3.75). This means that the formyl group is removing electrons from the aromatic ring making it deactivated toward electrophilic aromatic substitution.

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20.5: PREPARING CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. describe in detail the methods of preparing carboxylic acids discussed in previous chapters:
   a. the oxidation of alkylbenzenes.
   b. the oxidative cleavage of alkenes.
   c. the oxidation of primary alcohols and aldehydes.
2. discuss, in detail, the hydrolysis of nitriles:
   a. write an equation to illustrate the preparation of a carboxylic acid through nucleophilic attack by cyanide ion on an alkyl halide and hydrolysis of the nitrile which results.
   b. identify the carboxylic acid formed from the hydrolysis of a given nitrile, or from the reaction of a given alkyl halide with cyanide ion followed by hydrolysis of the resulting nitrile.
   c. identify the alkyl halide needed to prepare a given carboxylic acid by the formation and subsequent hydrolysis of a nitrile.
   d. identify the reagents needed to convert a given alkyl halide into a carboxylic acid containing one more carbon atom.
3. discuss, in detail, the carboxylation of Grignard reagents:
   a. write an equation describing the formation of a carboxylic acid from a Grignard reagent.
   b. identify the carboxylic acid obtained through the treatment of a given Grignard reagent with carbon dioxide followed by dilute acid.
   c. identify the Grignard reagent (or the alkyl halide required to form the Grignard reagent) that must be used to produce a given carboxylic acid by reaction with carbon dioxide.
   d. write the detailed mechanism for the formation of a carboxylic acid using a Grignard reagent.

STUDY NOTES

Review the methods of obtaining carboxylic acids presented in earlier sections:

1. oxidation of aromatic compounds—Section 16.9.
2. oxidative cleavage of alkenes—Section 8.8.
3. oxidation of primary alcohols and aldehydes—Sections 17.7 and 19.3.

Carboxylic acids can be prepared using a wide variety of reactions. Many carboxylic acid derivatives such as esters, amides, and anhydrides can undergo hydrolysis to form the parent carboxylic acids. The most common methods for synthesizing carboxylic acids can be separated into three major groups.

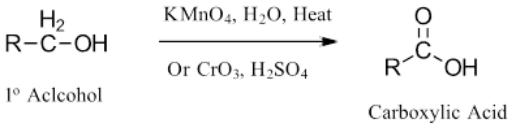
1. Oxidations
2. Carboxylation of Grignard Reagents
3. Hydrolysis of Nitriles

FORMING CARBOXYLIC ACIDS THROUGH OXIDATIONS

The carbon atom of a carboxyl group has a high oxidation state. It is not surprising, therefore, that many of the chemical reactions used for their preparation are oxidations. Such reactions have been discussed in previous sections of this text.

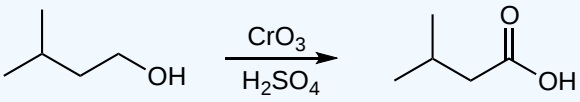
OXIDATION OF 1° ALCOHOLS

The oxidation of 1° alcohols to carboxylic acids can be performed with a wide variety of oxidizing agents including potassium permanganate ($KMnO_4$) and Jones reagent (CrO_3 & H_2SO_4). One of the main synthetic limitations of alcohol oxidations is that the necessary oxidizing agents often react with other oxidizable functional groups, such as aldehydes, alkyl arenes, and other alcohols. Because alcohols are often readily available this reaction is the most common oxidative reaction for creating simple carboxylic acids.



1° Alcohol — Carboxylic Acid

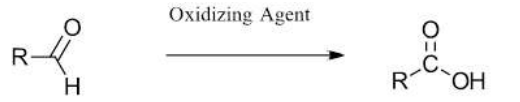
? EXERCISE 20.5.1



Oxidation of 3-methylbutan-1-ol to 3-methylbutanoic acid

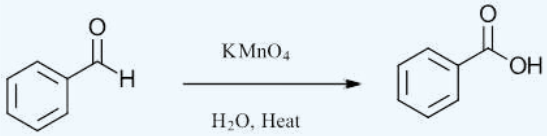
OXIDATION OF ALDEHYDES

In a similar fashion as 1° alcohols, aldehydes are also converted to carboxylic acids using a wide variety of oxidizing agents including potassium permanganate and Jones reagent.



Aldehyde — Carboxylic Acid

✔ EXAMPLE 20.5.1



Benzaldehyde — Benzoic Acid

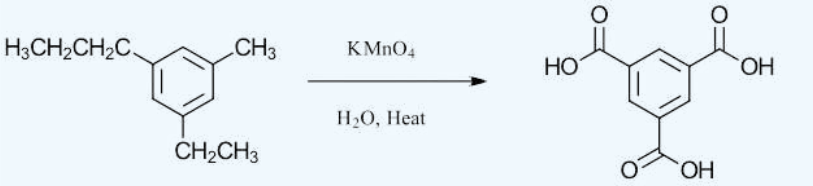
OXIDATION OF ALKYL ARENE SIDE-CHAINS

Primary and secondary carbons directly attached to an aromatic ring can be converted to carboxylic acids by reaction with strong oxidizing agents including potassium permanganate and Jones reagent. Tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that alkyl groups are ortho, para directors and after oxidation the carboxylic acid formed is a meta director.



Alkyl Substituted Arene — Carboxylic Acid

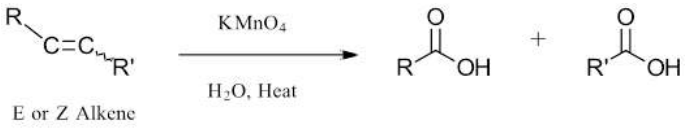
✔ EXAMPLE



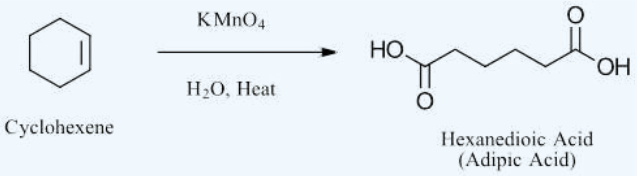
3-Ethyl-5-propyltoluene — 1,3,5-Benzenetricarboxylic acid (Trimesic acid)

OXIDATIVE CLEAVAGE OF ALKENES

Alkenes can undergo oxidative cleavage to form carboxylic acids by reacting with hot alkaline $KMnO_4$.

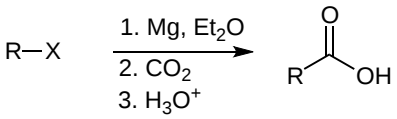


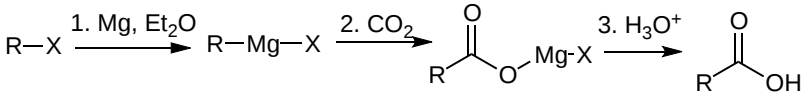
EXAMPLE



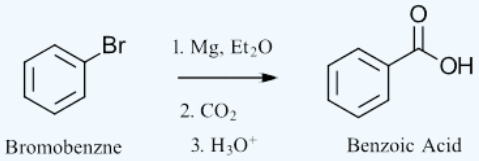
CARBOXYLATION OF GRIGNARD REAGENTS

In this method, an electrophilic halide is first transformed into a strongly nucleophilic Grignard reagent. The Grignard reagent adds to the C=O bond of carbon dioxide (an electrophile) to yield the salt of of a carboxylic acid called a halomagnesium carboxylate. This intermediate is then treated with a strong aqueous acid to form the carboxylic acid. Most alkyl or aryl halides can be used for this synthesis of carboxylic acids. The main limitation is that no functional groups incompatible with Grignard reagents can be present such has O-H, N-H, S-H, or C=O bonds.



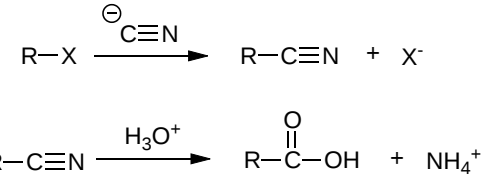


EXAMPLE



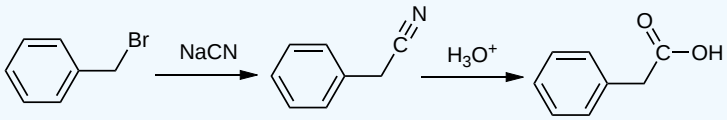
HYDROLYSIS OF NITRILES

Hydrolysis of nitriles to carboxylic acids requires two steps. First, an alkyl halide is reacted with a nucleophilic cyanide anion to form a nitrile intermediate by an S_N2 reaction. Subsequent hydrolysis of the nitrile is typically performed by heating with an acidic or basic aqueous solution and uses a mechanism discussed later in this chapter. Due to the requirements of the S_N2 reaction, only primary and secondary alkyl halides may be used for this reaction. Tertiary alkyl halides typically produce an alkene through E2 elimination reaction and aryl halides usually do not react.

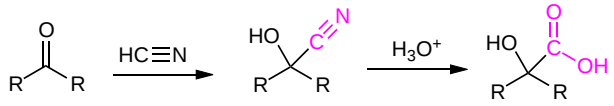


Two steps of nitrile formation and hydrolysis

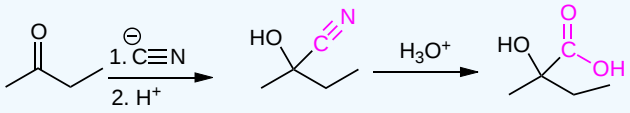
EXAMPLE



Aldehydes and ketones can be converted to cyanohydrins through nucleophilic addition of a cyanide anion to the carbonyl. The -CN group of the cyanohydrin can also be hydrolized to form an alpha hydroxy carboxylic acid.



EXAMPLE



conversion of butan-2-one to 2-hydroxy-2-methylbutanoic acid

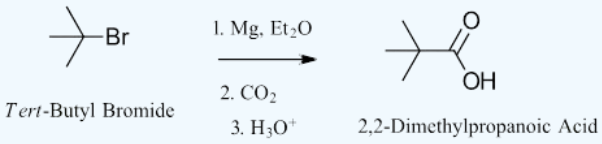
WORKED EXAMPLE 20.5.1: CHOOSING A SYNTHESIS PATHWAY TO A CARBOXYLIC ACID

Thus far this chapter has discussed three main methods for the creation of a carboxylic acid functional group: the oxidation of a 1º alcohol, the carboxylation of a Grignard reagent, and the hydrolysis of a nitrile. Select one of these three methods to perform the following transformation. Briefly explain why the other two methods would be unsuccessful.

a. Tert-Butyl Bromide → 2,2-Dimethylpropanoic acid.
b. Benzyl Bromide → Benzoic Acid
c. 3-Bromo-1-propanol → 4-Hydroxybutanoic acid

Solution A

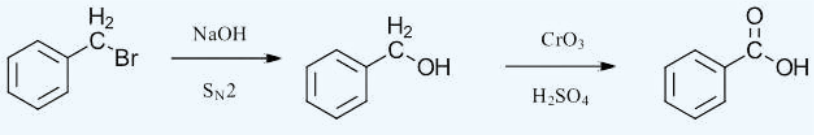
The product contains one more carbon than the reactant so the oxidation of a 1º alcohol would be an ineffective method. Also, the reactant contains a tertiary halide, so the S_N2 reaction required to form a nitrile would not be possible. The carboxylation of a Grignard reagent would be the most effective method because it allows for the addition of a carbon, it is not severely affected by the sterics of the tertiary halide, and there are no incompatible functional groups.



Tert-Butyl Bromide — 2,2-Dimethylpropanoic Acid

Solution B

The product and reactant have the same number of carbons so both the carboxylation of a Grignard reagent and hydrolysis of a nitrile would be ineffective for this conversion. Benzyl bromide is a primary alkyl halide which can easily be converted to a primary alcohol by an S_N2 reaction with NaOH. Once formed, the primary alcohol can be converted to a carboxylic acid using an oxidation reaction.

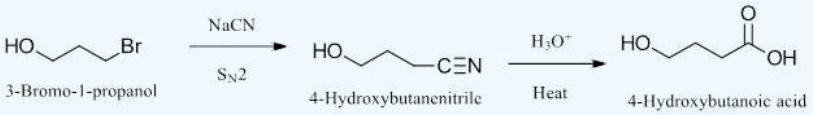


Benzyl Bromide — Benzyl Alcohol — Benzoic Acid

Solution C

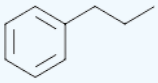
The product contains one more carbon than the reactant so the oxidation of a primary alcohol would not be an effective method. Also, the carboxylation of a Grignard reagent would not be an effect method because the presence of an incompatible alcohol functional

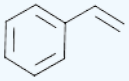
group in the reactant. The reactant contains a primary halogen which can readily be converted to a nitrile by an S_N2 reaction with NaCN. The resulting nitrile can be converted to a carboxylic acid through hydrolysis.



EXERCISE 20.5.1

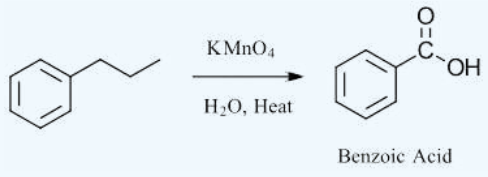
Show how the following molecules can be used to synthesize benzoic acid:

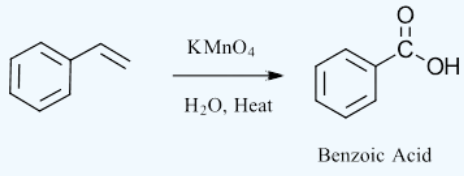
a. 

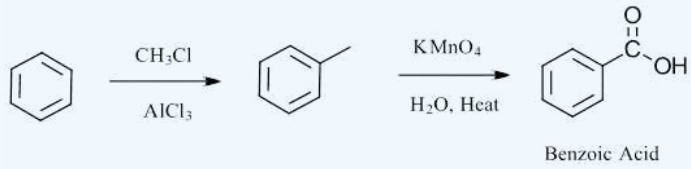
b. 

c. 

Answer

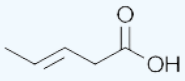
a. 

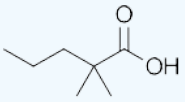
b. 

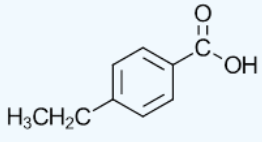
c. 

EXERCISE 20.5.2

give the structure of the bromide required to make the following using the carboxylation of a Grignard reagent:

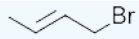
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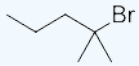
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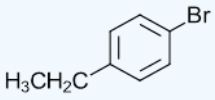
c. 

Answer

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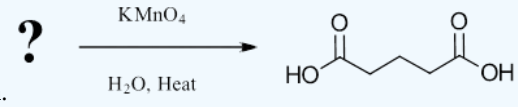
a. 

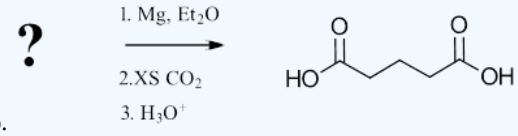
b. 

c. 

? EXERCISE 20.5.3

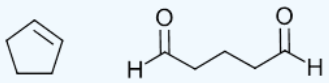
Give the possible reactants for the following reactions:

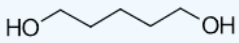
a. 

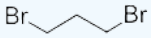
b. 

There are at least four possible answers for question a.

Answer



a. 

b. 

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20.6: REACTIONS OF CARBOXYLIC ACIDS - AN OVERVIEW

OBJECTIVES

After completing this section, you should be able to identify the four types of reaction which a carboxylic acid can undergo.

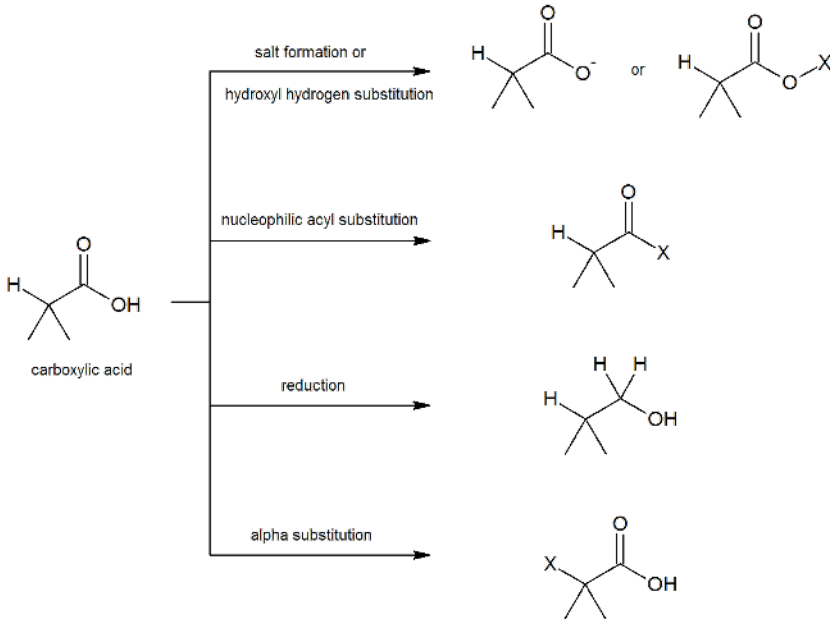
STUDY NOTES

You may wish to review Section 17.4 which discusses reduction of carbonyl compounds to form alcohols and Sections 20.2–20.4 which highlights the acidity of carboxylic acids, which is important to salt formation and substitution of the hydroxyl hydrogen. Nucleophilic acyl substitution (Chapter 21) and alpha substitutions (Chapter 22) are discussed later in more detail.

FOUR CATEGORIES OF CARBOXYLIC ACID REACTIONS

Carboxylic acid reactions are typically classified into four major categories:

1. As carboxylic acids are easily deprotonated, they readily form a carboxylate salt which can then potentially be reacted with an electrophile to complete a substitution of the hydroxyl hydrogen.
2. Nucleophilic acyl substitution reactions allow substitution of the hydroxyl group which leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). We will see these reactions in more detail in Chapter 21.
3. Like other carbonyl compounds, carboxylic acids can be reduced by reagents such as $LiAlH_4$.
4. While the proton on the carbon alpha to the carbonyl group is not as acidic as the hydroxyl hydrogen, it can be removed leading to substitution at the alpha position. The scheme summarizes some of the general reactions that carboxylic acids undergo.

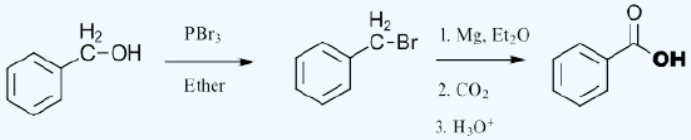


EXERCISE 20.6.1

Show how the following transformation can be performed. Multiple steps may be required.

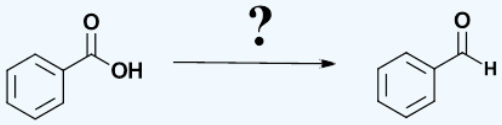


Answer

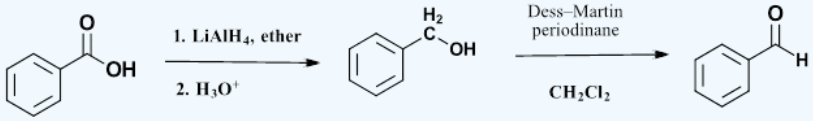


EXERCISE 20.6.2

Show how the following transformation can be performed. Multiple steps may be required.



Answer



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20.7: CHEMISTRY OF NITRILES

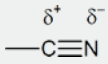
OBJECTIVES

After completing this section, you should be able to

1. discuss, in detail, the preparation of nitriles:
   a. write an equation to illustrate the formation of a nitrile by the nucleophilic attack of cyanide ion on an alkyl halide.
   b. write an equation to illustrate the formation of a nitrile by the dehydration of a primary amide.
   c. identify the product formed when a primary amide is treated with $SOCl_2$, P_2O_5, or $POCl_3$.
   d. identify the primary amide, the reagents, or both, needed to prepare a given nitrile by a dehydration reaction.
   e. write a detailed mechanism for the dehydration of a primary amide by thionyl chloride.
2. discuss, in detail, the reactions of nitriles:
   a. write an equation to describe the (acidic or basic) hydrolysis of a nitrile.
   b. write detailed mechanisms for the acidic and basic hydrolysis of nitriles.
   c. identify the products formed from the (acidic or basic) hydrolysis of a given nitrile.
   d. identify the nitrile, the reagents, or both, needed to obtain a given carboxylic acid from a hydrolysis reaction.
   e. write an equation to describe the reduction of a nitrile to give a primary amine.
   f. identify the product formed from the lithium aluminum hydride reduction of a given nitrile.
   g. identify the nitrile, the reagents, or both, needed to prepare a given amine by direct reduction.
   h. write a detailed mechanism for the reduction of a nitrile to a primary amine using lithium aluminum hydride.
   i. give an example of the reduction of a nitrile with diisobutylaluminum hydride.
   j. write an equation to illustrate the reaction of a nitrile with a Grignard reagent.
   k. identify the product formed from the reaction of a given nitrile with a given Grignard reagent.
   l. identify the nitrile, the Grignard reagent, or both, needed to prepare a given ketone.
   m. write a detailed mechanism for the reaction of a nitrile with a Grignard reagent.

STUDY NOTES

To be able to understand the driving force behind the reactions of nitriles, you must recognize the polarity of this group:

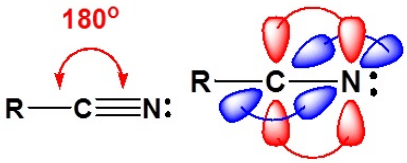


You can therefore expect to see similarities between the behaviour of the nitrile group and the similarly polarized carbonyl group:

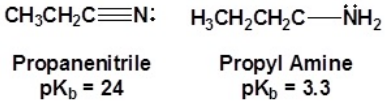


PROPERTIES OF NITRILES

The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bonds in the triple bond. The R-C-N bond angle in a nitrile is 180º which give a nitrile functional group a linear shape.



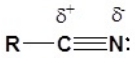
The lone pair electrons on the nitrogen of a nitrile are contained in a *sp* hybrid orbital. The 50% *s* character of an *sp* hybrid orbital makes the lone pair electrons closer to the nucleus and therefore less basic when compared to lone pair electrons on sp^3 hybridized nitrogen (25% *s* character) containing compounds such as amines.



Propanenitrile
$pK_b = 24$

Propyl Amine
$pK_b = 3.3$

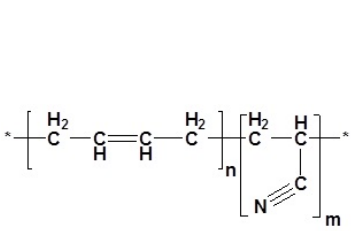
The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size. Also, the polar nature of nitriles promotes their solubility in water.



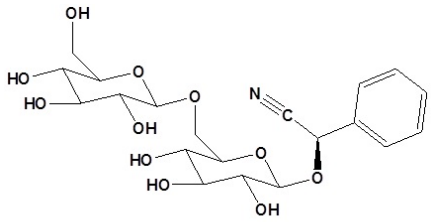
	Boiling Point
$CH_3CH_2C{\equiv}N$ Propanenitrile	96-98 °C
$CH_3CH_2C{\equiv}C{-}H$ Butyne	8.1 °C
$CH_3CH_2CH_2CH_3$ Butane	-1-1 °C

INTERESTING NITRILES

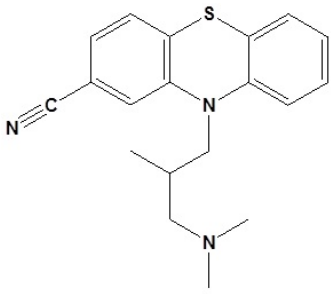
One of the most common occurrences of nitriles is in Nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals. Amygdalin is a naturally occurring molecule contained by certain plants to protect themselves against herbivores and insects. Acting as a sort of natural pesticide, amygdalin degrades to release poisonous hydrogen cyanide (HCN) when any plant material is chewed by an insect or animal. There are also several nitrile containing molecules that have medicinal uses such as Cyamemazine, which is an antipsychotic drug primarily used to treat schizophrenia and certain types of anxiety. Also, Citalopram is an antidepressant primarily used to treat depression, panic disorder, and social phobia. It is currently among the most prescribed drugs in the United States (#21 in 2019 with over 26,000,000 prescriptions).



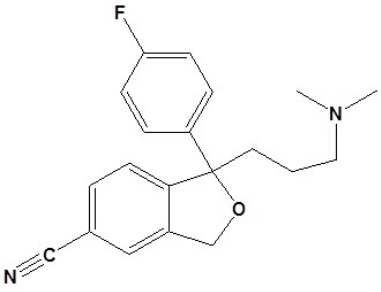
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



Cyamemazine: an antipsychotic

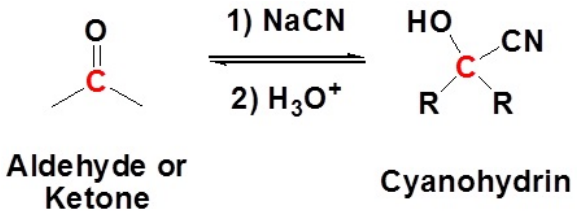


Citalopram: an antidepressant

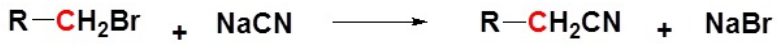
PREPARATION OF NITRILES

FORMATION OF A NITRILE FROM AN ALDEHYDE OR KETONE

Addition of cyanide (¯:C≡N) to an aldehyde or ketone forms a cyanohydrin

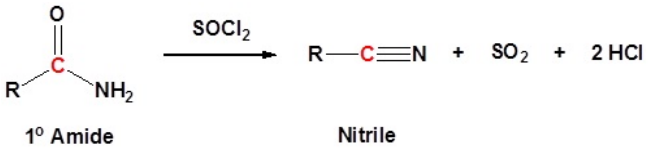


Nitriles are formed by an S_N2 reaction between primary and secondary alkyl halides and sodium cyanide. Tertiary and aryl halides cannot be used for this reaction.



FORMATION OF A NITRILE FROM A 1^O AMIDE

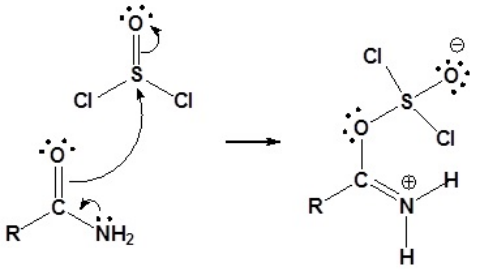
Primary amides can be converted to nitriles by dehydration with thionyl chloride ($SOCl_2$) or other dehydrating agents like such as P_2O_5, or $POCl_3$.



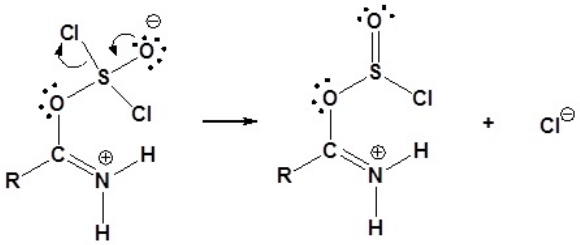
MECHANISM

For the reaction of primary amides with thionyl chloride, the mechanism begins with the lone pair of electrons from the nitrogen atom forming a protonated imine and pushing the pi electrons of the carbonyl to undergo nucleophilic attack on the sulfur of thionyl chloride. This forms a O-S sigma bond and causes the pi electrons of the thionyl bond (S=O) to be pushed onto the oxygen. The thionyl bond reforms in concert with the loss of a chloride leaving group (Cl^-). The protonated imine is neutralized by any base. The nitrile is then produced by an E2-like elimination reaction with a loss of sulfur dioxide (SO_2) and another chloride as the leaving groups.

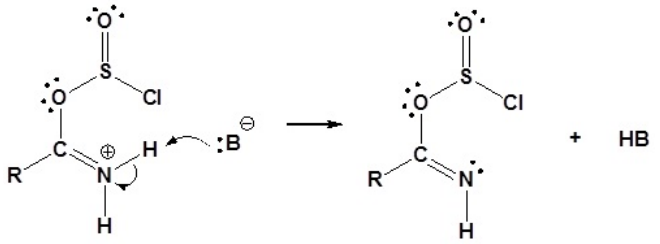
Step 1: Nucleophilic attack on thionyl chloride



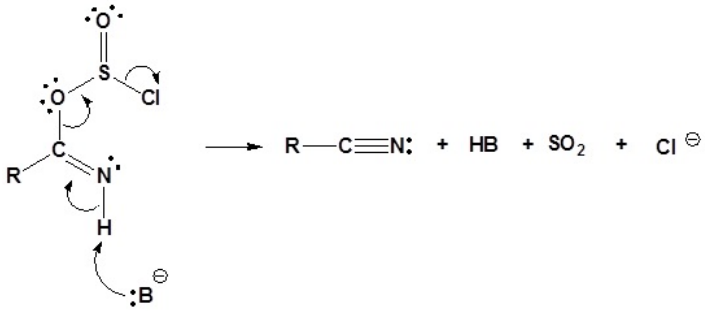
Step 2: Leaving group removal to reform the thionyl bond



Step 3: Deprotonation

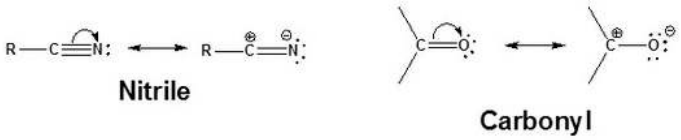


Step 4: E2-like reaction to form a nitrile

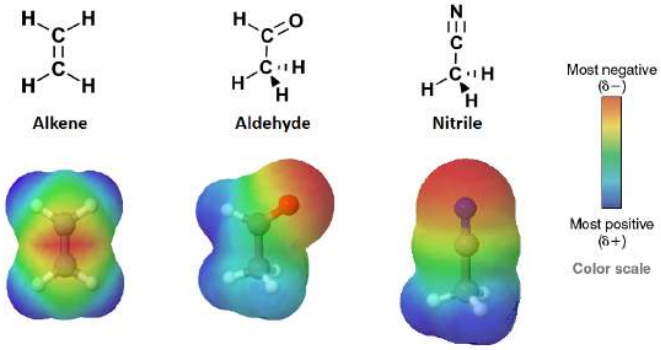


REACTIONS OF NITRILES

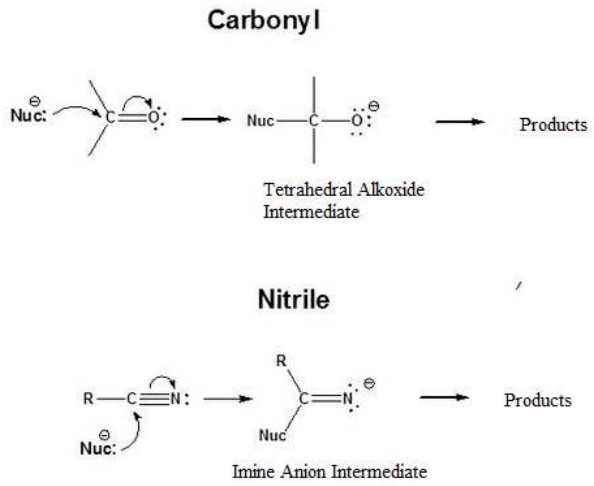
Nitriles are analogous to carbonyl groups in that they contain pi bonds, are strongly polarized, and contain electrophilic carbons.



The bond polarization of a nitrile can clearly be seen when comparing the electrostatic potential maps of an alkene, an aldehyde, and a nitrile. In the maps of the aldehyde and nitrile, the electron density in the pi bonds is pulled away from the carbon toward the electronegative oxygen and nitrogen. This gives the functional group carbons a slight positive charge making them electrophilic. In the map of the alkene, the electron density is centered on the carbon making the pi bond non-polar and the carbons not electrophilic.

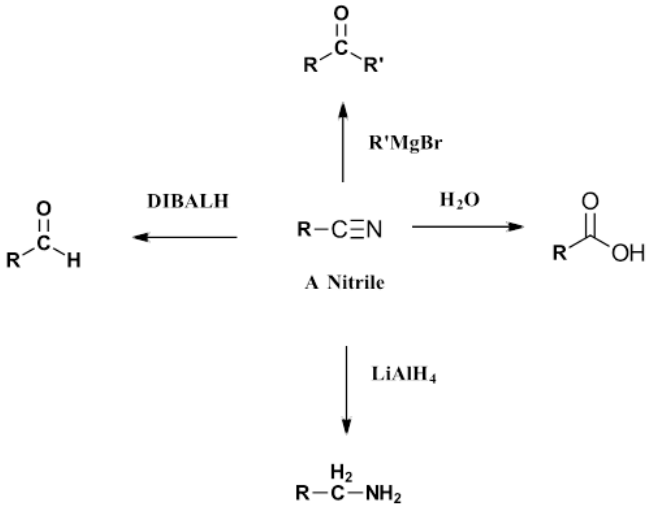


The triple bond of a nitrile reacts with negatively charged nucleophiles to form an imine anion intermediate in much the same fashion that carbonyls form a tetrahedral alkoxide intermediate. Because the imine anion intermediate still contains a pi bond and an electrophilic carbon, additional nucleophilic additions can occur to form a variety of functional groups including ketones, aldehydes, and amines.



GENERAL REACTIONS OF NITRILES

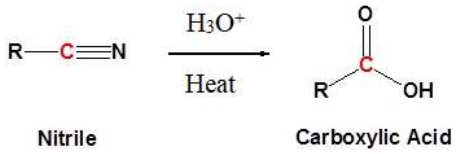
Nitriles undergo several types of reactions including hydrolysis to carboxylic acids, two different reductions with products that vary with the strength of the reducing agent and reaction with Grignard reagents that form ketones.



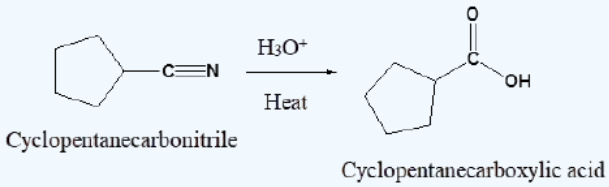
HYDROLYSIS OF NITRILES TO FORM CARBOXYLIC ACIDS

One of the more useful reaction involving nitriles is their hydrolysis to form carboxylic acids. This reaction occurs in either acidc or basic aqueous solutions with slight differences in each mechanism. In the case of acid catalysis, the nitrile becomes protonated. Protonation increases the electrophilicity of the nitrile so that it will accept water, a poor nucleophile. With base catalyzed hydrolysis, the strongly nucleophilic hydroxide anion is capable of directl addition to the carbon-nitrogen triple bond. During both mechanisms an amide intermediate is formed which usually is not isolated.

ACID CATALYZED HYDROLYSIS OF NITRILES



EXAMPLE



Cyclopentanecarbonitrile

Cyclopentanecarboxylic acid

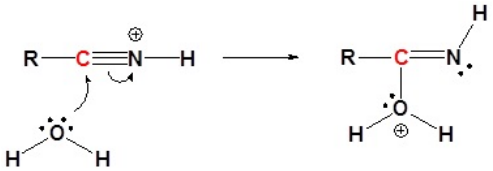
MECHANISM OF ACID CATALYZED HYDROLYSIS

The mechanism begins with the protonation of the nitrile to promote the addition of the weakly nucleophilic water molecule to the C-N triple bond. Once water has reacted with the nitrile carbon, a proton transfer and resonance occur to produce a protonated amide. Water acts as a weak base, deprotonating the carbonyl to form an amide and regenerating the hydronium catalyst. Further hydrolysis converts the amide to the carboxylic acid. The nitrile nitrogen is eventually removed as a leaving group and eventually forms ammonium (NH_4^+)

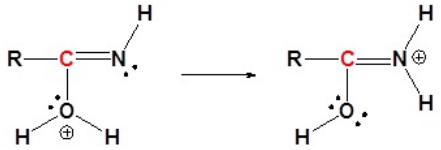
Step 1: Protonation



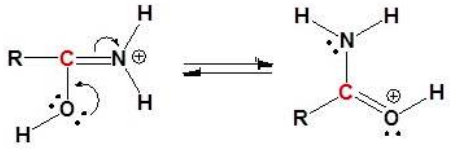
Step 2: Nucleophilic addition of water



Step 3: Proton Transfer



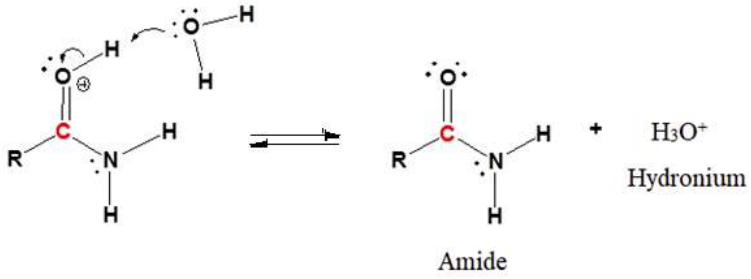
Step 4: Resonance to form a protonated amide



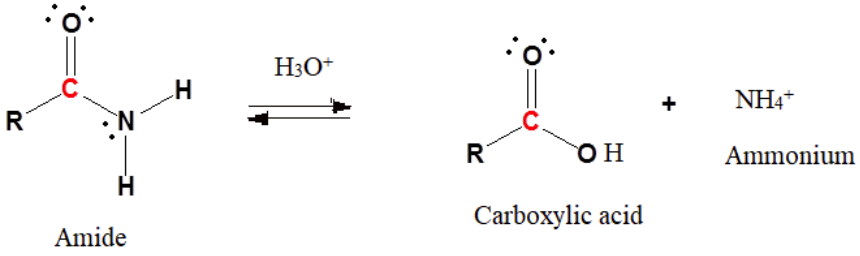
Protonated Amide

Step 5: Deprotonation to form an amide

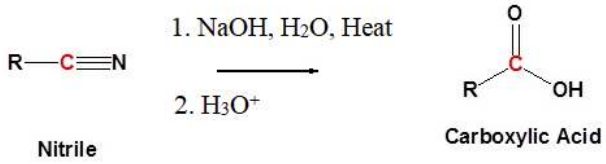
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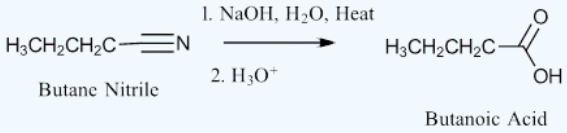
Step 6: Further hydrolysis of the amide forms a carboxylic acid. This mechanism can be found in Section 21.7



BASE CATALYZED HYDROLYSIS OF NITRILES



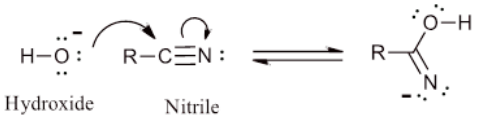
EXAMPLE



MECHANISM OF BASE CATALYZED HYDROLYSIS

Base catalyzed hydrolysis starts with the nucleophilic addition of a hydroxide ion to the C-N triple bond to form an imine anion. Subsequent protonation by water forms an amide tautomer, imidic acid, and regenerates the hydroxide catalyst. Tautomerization of imidic acid forms an amide which undergo further base catalyzed hydrolysis to form a carboxylic acid. During hydrolysis of the amide, nitrogen from the original nitrile is removed as a leaving group and eventually forms ammonium (NH_4^+)

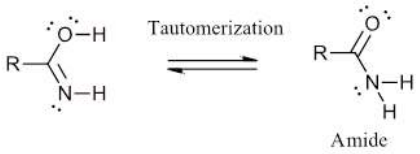
Step 1: Nucleophilic addition of hydroxide



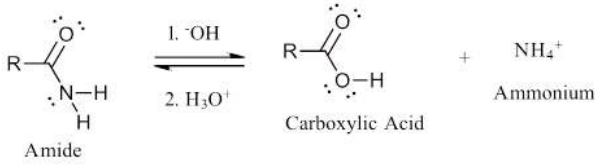
Step 2: Protonation by water to form an imidic acid and hydroxide



Step 3: Tautomerization of an imidic acid to form an amide

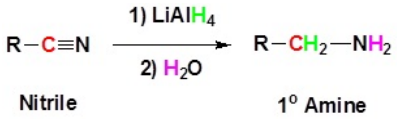


Step 4:) Further hydrolysis of the amide forms a carboxylic acid. This mechanism can be found in Section 21.7

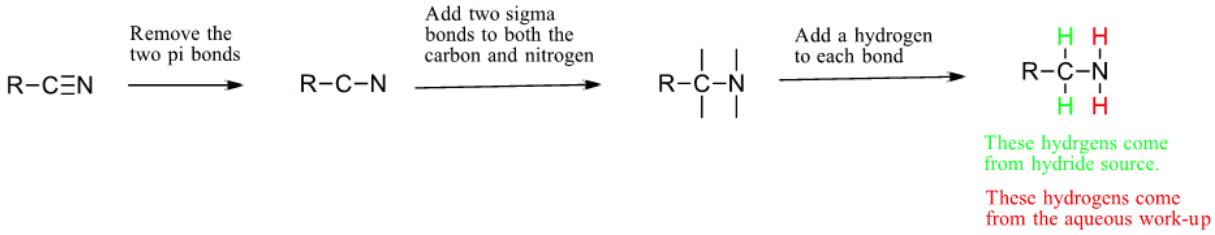


NITRILES CAN BE REDUCED TO 1° AMINES BY REACTION WITH LIALH$_4$

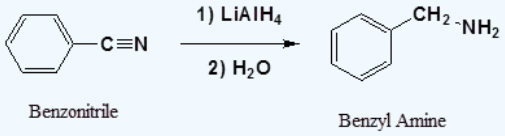
The reduction of nitriles with lithium aluminum hydride $LiAlH_4$ is an excellent method for the synthesis of primary amines. This reaction occurs via two nucleophilic additions of a hydride to the electrophilic carbon in the nitrile. Subsequent protonation with an aqueous work-up leads to the primary amine.



PREDICTING THE PRODUCT OF A HYDRIDE REDUCTION



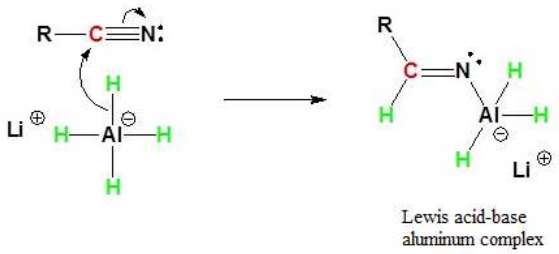
EXAMPLE 20.7.1



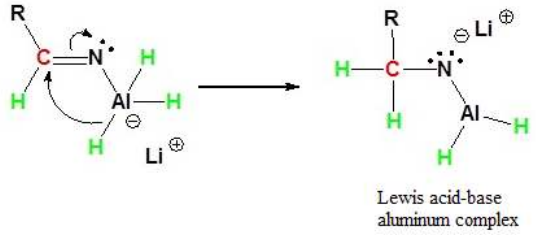
MECHANISM

During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. The imine ion is stabilized through formation of an anionic Lewis acid-base aluminum complex. The complex is vital for the continuation of the reaction because it shifts the negative charge from the nitrogen to the aluminum allowing for the imine carbon to remain electrophilic. Because the imine-aluminum complex still contains a pi bond and an electrophilic carbon, it can undergo a second nucleophilic addition of a hydride to form a dianion. The dianion is also stabilized through the formation of an anionic Lewis acid-base aluminum complex. During the aqueous work-up, the dianion is protonated by water to form a primary amine.

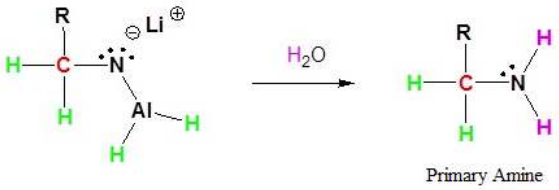
Step 1: Nucleophilic Attack by the Hydride



Step 2: Second nucleophilic attack by the hydride.

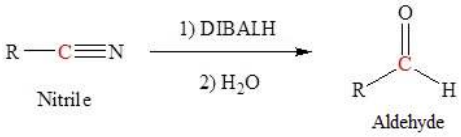


Step 3: Protonation by addition of water to give a primary amine

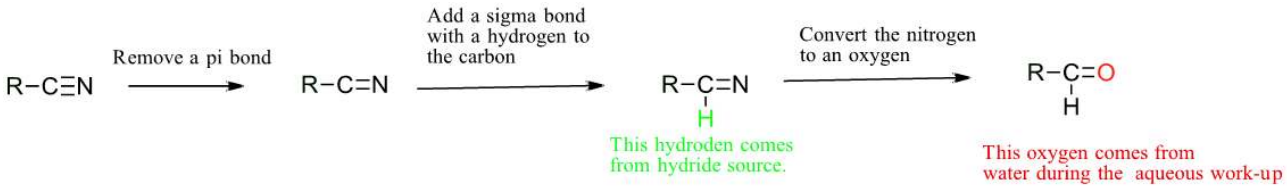


THE CONVERSION OF NITRILES TO ALDEHYDES BY REACTION WITH DIBALH

The use of DIBALH as a hydride source offers an efficient method for the synthesis of aldehydes. DIBALH only contains on hydride so the addition of one equivalent to a nitrile at low temperature (-78^{0}C) allows for the conversion to an aldehyde.

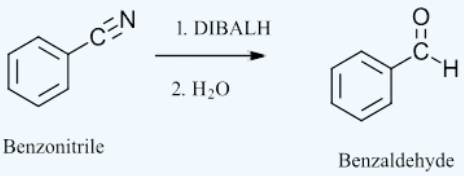


PREDICTING THE PRODUCT OF A REACTION WITH DIBALH



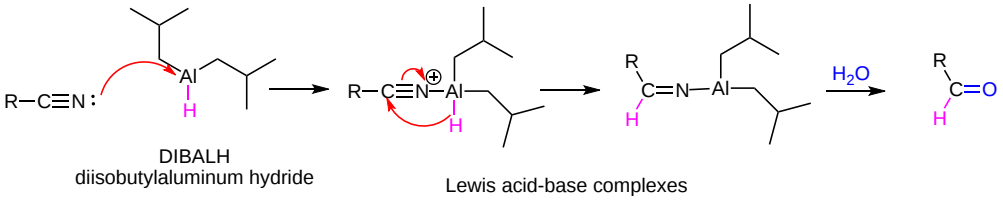
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EXAMPLE 20.7.1



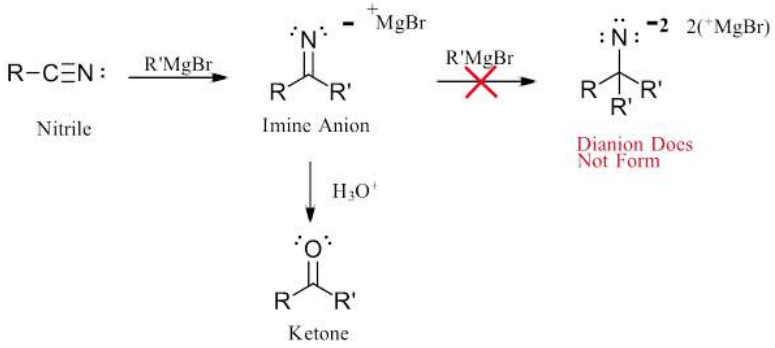
MECHANISM OF DIBALH REDUCTION OF NITRILES

The mechanism starts with the formation of a Lewis acid-base complex which increases the electrophilic character of the nitrile's carbon. The nucleophilic addition of a hydride forms an imine anion which is also stabilized through formation of a Lewis acid-base aluminum complex. Unlike the reduction with $LiAlH_4$, DIBALH only has a single hydride so a second nucleophlic addition to the imine anion does not occur. Subsequently, the imine anion undergoes hydrolysis during acidic aqueous work-up to from an aldehyde. The mechanism of imine anion hydrolysis is the reverse of an imine formation previously discussed.

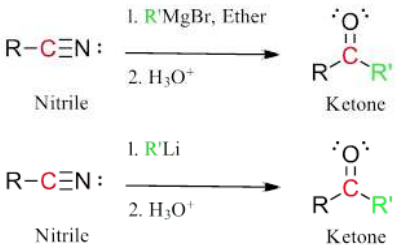


CONVERSION OF NITRILES TO KETONES WITH ORGANOMETALIC REAGENTS

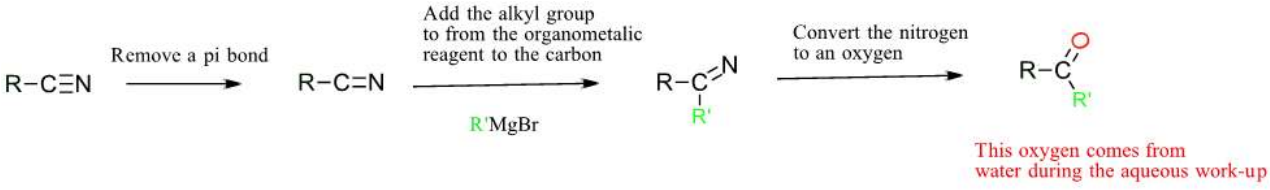
Some organometalic species, such as Grignard reagents or organolithium reagents, undergo nucleophilic addition to the electophillic carbon of a nitrile to form an intermediate imine anion. Despite the presence of a pi bond, the negative charge of the imine anion prevents any further nucleophilic additions. During an aqueous work-up, the imine anion is hydrolyzed by water to form a ketone.



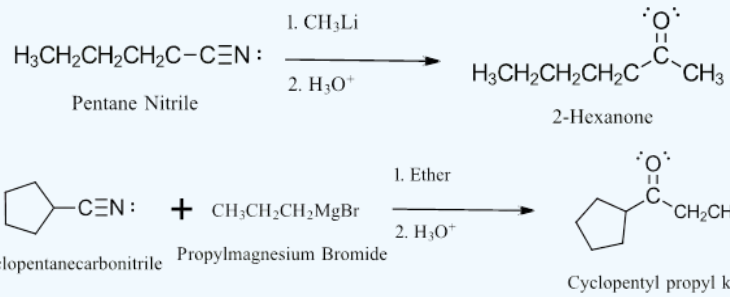
GENERAL REACTION



PREDICTING THE PRODUCT OF A REACTION WITH AN ORGANOMETALIC



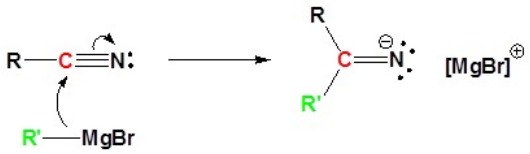
EXAMPLES



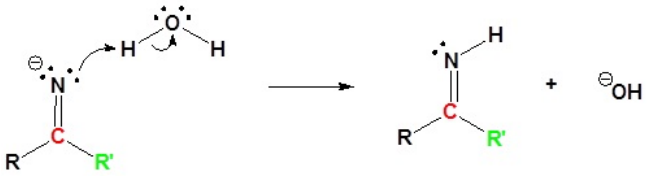
MECHANISM OF ORGANOMETALLIC ADDITION

The mechanism begins with the nucleophilic Grignard reagent reacting with the electrophilic carbon of the nitrile to form a salt of the imine anion. The imine salt is protonated to form an imine which is subsequently protonated to form a positively charged iminium ion. After nucleophilic attack by water and a proton transfer, the nitrogen from the nitrile is removed as a leaving group in the from of ammonia (NH_3). This step forms a protonated ketone called a ketonium ion which is subsequently deprotonated by ammonia to the neutral ketone and ammonium (NH_4^+).

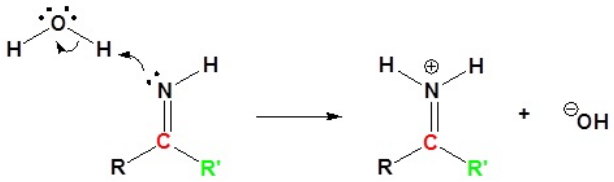
Step 1: Nucleophilic Attack by the Grignard Reagent to form an imine anion



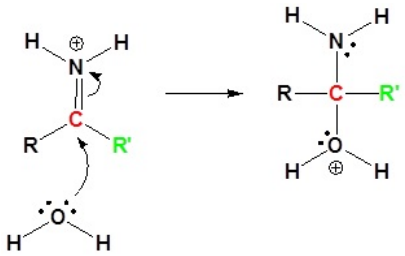
Step 2: Protonation to form an imine



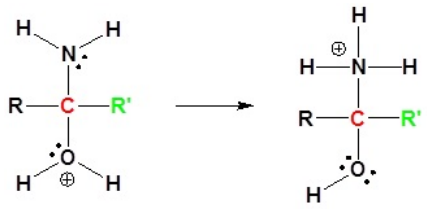
Step 3: Protonation to form an iminium ion



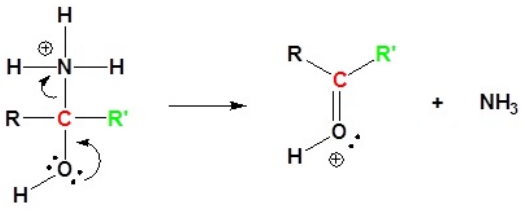
Step 4: Nucleophilic attack by water



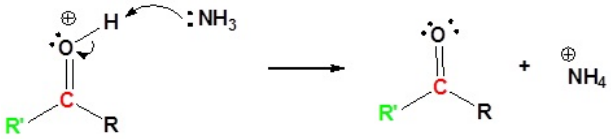
Step 5: Proton Transfer



Step 6: Removal of NH_3 as a leaving group to form a ketonium ion

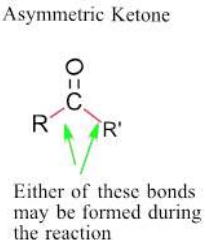


7) Deprotonation to form a ketone

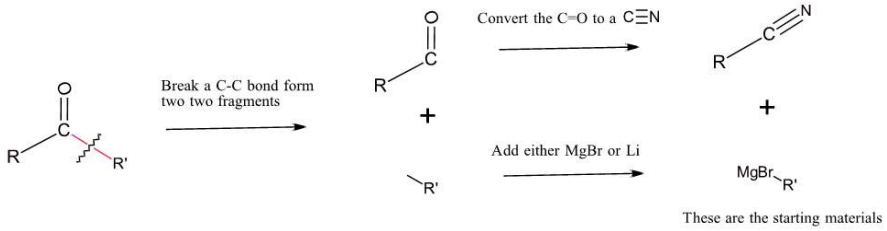


PLANNING THE SYNTHESIS OF A KETONE FROM A NITRILE

These reactions can be employed to plan synthetic routes to desired molecules from nitriles. Because a C-C bond is formed, the reaction of an organometallic reagent with nitrile is an effective method for the synthesis of ketones. Also, asymmetrical ketones offer the possibility of two separate synthesis routes.

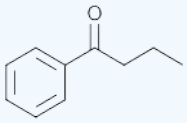


To plan a synthesis, we often think in reverse. Begin with the intended product (in this case the ketone). Break a C-C bond between the carbon in the carbonyl and an adjacent carbon. The fragment with the C=O becomes the nitrile starting material. The other fragment becomes either a Grignard or an organolithium reagent.



EXAMPLE 20.7.1

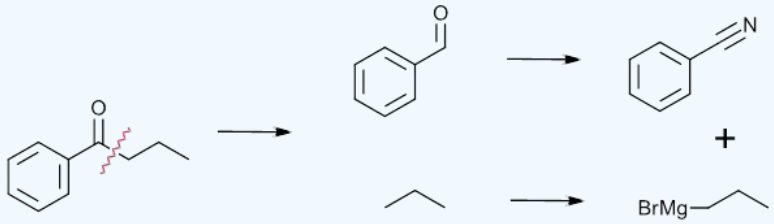
Plan a synthesis of the following molecule using the reaction of a organometallic reagent and a nitrile.



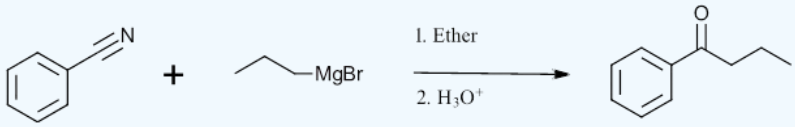
Solution

There are two possible pathways to synthesize this molecule.

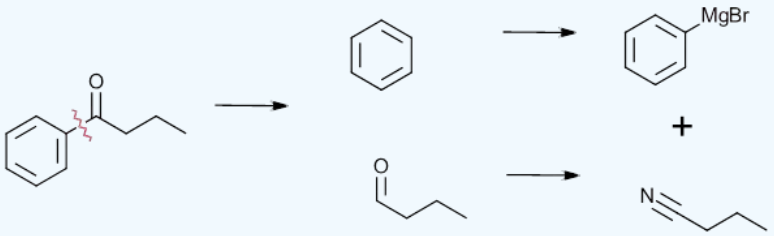
Solution 1



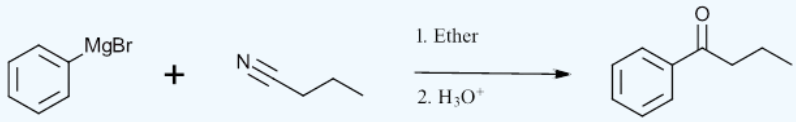
Pathway 1)



Solution 2



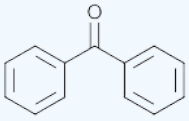
Pathway 2)



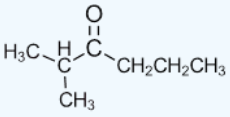
? EXERCISE 20.7.1

Show how the following compounds could be prepared from a nitrile:

a.

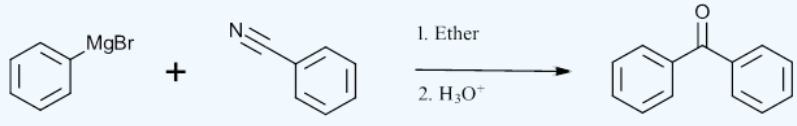


b.

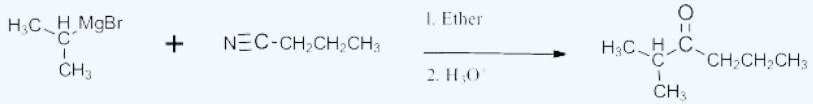


Answer

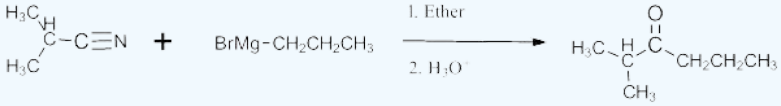
a.



https://chem.libretexts.org/@go/page/36556



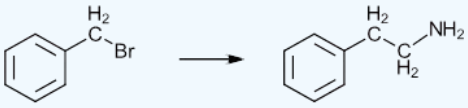
Or



b.

EXERCISE 20.7.2

Show how the following transformations could be preformed:

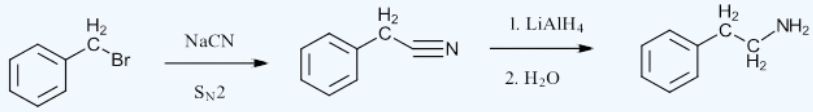


a.

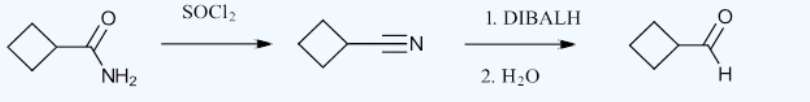


b.

Answer



a.



b.

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20.8: SPECTROSCOPY OF CARBOXYLIC ACIDS AND NITRILES

OBJECTIVES

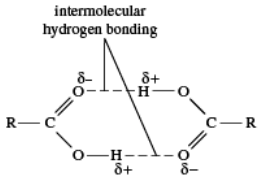
After completing this section, you should be able to

1. identify the two characteristic infrared absorptions displayed by all carboxylic acids.
2. state the approximate ^{1}H NMR absorption of a carboxylic acid proton.
3. use infrared and NMR spectroscopy data to assist in the identification of an unknown carboxylic acid, with or without the assistance of a table of characteristic absorptions.

SPECTROSCOPY OF CARBOXYLIC ACIDS

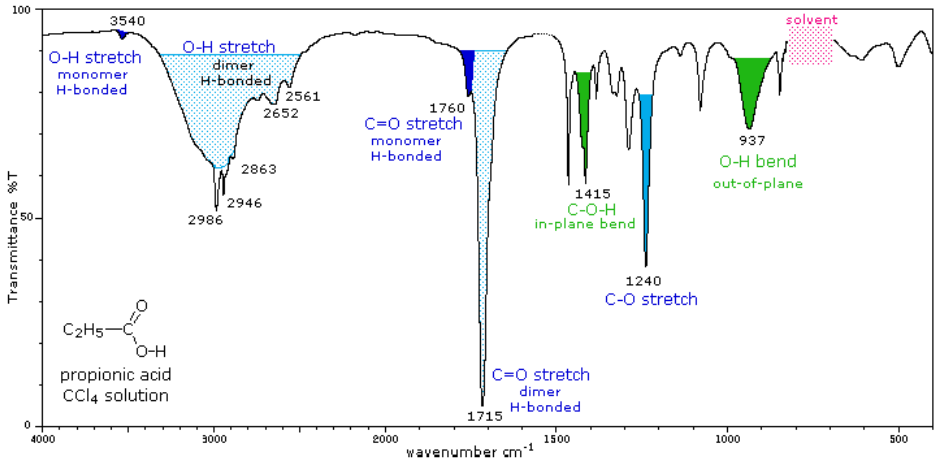
INFRARED SPECTROSCOPY

The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of propionic acid (propanoic acid) dissolved in CCl_4, shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases.



The Hydrogen Bonding Dimer of Carboxylic Acids

The O-H stretching absorption for such dimers is very strong and broad, extending from 2500 to 3300 cm^{-1}. This absorption overlaps the sharper C-H stretching peaks, which may be seen extending beyond the O-H envelope at 2990, 2950 and 2870 cm^{-1}. The smaller peaks protruding near 2655 and 2560 cm^{-1} are characteristic of the dimer. In ether solvents a sharper hydrogen bonded monomer absorption near 3500 cm^{-1} is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

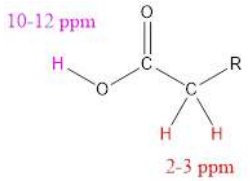


The Infrared Spectrum of Propanoic Acid

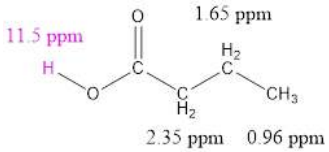
^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

The acidic O-H protons of carboxylic acids are highly deshielded due to the electronegativity of oxygen and anisotropy from the C=O carbonyl bond. They tend to be among the least shielded protons appearing far downfield in the 10–12 ppm region which is considered distinctive for carboxylic acids. Due to hydrogen bonding the proton of a carboxylic acid often appears as a broad singlet and adding D_2O causes the signal to disappear due to hydrogen-deuterium exchange. Protons on carbons adjacent to a carboxylic acid absorb in the 2-3 ppm

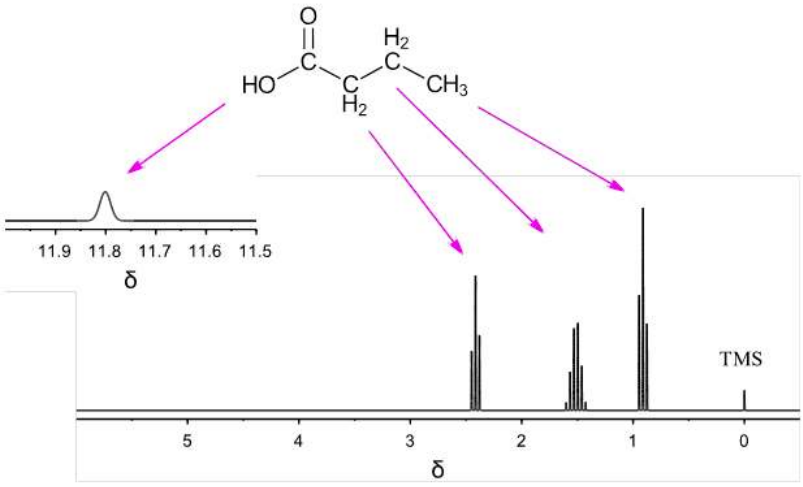
region. Some deshielding occurs due to the fact that the carbonyl oxygen is pulling electron density away from the carbonyl carbon which inductively pulls electron density away from the adjacent carbon.



The Typical ^{1}H Peaks for a Carboxylic Acid



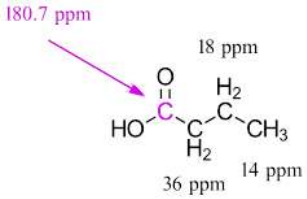
The ^{1}H Peaks for Butanoic Acid



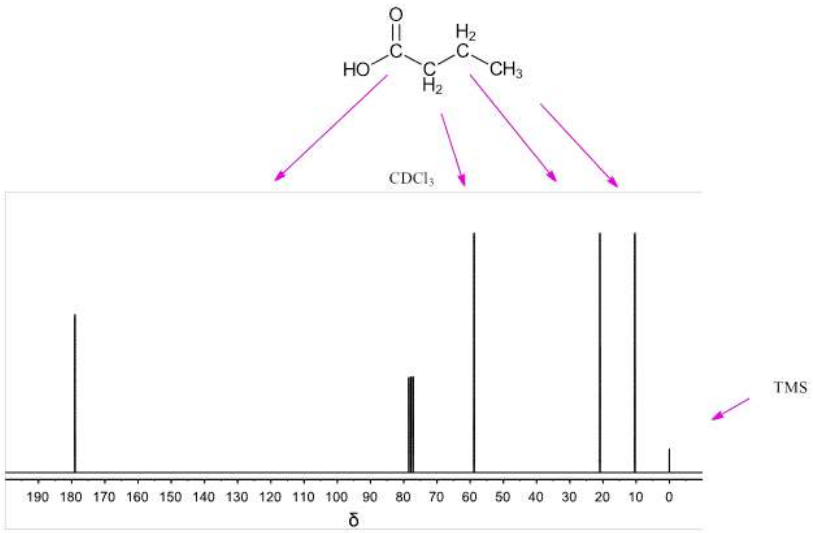
A ^{1}H NMR Spectra for Butanoic Acid

^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

The carbonyl carbon of a carboxylic acid is strongly deshielded (160-180 ppm) due to the presence of the highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm).



The ^{13}C Peaks for Butanoic Acid



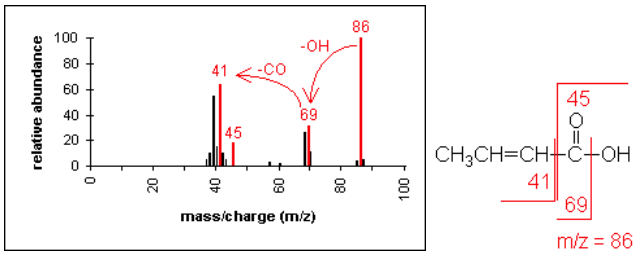
A ^{13}C NMR Spectra for Butanoic Acid

UV/VIS SPECTROSCOPY

Without additional conjugation, carboxylic acids absorb at about 210 nm, which is too low to be useful.

MASS SPECTROMETRY

In short chain acids, peaks due to the loss of OH (molecular ion less 17) and COOH (molecular ion less 45) are prominent due to cleavage of bonds next to C=O.

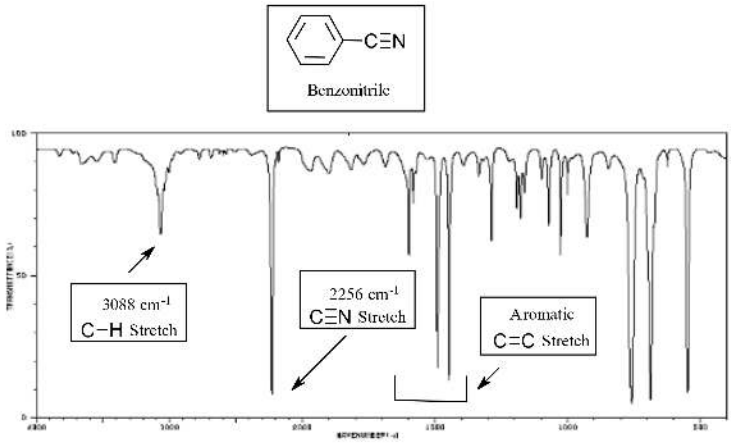


The Fragmentation of 2-Butenoic acid ($C_4H_6O_2$): MW = 86.09

SPECTROSCOPY OF NITRILES

INFRARED SPECTROSCOPY

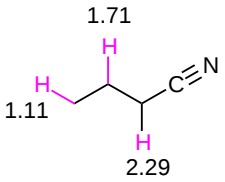
The CN triple bond stretch of nitriles appears in a distinctive region of an IR spectra, near 2250 cm^{-1}. One of the only other absorptions to appear in this region is the CC triple bond stretch of an alkyne (2100-2250 cm^{-1}).



Infrared Spectrum of Benzonitrile

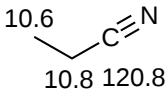
^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

Protons on carbons adjacent to a nitrile absorb in the 2-3 ppm region. Some deshielding occurs due to the fact that the sp hybridized nitrile carbon is more electronegative than the adjacent sp^3 hybridized carbon.



^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

The nitrile carbon absorbs in the 115–120 ppm region which not as far downfield as a typical carbonyl carbon (180-220 ppm).

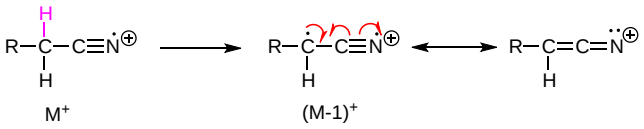


UV/VIS SPECTROSCOPY

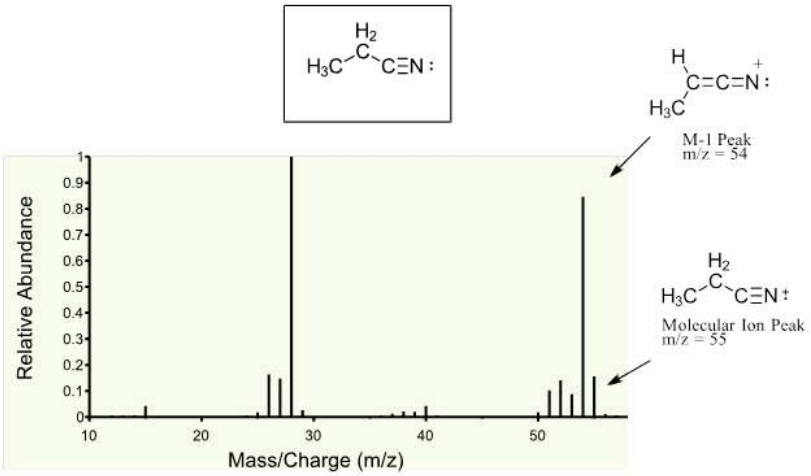
Most nitriles do not show absorption above 200 nm which does not make UV/Vis spectroscopy a useful tool to characterize them.

MASS SPECTROMETRY

The molecular ion (M^+) peaks of simple nitriles are often weak or not present in a mass spectra. There is often a M-1 peak due to the loss of a -H.



Mechanism for the Formation of a M-1 Peak in Mass Spectra

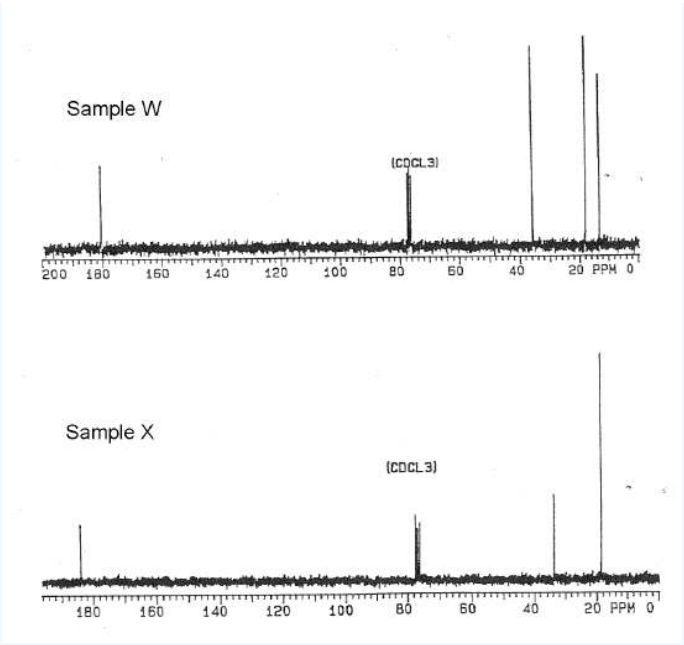


Mass Spectra of Propanenitrile

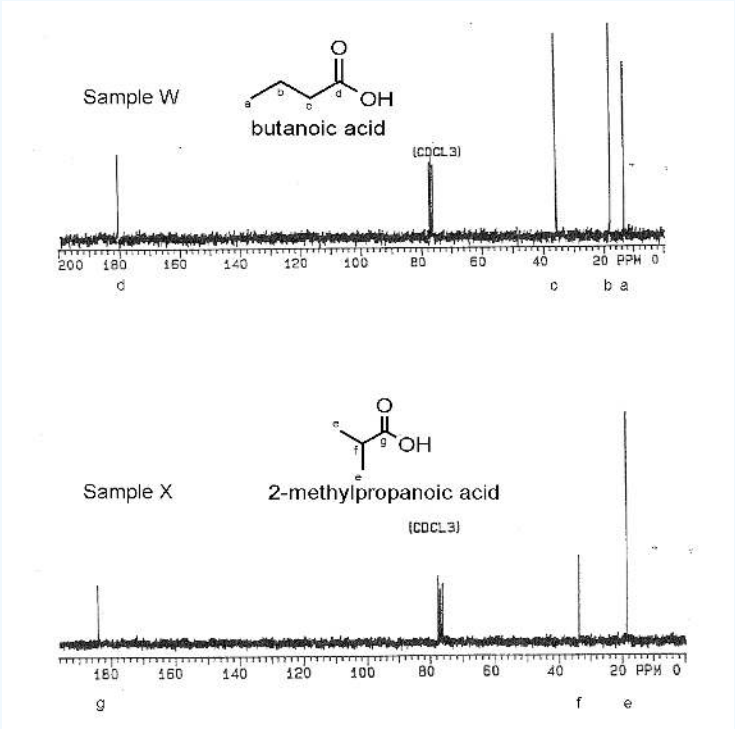
? EXERCISE

Sample W is a reactant for a wide range of biochemical processes. Sample X was isolated from vanilla beans. Elemental analysis indicated the compounds are structural isomers with the composition: 54.52% C, 9.16% H and 36.32% O. The IR spectrum for each compound showed a broad absorption from 3500 - 2500 cm^{-1} and a strong band near 1710 cm^{-1}. The ^{1}H NMR is being serviced, so only the ^{13}C NMR spectra shown below were available.

Name and draw the bond-line structures for Samples W and X and correlate the ^{13}C NMR spectral signals to their respective compounds.



Answer



IR spectrum of benzonitrile. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

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20.S: CARBOXYLIC ACIDS AND NITRILES (SUMMARY)

CONCEPTS & VOCABULARY

20.0 Chapter Objectives and Introduction to Carboxylic Acids

- Carboxylic acids are defined as molecules that have a hydroxyl group bonded to a carbonyl group (RCOOH).
- Fatty acids are naturally occurring carboxylic acids that are important components of lipids.
- Fatty acids can either be saturated (all carbon-carbon bonds are single bonds) and unsaturated (one or more carbon-carbon double bonds).
- Several other functional groups can be prepared from carboxylic acids and are considered derivatives (acyl halides, anhydrides, esters, amides and nitriles).

20.1 Naming Carboxylic Acids and Nitriles

- Carboxylic acids are named following IUPAC rules with ending -oic acid.
- When carboxylic acids are named as an attachment to a ring, add -carboxylic acid to the name of the cyclic compound.
- Nitriles are named following IUPAC rules with the ending -nitrile or -carbonitrile.

20.2 Structure and Properties of Carboxylic Acids

- Carboxylic acids have trigonal planar shape around the carbonyl carbon and due to resonance structures, all the atoms of the functional group are co-planar.
- Conjugation in carboxylic acids increases acidity of the hydroxyl hydrogen compared to alcohols. The conjugate base (carboxylate) is stabilized by resonance.
- Carboxylic acids form hydrogen bonded dimers yielding higher boiling points than for other molecules of similar size.
- Small carboxylic acids are often soluble in water due to hydrogen bonding. Larger carboxylic acids are often slightly soluble in water, though when converted to a carboxylate salt by treating with base, become water soluble.

20.3 Biological Acids and the Henderson-Hasselbalch Equation

- Carboxylic acids are fully protonated in acidic solutions.
- Carboxylic acids are fully dissociated in basic solutions.
- The Henderson-Hasselbalch equation can be used to relate pH, pKa and ratio of concentrations of acid and conjugate base.

20.4 Substituent Effects on Acidity

- Withdrawing groups (through inductive or resonance effects) can stabilize carboxylates, increasing acidity of carboxylic acids.
- Donating groups (through inductive or resonance effects) destabilize carboxylates, decreasing acidity of carboxylic acids.
- Nearly all substituents in ortho positions increase acid strength whether donating or withdrawing, this is called the *ortho*-effect.

20.5 Preparing Carboxylic Acids

- Carboxylic acids can be prepared through oxidation of several functional groups including: 1° alcohols, aldehydes, alkyl arene side chains, and alkenes.
- Carboxylic acids can also be prepared by carboxylation of Grignard reagents and hydrolysis of nitriles.

20.6 Reactions of Carboxylic Acids: An Overview

- There are four main categories of carboxylic acid reactions:
  - Acid/base reaction (salt formation)
  - Nucleophilic acyl substitution
  - Reduction
  - Substitution alpha to the carbonyl

20.7 Chemistry of Nitriles

- Nitriles have linear geometry due to the *sp* hybrid orbitals on carbon and nitrogen.
- Nitriles are less basic than amines.
- Nitriles can be prepared from aldehydes, ketones, or amides.
- Nitriles react similarly to carbonyl compounds where nucleophiles will attack the carbon end of the nitrile.
- Nitriles can be hydrolyzed to carboxylic acids under basic or acidic conditions.
- Nitriles can be reduced to amines by hydride reduction.
- Nitriles can be converted to aldehyde by reaction with DIBALH.

- Nitriles can be converted to ketones by reaction with organometallic compounds.

20.8 Spectroscopy of Carboxylic Acids and Nitriles

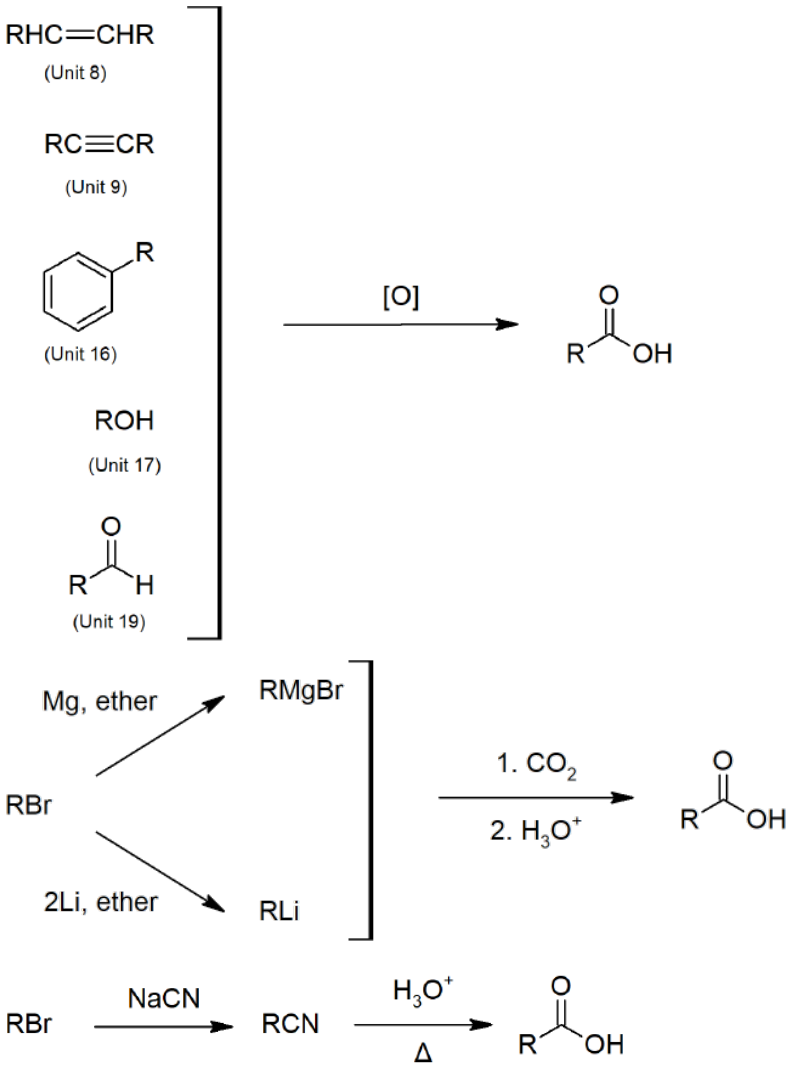
- IR of carboxylic acids typically show a very strong and broad OH stretch from about 2500 to 3300 cm^{-1} as well as a strong carbonyl stretch around 1710 cm^{-1}.
- ^{1}H NMR of carboxylic acids show the OH proton between 10-12 ppm as well as hydrogens on carbon adjacent to the carbonyl around 2-3 ppm.
- ^{13}C NMR of carboxylic acids show the carbonyl carbon at 160-180 ppm.
- Mass spectra of carboxylic acids often have fragments for OH (loss of 17) and COOH (loss of 45).
- The most identifying characteristic of IR of nitriles is the CN triple bond stretch which appears near 2250 cm^{-1}.
- ^{1}H NMR of nitriles show protons on the carbon next to the nitrile at around 2-3 ppm.
- ^{13}C NMR of nitriles show the nitrile carbon in the 115-120 ppm range.
- Mass spectra of nitriles will often not have a visible molecular ion, but instead exhibit a strong M-1 peak.

SKILLS TO MASTER

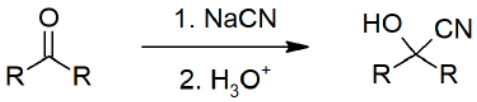
- Skill 20.1 Name carboxylic acids and nitriles using IUPAC rules.
- Skill 20.2 Draw the structure of carboxylic acids and nitriles from the IUPAC name.
- Skill 20.3 Describe the geometries and approximate bond angles of carboxylic acids and nitriles.
- Skill 20.4 Explain the acidity of carboxylic acids based on conjugate base stabilization.
- Skill 20.5 Explain physical properties of carboxylic acids.
- Skill 20.6 Describe the structure of carboxylic acids in buffered solutions.
- Skill 20.7 Use the Henderson-Hasselbach equation to relate pH, pK_a, and acid/conjugate base concentrations.
- Skill 20.8 Explain inductive effects on acidity.
- Skill 20.9 Explain relative acidity of aromatic acids.
- Skill 20.10 Draw mechanisms for preparing carboxylic acids including:
  - Oxidations
  - Carboxylation of Grignard reagents
  - Hydrolysis of Nitriles
- Skill 20.11 List the four categories of carboxylic acid reactions.
- Skill 20.12 Draw reactions for preparing nitriles including formation from:
  - aldehyde or ketone
  - 1° amide
- Skill 20.13 List general reactions of nitriles.
- Skill 20.14 Draw mechanisms for reactions of nitriles including:
  - Hydrolysis to acids (acidic and basic mechanisms)
  - Reduction to 1° amines
  - Conversion to aldehyde by reaction with DIBALH.
  - Conversion to ketones by reaction with organometallic compounds.
- Skill 20.15 Plan a synthesis of a ketone from a nitrile.
- Skill 20.16 Use IR, NMR and MS to identify carboxylic acids and nitriles.

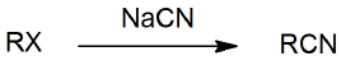
SUMMARY OF REACTIONS

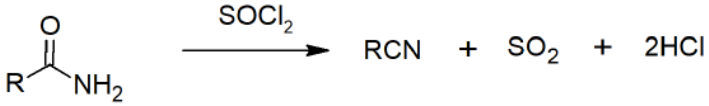
Carboxylic Acid Preparation



Nitrile Preparation

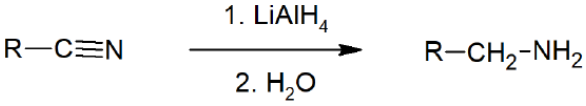


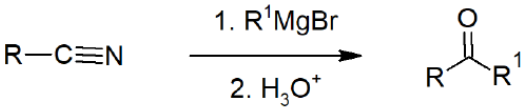




Reaction of Nitriles

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CHAPTER OVERVIEW

21: CARBOXYLIC ACID DERIVATIVES- NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

The compounds discussed in this chapter are all considered to be derived from carboxylic acids, and include acid halides, acid anhydrides, esters and amides (thioesters and acyl phosphates are also briefly mentioned). As you proceed through the chapter, you should be looking for similarities in behaviour among the various classes of compounds. These similarities can be readily understood once you appreciate the fact that, in most of their reactions, carboxylic acid derivatives react via the nucleophilic acyl substitution mechanism.

In this chapter, we describe the nomenclature of the various types of carboxylic acid derivatives, and explain the relative reactivity of these compounds in terms of resonance contributions to the ground state of each type of compound.

We describe the reactions of carboxylic acids, acid halides, acid anhydrides, esters, amides, polyamides and polyesters in detail, and discuss the biological importance of thiol esters briefly. The chapter concludes with a look at how infrared spectroscopy and NMR spectroscopy can be used in the identification of unknown carboxylic acid derivatives.

21.0: Chapter Objectives and Introduction to Carboxylic Acid Derivatives
21.1: Naming Carboxylic Acid Derivatives
21.2: Nucleophilic Acyl Substitution Reactions
21.3: Nucleophilic Acyl Substitution Reactions of Carboxylic Acids
21.4: Chemistry of Acid Halides
21.5: Chemistry of Acid Anhydrides
21.6: Chemistry of Esters
21.7: Chemistry of Amides
21.8: Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives
21.9: Polyamides and Polyesters - Step-Growth Polymers
21.10: Spectroscopy of Carboxylic Acid Derivatives
21.S: Carboxylic Acid Derivatives (Summary)

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21.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this chapter are used in conjunction with any of the reactions described in previous chapters.
3. solve road-map problems that require a knowledge of the chemistry of carboxylic acid derivatives.
4. define, and use in context, any of the key terms introduced in this chapter.

After completing this section, you should be able to

1. identify, and give an example of
   a. an acid halide.
   b. an acid anhydride.
   c. an ester.
   d. an amide.
2. write the general form of a nucleophilic acyl substitution reaction.

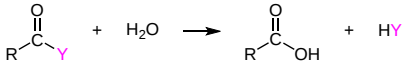
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

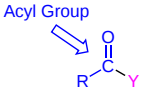
- acyl derivative
- nucleophilic acyl substitution reaction

CARBOXYLIC ACID DERIVATIVES

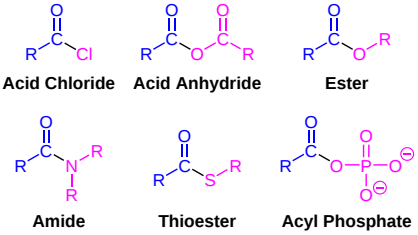
Carboxylic acid derivatives are formed when the hydroxyl group of a carboxylic acid is replaced by some other group, **Y**, such that it can be hydrolyzed back to the acid.



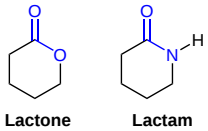
These compounds are also called the **acyl derivatives** of a carboxylic acid because they usually contain an acyl group bonded to a substituent which can act as a leaving group in a nucleophilic acyl substitution reaction.



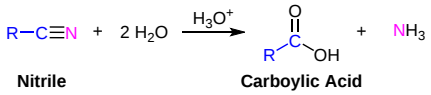
Although there are many types of carboxylic acid derivatives known, this chapter focuses on six: acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.



Cyclic esters and amides are referred to as **lactones** and **lactams**, respectively.



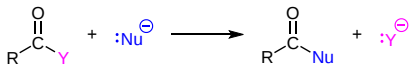
Nitriles, $RC \equiv N$, discussed in the last chapter, are often are considered to be carboxylic acid derivatives, even though the acyl group is not present, because hydrolysis of nitriles leads to carboxylic acids.



Nitrile **Carboylic Acid**

NUCLEOPHILIC ACYL SUBSTITUTION REACTION

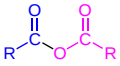
The main type of reaction for carboxylic acid derivatives is called nucleophilic acyl substitution. This reaction involves the replacement of the **Y** group by attack of a nucleophile $Nu^{\ominus}$ at the carbonyl carbon with subsequent cleavage of the **C—Y** bond.



Y = Leaving Group

PHYSICAL PROPERTIES OF CARBOXYLIC ACID DERIVATIVES

The intermolecular forces of the respective acyl group combine with the size and structure of the Y-group to determine the physical properties of the the carboxylic acid derivatives as shown in the summary below.

Name	Structure	Intermolecular Forces	Relative Boiling Point (°C)	Soluble in H_2O	General Comments
Acid Chloride		Polar, No H-Bonding	51	No	Acrid Piercing Odors
Acid Anhydride		Polar, No H-Bonding	140	No	Acrid Piercing Odors
Ester		Polar, No H-Bonding	57	No	Volatile Fragrant Liquids
Carboxylic Acid		H-Bonding Dimer	118	Yes, if C < 5	Acrid Piercing Odors
Amide		Complex H-Bonding	221	Yes if C < 4	Biological Important (Proteins)
Nitrile		Among the most polar compounds with out H-Bonding	82	Yes if C < 4	CH_3CN is a useful polar aprotic solvent

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21.1: NAMING CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

After completing this section, you should be able to

1. provide a satisfactory name for an acid halide of given structure.
2. draw the condensed or shorthand structure of an acid halide, given either its commonly used or systematic name.
3. provide a satisfactory name for an acid anhydride of given structure.
4. draw the condensed or shorthand structure of an acid anhydride, given either its trivial or IUPAC name.
5. provide an acceptable name for an amide of given structure.
6. draw the condensed or shorthand structure of an amide, given its trivial or IUPAC name.
7. provide an acceptable name for an ester of given structure.
8. draw the condensed or shorthand structure of an ester, given either its trivial or IUPAC name.
9. provide an acceptable name for a thioester of given structure.
10. draw the condensed or shorthand structure of a thioester, given its trivial or IUPAC name.
11. provide an acceptable name for an acyl phosphate.
12. draw the condensed or shorthand structure of an acyl phosphate, given either its trivial or IUPAC name.

NOMENCLATURE OF ACID HALIDES, RCOX

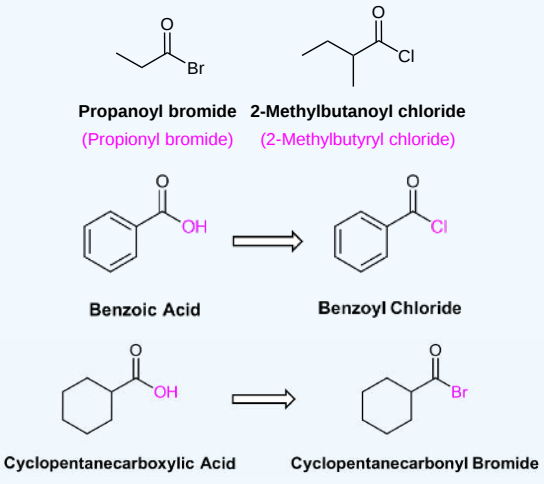
The nomenclature of acid halides starts with the name of the corresponding carboxylic acid. If the corresponding carboxylic acid has an **–oic acid** or **–ic acid** ending it is removed and replaced with the ending **-oyl** followed by the first syllable of the name of the halogen along with an **–ide** ending.

However there are a number of specific exceptions where IUPAC allows the ending **-yl** to be used instead. Examples are formic ⇒ formyl, acetic ⇒acetyl, propionic ⇒propionyl, butyric ⇒butyryl, oxalic ⇒ oxalyl, and succinic ⇒ succinyl.

When the corresponding acid includes a **-carboxylic acid** ending, it is removed and replaced with the ending **-carbonyl.** This is followed by the first syllable of the name of the halogen along with an **–ide** ending

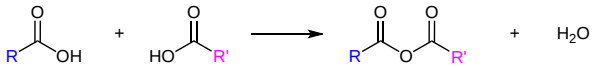
The carbonyl carbon is given the #1 location number. The acid halide functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

EXAMPLE 21.1.1



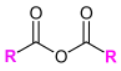
NOMENCLATURE OF ANHYDRIDES, RCO_2COR'

An anhydride functional group results when two carboxylic acids combine and lose water (anhydride = without water). The names of anhydrides come from the names of the two combined carboxylic acids. The carbonyl carbon is given the #1 location number on both chains. The anhydride functional group is assumed to be on the end of the each parent chain, so it is not necessary to include the functional group location number in the name.



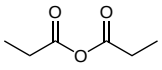
Carboxylic Acids **Anhydride** **Water**

Symmetrical anhydrides made from unsubstituted carboxylic acids and cyclic anhydrides made from dicarboxylic acids are named based on their corresponding carboxylic acid. The ending **-acid** is replaced with **-anhydride**. This is true for both the IUPAC and common nomenclature. An anhydride is symmetrical when it is acyclic and the acyl R groups are the same.

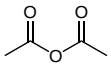


Symmetrical Anhydride

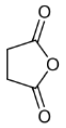
EXAMPLE



Propanoic anhydride
(Propionic anhydride)

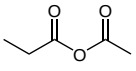


Ethanoic anhydride
(Acetic anhydride)

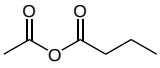


Succinic Anhydride

An unsymmetrical anhydride is created from two different carboxylic acids. For unsymmetrical anhydrides, name both acids *alphabetically* with a space between them. Then add the end word **anhydride**.



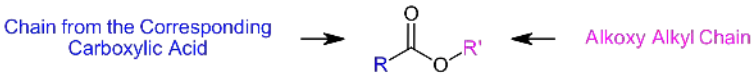
Ethanoic propanoic anhydride
(Acetic propionic anhydride)



Butanoic ethanoic anhydride
(Acetic butyic anhydride)

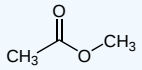
NOMENCLATURE OF ESTERS, RCO_2R'

Esters consist of two distinctly different carbon chains which need to be named separately. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the singly bonded oxygen, is called the alkoxy alkyl chain.

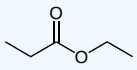


Esters are named as if the alkoxy alkyl chain is a substituent **(Prefix + yl)**. This is followed by the name of the corresponding carboxylic acid part of the ester with **-ic acid** or **-oic acid** replaced with the ending **–ate**. The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

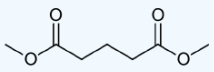
✔ EXAMPLE 21.1.2



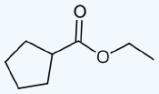
Methyl ethanoate



Ethyl propanoate



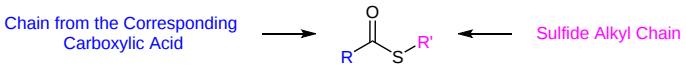
Dimethyl glutarate



Ethyl cyclopentanecarboxylate

NOMENCLATURE OF THIOESTERS, RCOSR'

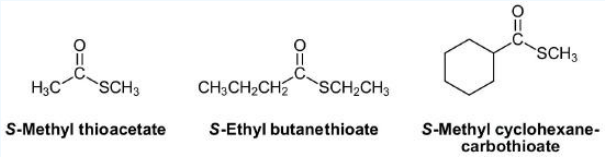
Thioesters have two distinctly different carbon chains. One carbon chain is from the corresponding carboxylic acid and the other chain, attached to the sulfur, is called the sulfide alkyl chain.



Thioesters are named as if the sulfide alkyl chain is a substituent with the letter *S* preceding **(*S*-Prefix + yl)**. This is followed by the parent chain of the corresponding carboxylic acid, named as an alkane with the ending **–thioate** added. For thioesters attached to a carbon ring the ending **-carboxylic acid** is replaced with **-carbothioate**. When using the common names of the carboxylic acid the **-ic acid** ending is replaced **-ate** and the prefix **thio-** is added.

The carbonyl carbon is given the #1 location number. The carbonyl functional group is assumed to be on the end of the parent chain, so it is not necessary to include the functional group location number in the name.

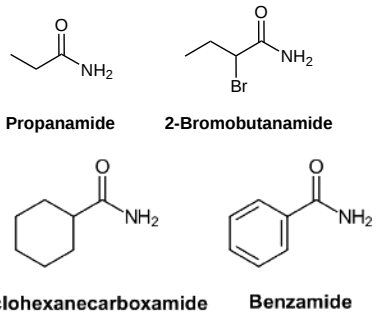
EXAMPLE 21.1.3



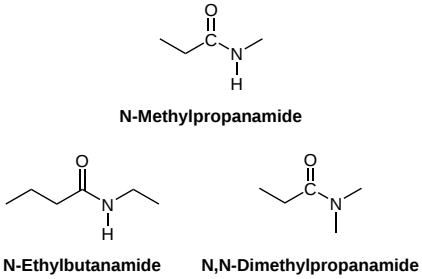
NOMENCLATURE OF AMIDES, $RCONH_2$, RCONHR', RCONR'R''

Primary amides ($RCONH_2$) are named by changing the name of the corresponding acid by removing the **-oic acid** or **-ic acid** endings and adding **-amide**. Amides derived from a cyclic carboxylic acid have the **-carboxylic acid** ending replaced with **-carboxamide**. The carbonyl carbon is given the #1 location number. It is not necessary to include the location number in the name because it is assumed that the functional group will be on the end of the parent chain.

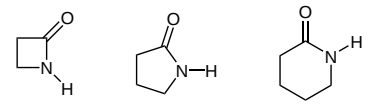
EXAMPLE



Secondary (RCONHR') and tertiary (RCONR'R'') amides are named by using an upper case N to designate that the alkyl groups are attached to the nitrogen atom. These alkyl groups are named as substituents **(Prefix + yl)**.



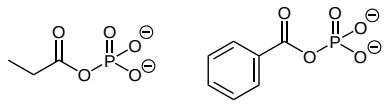
Cyclic amides are called lactams. A Greek letter identifies the location of the nitrogen on the alkyl chain relative to the carboxyl carbonyl group.



b-Lactam g-Lactam d-Lactam

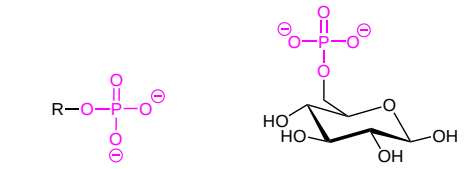
NOMENLCATURE OF ACYL PHOSPHATES, $RCOOPO_3^{2-}$

Acyl phosphates are named following the rules as acid halides except name of the halogen is replaced with the word **phosphate**. If there is an alkyl group attached to one of the phosphate oxygens, it is named as a substituent **(parent + yl)** and listed before the end word phosphate.



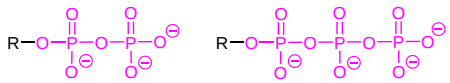
Propanoyl Phospate **Benzoyl Phosphate**

When a phosphate ion is attached to a carbon atom on an organic molecule, the chemical linkage is referred to as a phosphate ester, and the whole species is called an organic monophosphate. Glucose-6-phosphate is an example.



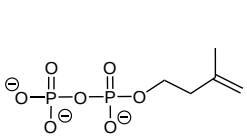
Organic monophosphate **Glucose-6-phosphate**

If an organic molecule is linked to two or three phosphate groups, the resulting species are called organic diphosphates and organic triphosphates.

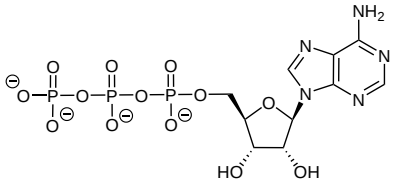


Organic diphosphate (ROPP) **Organic triphosphate (ROPPP)**

Isopententyl diphosphate and adenosine triphosphate (ATP) are good examples:

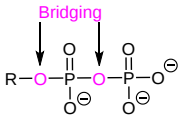


Isopentenyl diphosphate

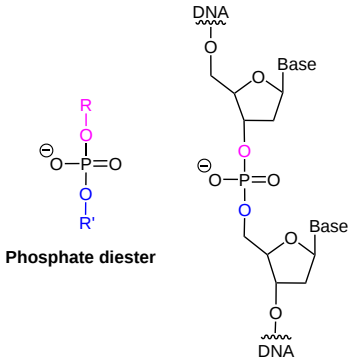


ATP

Oxygen atoms in phosphate groups are referred to either 'bridging' and 'non-bridging', depending on their position. An organic diphosphate has two bridging and five non-bridging oxygens.

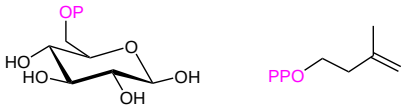


When a single phosphate is linked to two organic groups, the term 'phosphate diester' is used. The backbone of DNA is composed of phosphate diesters.



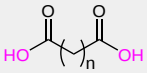
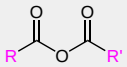
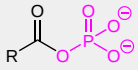
The term 'phosphoryl group' is a general way to refer to all of the phosphate-based groups mentioned above.

Phosphate groups on organic structures are sometimes abbreviated simply as 'P', a convention that we will use throughout this text. For example, glucose-6-phosphate and isopentenyl diphosphate are often depicted as shown below. Notice that the 'P' abbreviation includes the oxygen atoms and negative charges associated with the phosphate groups.



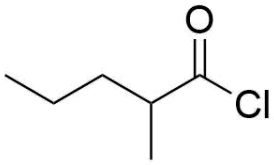
Glucose-6-phosphate **Isopentenyl diphosphate**

Nomenclature of Carboxylic Acids and Carboxylic Acid Derivatives

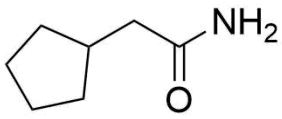
Functional Group	Structure	Suffix Name
Carboxylic acid		-oic acid
Carboxylate		-oate
Ester		-oate
Dicarboxylic acid		-dioic acid
Acyl halide		-oyl halide
Anhydride		-ic anhydride
Amide		-an amide
Acyl Phosphate		-oyl phosphate
Nitrile	R—C≡N	-ane nitrile

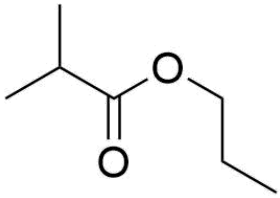
EXERCISES

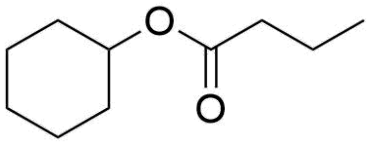
1) Name the following compounds using IUPAC conventions

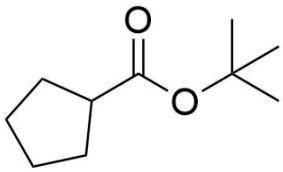


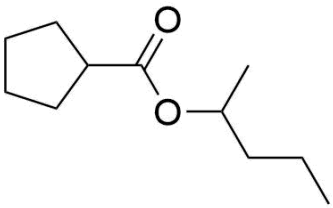
(a)

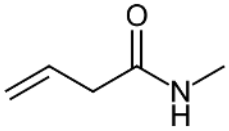
(b) 

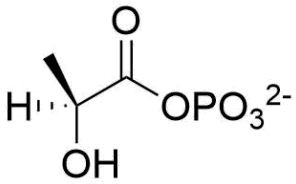
(c) 

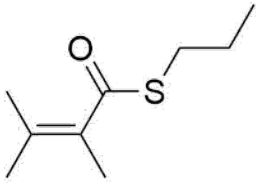
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

2) Draw structures corresponding to the following names:

a. benzoic anhydride
b. phenyl hexanoate
c. methyl benzoate
d. 3-chloro-N-ethylbenzamide
e. pentanamide
f. N-phenylethanamide

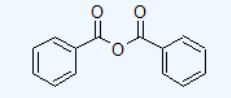
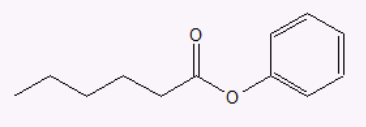
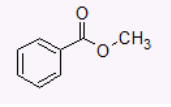
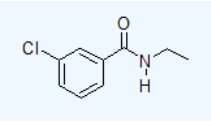
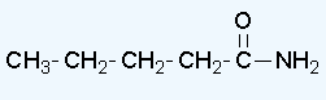
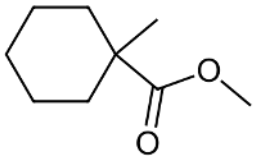
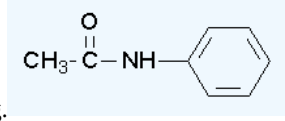
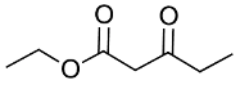
g. Methyl 1-methylcyclohexanecarboxylate
h. Ethyl 3-oxopentanoate
i. *S*-Methyl *p*-bromothiobenzoate
j. Formic propanoic anhydride
k. cis-2-Methylcyclopentanecarbonyl bromide

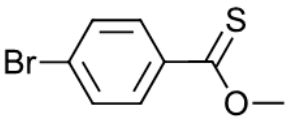
SOLUTIONS

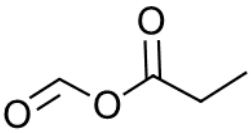
1)

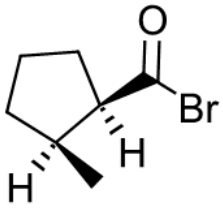
a. 2-methylpentanoyl chloride
b. 2-cyclopentylacetamide
c. propyl 2-methylpropanoate
d. cyclohexylbutanoate
e. sec-butyl cyclopentanecarboxylate
f. 1-methylbutylcyclopentane carboxylate
g. N-methyl-3-butenamide
h. (S)-2-hydroxypropanoyl phosphate
i. *S*-propyl 2,3-dimethyl-2-butenethioate

2)

a. 
b. 
c. 
d. 
e. 
f. 
g. 
h. 

i. 

j. 

k. 

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21.2: NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS

OBJECTIVES

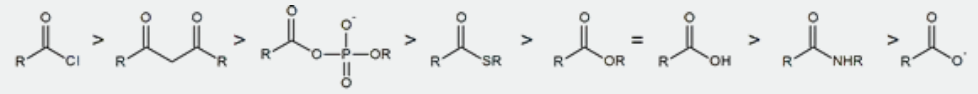
After completing this section, you should be able to

1. compare the reactions of carboxylic acid derivatives with nucleophiles to the reactions of aldehydes and ketones with nucleophiles.
2. arrange a given list of carboxylic acid derivatives in order of increasing or decreasing reactivity towards nucleophiles.
3. explain the difference in reactivity towards nucleophiles of two or more given carboxylic acid derivatives.
4. explain why esters and amides are commonly found in nature, but acid halides and acid anhydrides are not.

STUDY NOTES

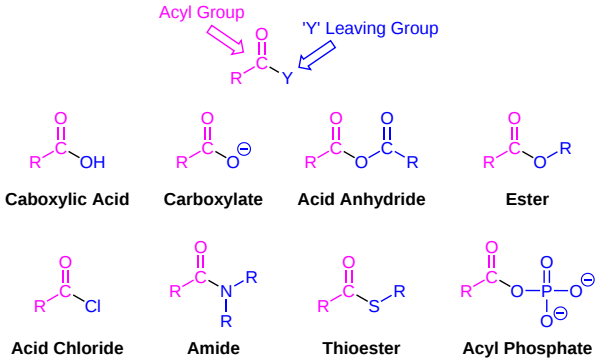
The general nucleophilic acyl substitution reaction, and its mechanism, were discussed earlier in "III. General Reactions of Carbonyl Compounds." Review if necessary.

The reading describes the relative reactivities of "biologically relevant acyl groups." Both acid anhydrides and acid halides readily react with water and cannot exist for any length of time in living organisms. The following scheme illustrates the relative reactivities of most carboxylic acid derivatives that you will encounter.



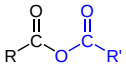
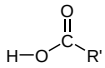
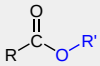
CARBOXYLIC ACID DERIVATIVES AND ACYL GROUPS

Carboxylic acid derivatives can be distinguished from aldehydes and ketones by the presence of a group containing an electronegative heteroatom - usually oxygen, nitrogen, sulfur or phosphorus – bonded directly to the carbonyl carbon and represented by the symbol **Y**. The rest of the carboxylic acid derivative is called the **acyl group** which is made up of the carbonyl group and the attached alkyl group (R). Being electronegative, the Y group has the potential of receiving electrons from the alkoxide intermediate created during a nucleophilic acyl substitution and acting as a leaving group. Elimination of a leaving group allows for carbonyl bond reformation and C-Y bond cleavage to complete a substitution reaction.



The stability of a negative charge on a Y group can be gauged by the pK_a of its corresponding conjugate acid (HY). A low conjugate acid pK_a implies that the Y leaving group is a weak base with a stable negative charge and thus would make an efficient leaving group. Likewise, a high conjugate acid pK_a means the Y group would likely make a poor leaving group. As shown in the table below, the conjugate acids of the possible carbide ($R:^-$) and hydride ($H:^-$) leaving groups of aldehydes and ketones have a relatively high pK_a, while those of the Y leaving groups of carboxylic acid derivatives are much lower. In fact, the stability of the leaving groups is an important factor in determining the reactivity of different carboxylic acid derivatives toward nucleophilic acyl substitutions. Based on the pK_a data we can deduce that amides will most likely be the least reactive of the carboxylic acid derivatives.

Carbonyl Compounds and their Leaving Groups

Name	Carbonyl Compound	Leaving Group	Conjugate Acid of the Leaving Group	pK_a
Acid Chloride		Cl^-	H-Cl	-7
Acid Anhydride				3-5
Ester		$^-OR'$	H-OR'	15-16
Carboxylic Acid		^-OH	H-OH	15.7
Amide		$^-NH_2$	$H-NH_2$	36
Ketone		$^-R'$	H-R'	50
Aldehyde		^-H	H-H	Very Large

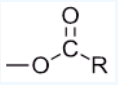
EXAMPLE 21.2.1

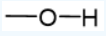
What is the 'Y' group in:

a. an acid anhydride?

b. a carboxylic acid?

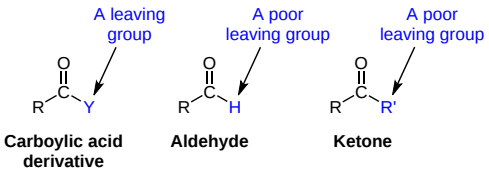
Answers

a. 

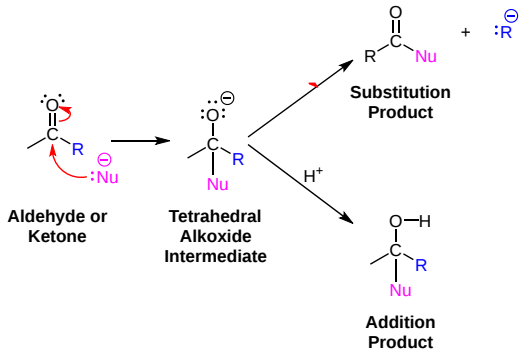
b. 

THE MECHANISM OF NUCLEOPHILIC ACYL SUBSTITUTION

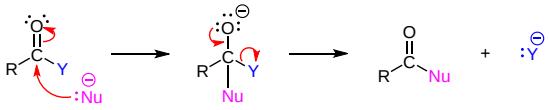
Aldehydes and ketones, along with carboxylic acid derivatives all have the C=O carbonyl bond in common. Thus, the electrophilic character of the carbonyl carbon plays an important part in the reactivity of all of these compounds. Because the carbonyl carbon of aldehydes and ketones do not contain suitable leaving groups, their primary reaction is fundamentally different than carboxylic acid derivatives. Remember that aldehydes and ketones tend to undergo nucleophilic addition to form a tetrahedral alkoxide intermediate. Once formed, the negative charge of the alkoxide intermediate cannot be transferred to other substituents because the potential carbide ($R:^-$) and hydride ($H:^-$) leaving groups are too unstable. Instead the negative charge is held by the alkoxide until protonation converts it into an alcohol.



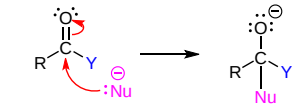
https://chem.libretexts.org/@go/page/36399



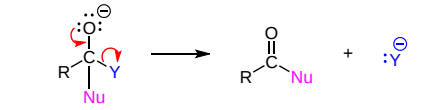
Carboxylic acid derivatives tend to undergo a reaction called nucleophilic acyl substitution. In the same fashion as nucleophilic addition, this mechanism starts with a nucleophilic attack on an electrophilic carbonyl carbon, forming a tetrahedral alkoxide intermediate. The alkoxide negative charge can gain stability by being transferred to the Y leaving group. Elimination of the Y leaving group in the second mechanistic step, allows the C=O carbonyl bond to reform thus creating a new acyl compound. The reaction is considered a substitution due to the Y group of the carboxylic acid derivative being exchanged with an incoming nucleophile.



1) NUCLEOPHILIC ADDITION



2) LEAVING GROUP REMOVAL

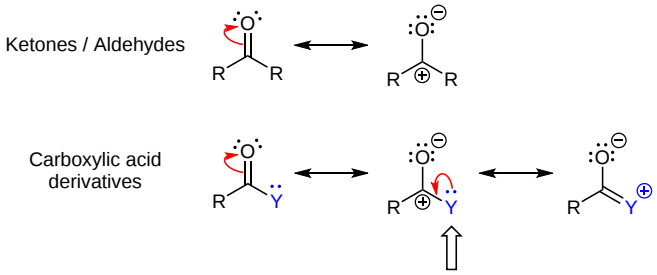


THE RELATIVE REACTIVITY OF CARBOXYLIC ACID DERIVATIVES

The relative reactivity of carboxylic acid derivatives is an important concept for entering into a detailed examination of nucleophilic acyl substitutions. There are two main concepts directly relating to the mechanism which when combined lead to an overall explanation of the differences in reactivity: the stability of the carbonyl and the effectiveness of the Y leaving group.

CARBONYL STABILITY

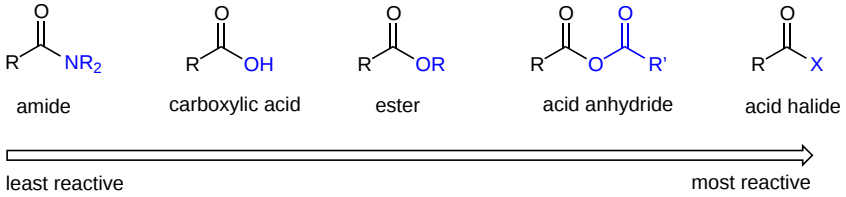
The rate of the first mechanistic step is mainly affected by the stability of the carbonyl moiety. Stabilization reduces the electrophilic character of the carbonyl carbon by reducing its partial positive charge which in turn reduces the rate of this step of the mechanism. The ability of substituents attached to the carbonyl carbon to donate or withdraw electron density is the primary factor determining carbonyl stabilization. As previously discussed, the presence of two electron donating alkyl substituents reduces the partial positive charge on the carbonyl carbon of ketones making them less reactive to nucleophilic attack than aldehydes. The Y group heteroatom's ability to stabilize a carbonyl by donating electrons through resonance makes most carboxylic acid derivatives even less reactive. Overall, delocalization of the carbonyl carbon's partial positive charge onto the adjacent Y group heteroatom reduces the electrophilic character of the carbonyl. The electronegativity of the Y group heteroatom generally determines extent of this stabilization. The less electronegative the Y group heteroatom the better it is able to stabilize the resonance structure with the delocalized positive charge reducing the carbonyl's electrophilicity.



LEAVING GROUP ABILITY

The leaving group ability of the Y group is the most important factor in determining the rate of the second mechanistic step of nucleophilic acyl substitution. As discussed above, the effectiveness of a leaving group is related to its ability to stabilize a negative charge particularly through having a relatively high electronegativity or having the ability to delocalize the negative charge through resonance. The Y group structural features which allow for the stabilization of a negative charge also allow for the stabilization of the transition state of the second step of the mechanism. Overall, the better the leaving group ability of the Y group, the higher the rate of second step of the mechanism.

These two effects, carbonyl stability and leaving group ability, when combined predict the relative reactivity of carboxylic acid derivatives. Fortunately, the effects tend to work synergistically. Y groups that are effective leaving groups also tend to poorly stabilize carbonyls through resonance making reaction rates of nucleophilic acyl substitution higher. Likewise, poor leaving groups tend to effectively stabilize carbonyls through resonance and reduce reaction rates. In fact, depending on the carbonyl structure, either step one or step two of the mechanism can be the rate determining step. For Y groups with a poor leaving group ability, the second step of the mechanism is rate determining because of the weakly stabilized transition state. The first step of the mechanism is rate determining for Y groups with good leaving group ability because they tend to stabilize the starting material's carbonyl increasing the energy distance to the first transition state.

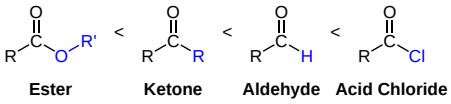


How the two effects actually combine to produce the overall reactivity for each carboxylic acid derivative is slightly different. As comparison of one of the more reactive carboxylic acid derivatives, acid chlorides, and one of the least reactive, amides, will be used as a discussion.

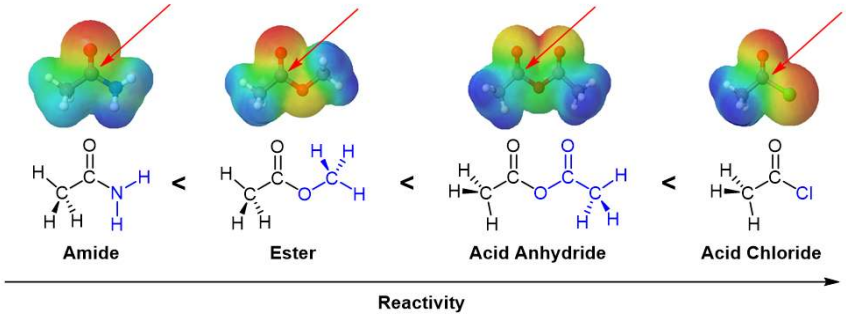
In amides, the nitrogen atom is a powerful electron donating group by resonance. Nitrogen is less electronegative than oxygen and can therefore better stabilize the resonance structure of the delocalized positive charge than most other acid derivatives. This lowers the energy of the starting material which increases the overall energy barrier. Likewise, $-NH_2$ is a relatively poor leaving group (since it is the conjugate base of a very weak acid RNH_2) which increases the transition state energy of the second step of the mechanism also increasing the overall energy barrier. The two effects combine to increase the overall energy barrier which must be overcome during the reaction, causing reaction rates to decrease and making amides very unreactive toward nucleophilic acyl substitution.

In acid chlorides the -Cl is a very effective leaving group making the energy barrier of the second step relatively small. However, this does not have a significant effect since the first step of the mechanism is rate determining. The resonance stabilization offered by the chlorine atom is ineffective due to the poor overlap between the chlorine 3p orbital and the carbon 2p orbital. The poor overlap means that acid chlorides are much less stabilized by resonance than amides. In addition, since chlorine is more electronegative than nitrogen was in the amide example, the inductive electron-withdrawing effects of chlorine become important. This destabilizes the carbonyl and increases the electrophilic character of the carbonyl carbon. The energy barrier of the first step of the mechanism is small due to the lack of stabilization in the acid chloride starting material. Therefore the overall rate of reaction for acid chlorides is high making them very reactive towards nucleophilic acyl substitutions.

As a general rule, stabilizing effects from the Y heteroatom tends to make carboxylic acid derivatives less reactive toward the initial nucleophilic attack than aldehydes and ketone. One notable exception is acid chlorides, where the destabilizing inductive electron-withdrawing properties of the chlorine outweigh the resonance stabilizing effects making them more reactive towards nucleophilic attack. This point will become important later in the chapter where it will be used to explain the outcome of certain reactions.

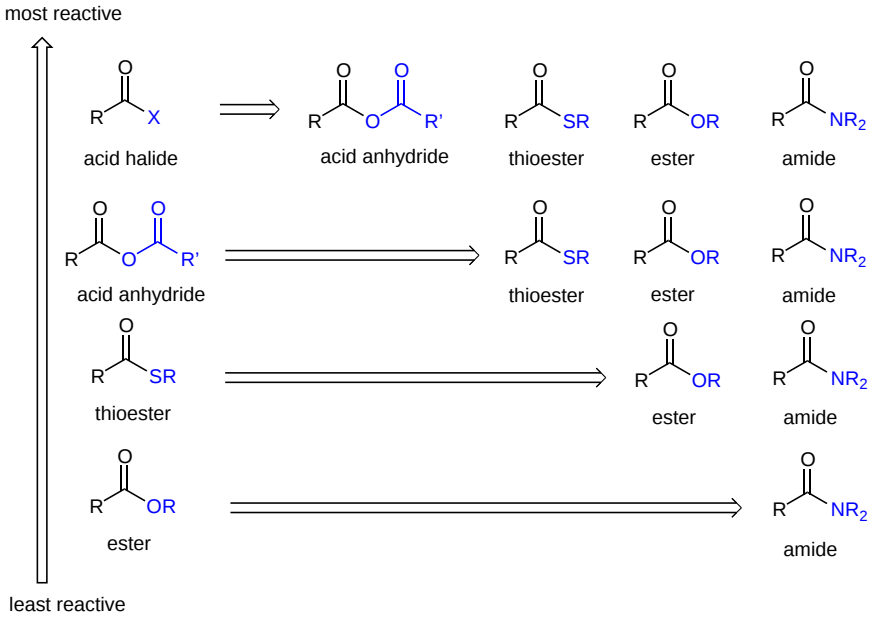


The reactivity of a carboxylic acid derivative can be visualized by using an electrostatic potential map to look at the electron density around the carbonyl carbon. A blue/green color represents the amount of positive charge present. The carbonyl carbons of the amide and ester have a relatively small amount of positive charge making them among the least reactive toward nucleophilic attack. The acid chloride's and anhydride's carbonyl carbon has more of a blue/color color indicating a higher positive charge and making them more reactive than the amide and ester.



ACID DERIVATIVE INTERCONVERSION

From this understanding of reactivity, multiple step synthesis strategies can be developed. Typically more reactive carboxylic acid derivatives can be used to synthesize less reactive derivatives as illustrated in the diagram below. As will be shown later in this chapter, highly reactive acid chlorides, when combined with the appropriate nucleophile, can be directly converting into acid anhydrides, thioester, esters, and amides. However, the less reactive amides cannot be directly converted into ester, thioester, anhydrides, or acid chlorides. It is possible to make these conversions with an amide but multiple reaction steps are required.



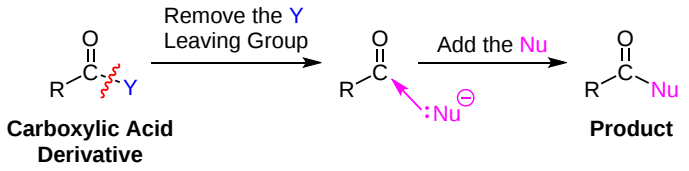
The nucleophiles required to make the conversion from one carboxylic acid derivative to another are common and have been discussed multiple times in this text. Because the same nucleophile is typically used to convert to a specific carboxylic acid derivative conversion, the reactions are given generic names.

- **Hydrolysis:** A reaction with water as a nucleophile to create a carboxylic acid.
- **Alcoholysis:** A reaction with an alcohol nucleophile to create an ester.
- **Aminolysis:** A reaction with ammonia or an amine nucleophile to create an amide.
- **Reduction:** A reaction with a hydride nucleophile to create an aldehyde or 1º alcohol.
- **Organometallic:** A reaction with a carbanion nucleophile from an organometallic reagent to create a ketone or a 3º alcohol.

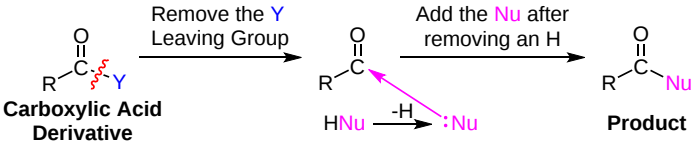
PREDICTING THE PRODUCT OF A NUCLEOPHILIC ACYL SUBSTITUTION REACTION

There are two major pieces of a nucleophilic acyl substitution reaction which need to be identified in order to predict the product: the leaving group of the carboxylic acid derivative (Y) and the nucleophile. It is important to identify if the nucleophile is neutral (i.e. water, alcohols, ammonia, amines) or negatively charged (i.e. hydroxide, alkoxides, hydrides, carbanions). Also, it is important to note that certain hydride and organometallic reagents are capable of a double addition to carboxylic acid derivatives where the first step is a nucleophilic acyl substitution and the second is a nucleophilic addition.

Negatively Charged Nucleophiles



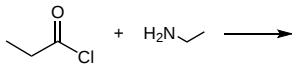
Neutral Nucleophiles



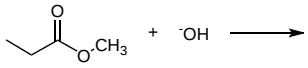
WORKED EXAMPLE

Draw the expected products of the following reactions:

a)

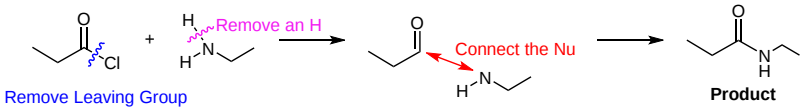


b)

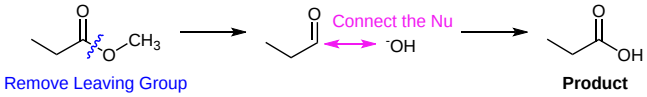


SOLUTIONS

a) The nucleophile is neutral.



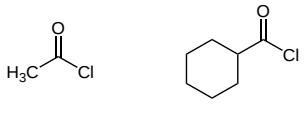
b) The nucleophile is negatively charged.



EXAMPLES

1) Which of the following compounds would be expected to be the most reactive towards nucleophilic acyl substitution? Briefly explain your answer.

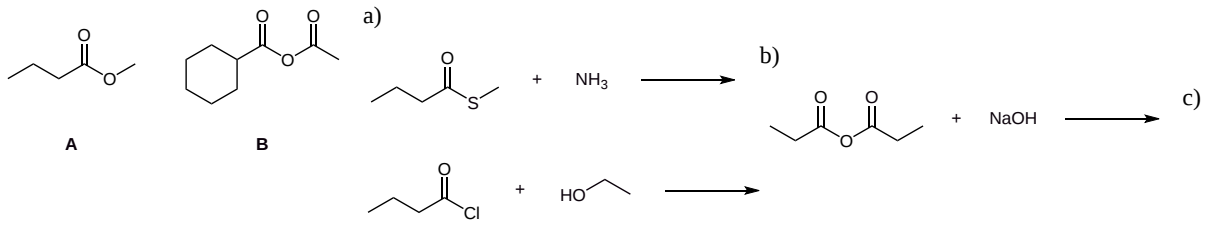
a)



b)

2) Draw the expected products of the following reactions:

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SOLUTIONS

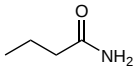
1)

a) Compound A would expected to be the more reactive. For two compounds with the same carboxylic acid derivative group the one with the least steric crowding on the acyl side is typically the most reactive.

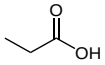
b) Compound B would be expected to be the more reactive. In general acid anhydrides are more reactive than ester.

2)

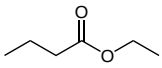
a)



b)



c)



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21.3: NUCLEOPHILIC ACYL SUBSTITUTION REACTIONS OF CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the formation of
   a. an acid chloride from a carboxylic acid.
   b. an ester from a carboxylic acid.
   c. an amide from a carboxylic acid.
   d. an alcohol from carboxylic acid.
2. write an equation to represent the formation of a cyclic anhydride from a dicarboxylic acid.
3. write the detailed mechanism for the reaction of a carboxylic acid with thionyl chloride.
4. identify the reagents necessary to convert a given carboxylic acid to a given acid chloride, ester, amide or alcohol.
5. identify the carboxylic acid required for a direct synthesis of a given acid chloride, amide, ester or alcohol.
6. write an equation to describe the formation of an ester through the nucleophilic attack of a carboxylate anion on an alkyl halide.
7. write a detailed mechanism for the Fischer esterification reaction.
8. describe the evidence from isotopic labelling experiments that is commonly cited to support the generally accepted mechanism of the Fischer esterification reaction.
9. explain why the direct conversion of a carboxylic acid to an amide can only be achieved with difficulty and at a high temperature.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Fischer esterfication reaction

STUDY NOTES

If necessary, review the S_N2 reaction between a carboxylate anion and a primary alkyl halide (Sections 11.2 and 11.3).

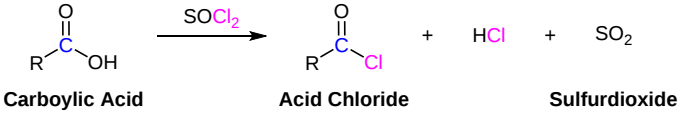
You should recall that the oxygen-18 isotope, ^{18}O, has a nucleus containing eight protons and ten neutrons. Because it is non-radioactive, ^{18}O can be safely employed in the investigation of reaction mechanisms.

The poor leaving group ability of -OH makes carboxylic acids relatively unreactive towards nucleophilic acyl substitutions. The addition of a strong acid protonates the carbonyl oxygen making the carbonyl carbon more electrophilic and circumventing this problem. Also, the substitution reaction can be promoted by converting -OH into a better leaving group. Despite the lack of reactivity, under the right conditions carboxylic acids can be successfully converted into acid chlorides, acid anhydrides, esters, and amides through nucleophilic acyl substitution.

CONVERSION OF CARBOXYLIC ACIDS TO ACID CHLORIDES

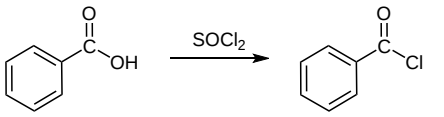
Carboxylic acids can be converted to acid chlorides by reaction with thionyl chloride ($SOCl_2$). During the reaction with thionyl chloride, the hydroxyl group of the carboxylic acid is converted to an acyl chlorosulfite moiety which is a better leaving group. During the reaction a nucleophilic chloride anion is produced which reacts with the acyl chlorosulfite intermediate through nucleophilic acyl substitution to produce an acid halide.

GENERAL REACTION



Carboxylic Acid **Acid Chloride** **Sulfurdioxide**

EXAMPLE

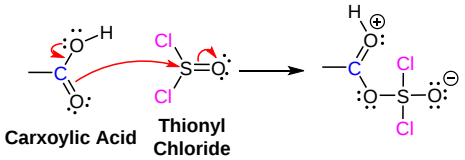


Benzoic Acid **Benzoyl Chloride**

MECHANISM

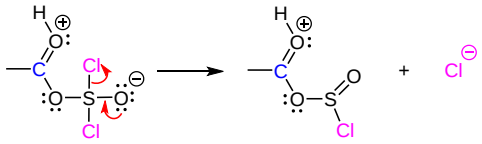
The O=S-Cl bonds of thionyl chloride are analogous to the O=C-Cl bonds of an acid halide in that they can undergo a type of nuleophilicy acyl substitution. During the first step of the mechanism, the carboxylic acid reactant acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Reforming the S=O bond and eliminating a cloride anion (Cl^-) as a leaving group creates a protonated acyl chlorosulfite. The chlorosulfite group represents an excellent leaving group due to its ability to stabilize a negative charge. The carbonyl of the protonated acyl chlorosulfite intermediate is activated to nucleophilic attack, and promptly reacts with the nucleophilic chloride anion created during the second step of the mechanism to produce a tetrahedral alkoide intermediate. Subsequent reforming of the protonated carbonyl bond eliminates the chlorosulfite group as sulfurdioxide (SO_2) and a chloride anion. Lastly, the chloride anion deprotonates the carbonyl to form the acid chloride product.

1) Nucleophilic attack on S=O bond



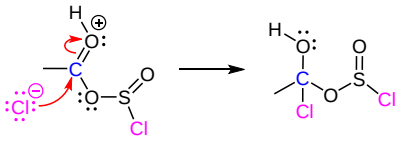
Carxoylic Acid **Thionyl Chloride**

2) Removal of Cl leaving group

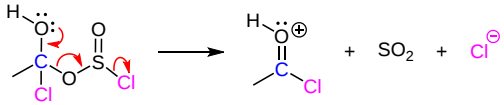


Protonated Acyl Chlorosulfite

3) Nucleophilic attack on the carbonyl

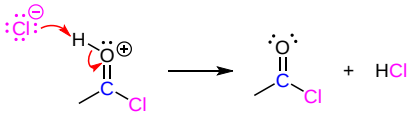


4) Leaving group removal



Protonated Acid Chloride

5) Deprotonation

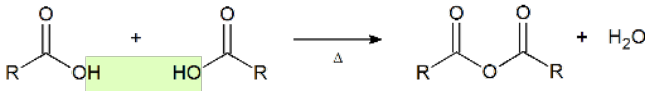


Acid Chloride

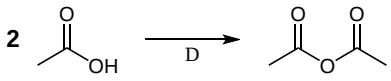
ACID ANHYDRIDE FORMATION

An acid anhydride (or just anhydride) is the product of condensation of two carboxylic acid molecules with the release of a water molecule. The most common anhydride in organic chemistry is acetic anhydride, due to the high temperatures needed to remove water.

GENERAL REACTION



EXAMPLE

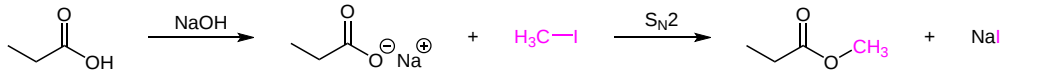


Acetic Acid **Acetic Anhydride**

CONVERSION OF CARBOXYLIC ACIDS INTO ESTERS BY ALKYLATION

Carboxylic acids can be easily converted into their conjugate bases through deprotonation with a base, such as sodium hydroxide. The resulting carboxylate can be alkylated using by an S_N2 reaction with either a methyl or primary halide. If a methyl ester is required, methyl iodide (CH_3I) is a commonly used reagent.

EXAMPLE

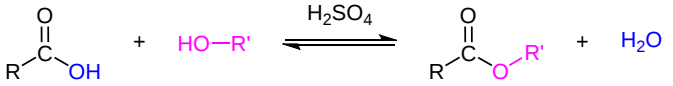


Propanoic Acid **Sodium Propanoate** **Methyl Iodide** **Methyl Propanoate** **Sodium Iodide**

CONVERSION OF CARBOXYLIC ACIDS TO ESTERS: THE FISCHER ESTERIFICATION

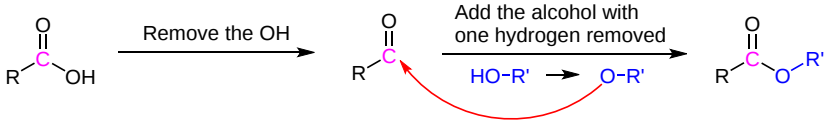
Alcohols can be used as nucleophiles to convert carboxylic acids to esters. Due to the poor leaving group ability of -OH in carboxylic acids, an acid catalyst is required to speed up the reaction. Usually the alcohol starting material is used as the reaction solvent so that it can be present in a large excess. This helps to increase the reaction's yield by pushing reaction equilibrium to the right which can be understood via Le Chatelier's principle.

GENERAL REACTION

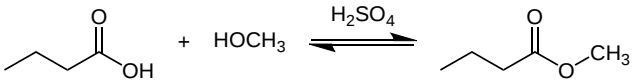


Carxoylic Acid **Alcohol** **Ester** **Water**

PREDICTING THE PRODUCTS OF A FISCHER ESTERIFICATION



EXAMPLE

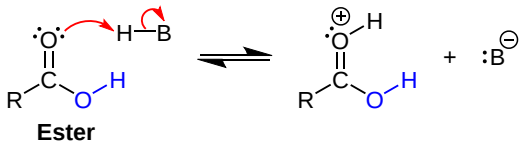


Butanoic Acid **Methyl Butanoate**

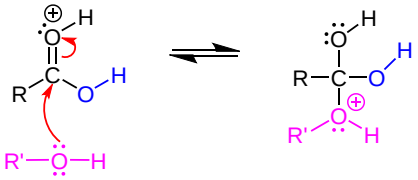
MECHANISM

The mechanism begins with protonation of the carbonyl to increase its electrophilic character. A tetrahedral alkoxide intermediate is formed when the alcohol nucleophile adds to the protonated carbonyl, pushing the carbonyl pi electrons onto the oxygen. A different tetrahedral alkoxide intermediate is created when a proton is then transferred to one of the hydroxides (OH), turning it into a good leaving group. Reforming the protonated carbonyl bond then eliminates water as a leaving group. Finally, deprotonation of the carbonyl by water creates the ester product and regenerates the acid catalyst. All the steps of the mechanism are reversible

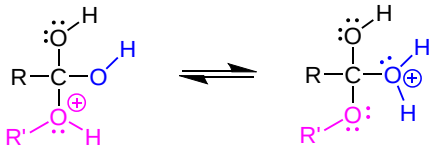
1) Protonation of the carbonyl



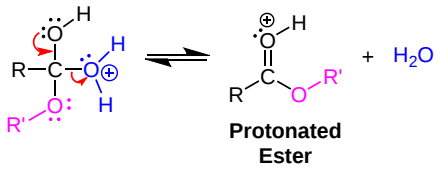
2) Nucleophilic attack on the carbonyl



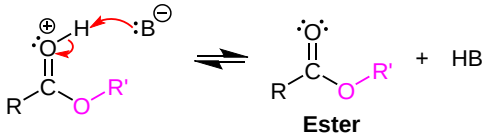
3) Proton transfer



4) Removal of water as a leaving group

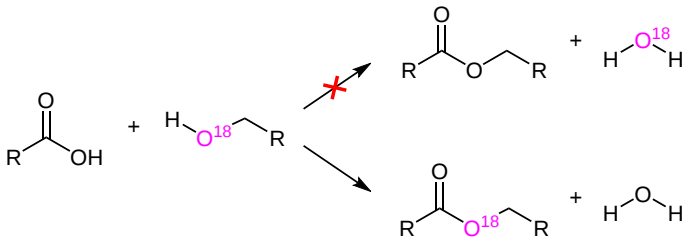


5) Deprotonation



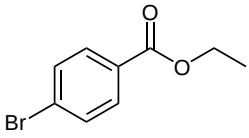
ISOTOPIC LABELING

Evidence to support the Fischer esterification mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with an oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated. This shows that the C-OH bond of the carboxylic acid and the H-OR bond of the alcohol that is broken during the reaction.

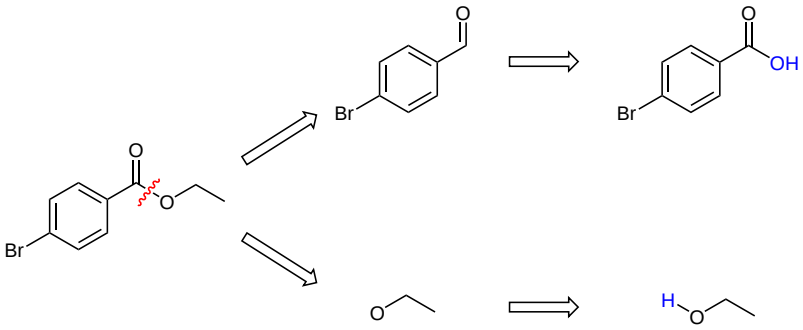


WORKED EXAMPLE: PLANNING A SYNTHESIS USING A FISCHER ESTERIFICATION

HOW COULD THE FOLLOWING MOLECULE BE MADE USING A FISCHER ESTERIFICATION?

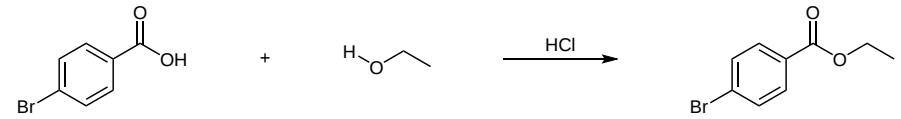


ANALYSIS



The key bond formed during a Fischer Esterification is the C-O sigma bond. The target molecule can be separated into the two required starting materials by breaking this bond. The carbonyl carbon fragment gains an –OH to become a carboxylic acid and the oxygen fragment gains an H to become an alcohol. The carboxylic acid and the alcohol are reacted using a strong acid catalyst.

SOLUTION

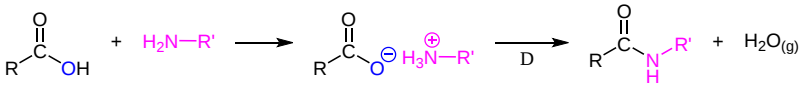


***p*-Bromo Benzoic Acid** **Ethanol** **Ethyl *p*-Bromo Benzoate**

DIRECT CONVERSION OF CARBOXYLIC ACIDS TO AMIDES

The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a stable carboxylate salt. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C, water is driven off and an amide is formed. Due to the extreme conditions, this reaction is rarely used. When converting to an amide it is preferred to convert the carboxylic acid to a more reactive form such as an acid chloride first and then convert this molecule to an amide.

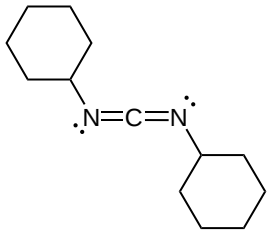
GENERAL REACTION



Ammonium Carboxylate Salt

CONVERSION OF CARBOXYLIC ACIDS TO AMIDES USING DCC

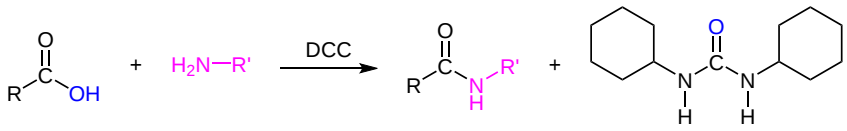
The formation of amides from carboxylic acids and amines is a reaction of great importance in biochemistry. Proteins are formed through the creating of amide bonds between amino acid residues, so a great deal of research has been performed to find efficient methods. The direct conversion of a carboxylic acids to amides is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. One solution to this problem is through the use of dialkylcarbodiimides (R-N=C=N-R) coupling reagents, such as dicyclohexylcarbodiimide (DCC).



Dicyclohexylcarbodiimide (DCC)

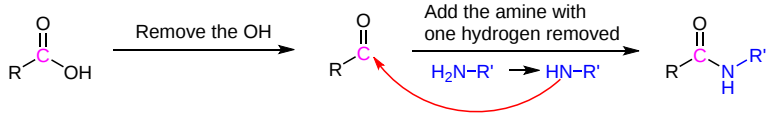
During a DCC amide coupling, the OH of a carboxylic acid is made into a good leaving group which can then be replaced by an amine during nucleophilic acyl substitution. Using DCC as a coupling reagent, 1º and 2º amines can be used to create 2º and 3º amides respectfully.

BASIC REACTION

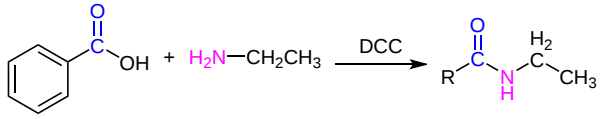


Carboxylic Acid **Amine** **Amide** **N,N'-Dicyclohexylurea**

PREDICTING THE PRODUCTS OF DCC COUPLING



EXAMPLE

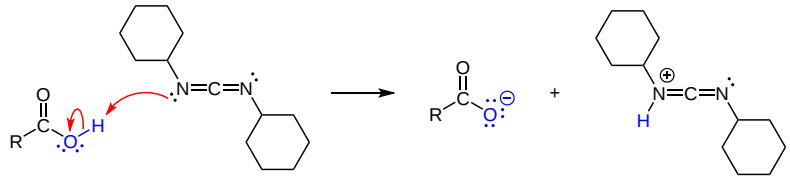


Benzoic Acid **Ethyl Amine** **N-Ethylbenzamide**

MECHANISM

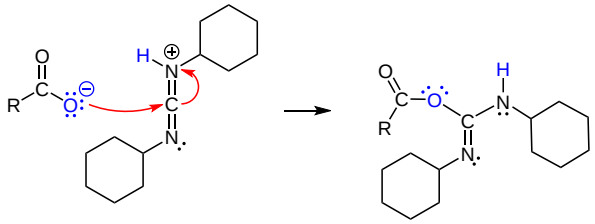
DCC deprotonates the carboxylic acid to form a carboxylate, which is a better nucleophile. The corresponding protonation of DCC increases the electrophilic character of its C=N imide bond. The caboxylate nucleophile then adds to the imide bond and pushes the C=N pi electrons onto the nitrogen. The amine nucleophile can now add itself to the carbonyl bond as part of a nuleophilic acyl substitution. The DCC coupled oxygen is eliminated as dicyclohexylurea, a good leaving group, to create the amide product.

1) Deprotonation

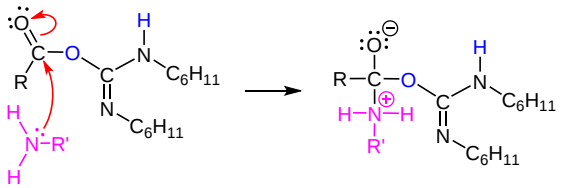


Carboxylic Acid **DCC** **Carboxylate** **Protonated DCC**

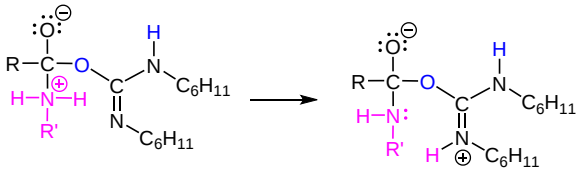
2) Nucleophilic attack by the carboxylate



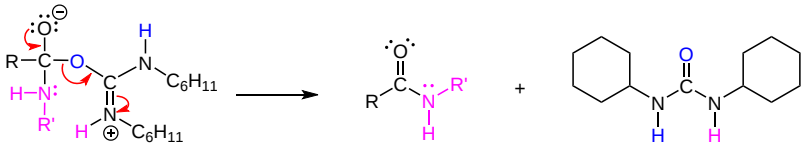
3) Nucleophilic attack by the amine



4) Proton transfer



5) Leaving group removal

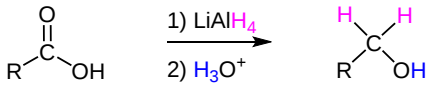


CONVERSION OF CARBOXYLIC ACIDS TO 1^{O} ALCOHOLS

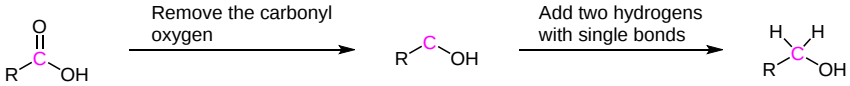
LITHIUM ALUMINUM HYDRIDE ($LiALH_4$)

Hydride nucleophiles from lithium aluminum hydride ($LiAlH_4$) can reduce carboxylic acids to 1° alcohols. Note that $NaBH_4$ is not a strong enough reducing agent to convert carboxylic acids or esters to alcohols. Because the incoming nucleophile is an "H" the reaction first produces an aldehyde intermediate which available for further hydride additions. The aldehyde intermediate is difficult to isolate because it is more reactive than the original carboxylic acid. This reaction represents the first example in this chapter where a carboxylic acid derivative can undergo a double nucleophilic addition. In the mechanism of this reaction, a nucleophilic acyl substitution is followed by a nucleophilic addition allowing for two hydride nucleophiles being added to the electrophilic carbonyl carbon of a carboxylic acid.

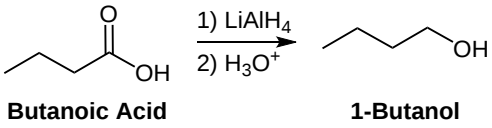
GENERAL REACTION



PREDICTING THE PRODUCT OF A HYDRIDE REDUCTION



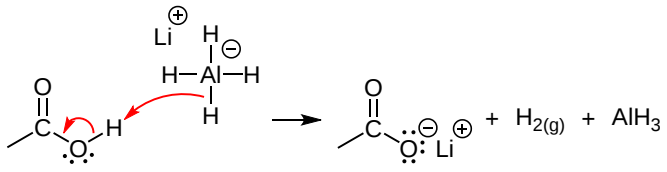
EXAMPLE



POSSIBLE MECHANISM

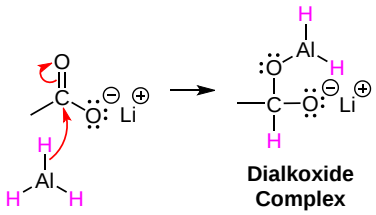
Although the mechanism of this reaction is not precisely known, much of it is understood. Initially, a hydride deprotonates the carboxylic acid to form a lithium carboxylate, hydrogen gas (H_2), and aluminum hydride. Then a hydride nucleophile, from aluminum hydride, adds to the carbonyl carbon as part of a nucleophile acyl substitution. The resulting high-energy dianion intermediate forms a Lewis Acid/Base complex with aluminum, making one of the oxygens a good leaving group (the negative charge on the oxygen complexed to aluminum is not shown in step 2 below). The carbonyl bond is reformed along with the elimination of $OAlH_2$ as a leaving group to form an aldehyde. A hydride nucleophile from another molecule of $LiAlH_4$ adds to the re-formed carbonyl carbon as part of a nucleophilic addition. The resulting alkoxide intermediate is protonated during an acidic work-up to form the 1° alcohol product. Due to the formation of a dianion intermediate the reaction requires relatively high temperature and long reaction times.

1) Deprotonation



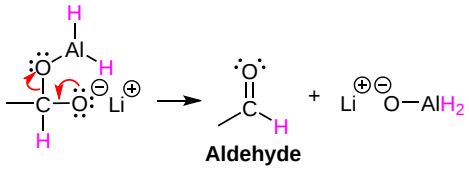
Carboxylic Acid

2) Nucleopilic attack by a hydride anion



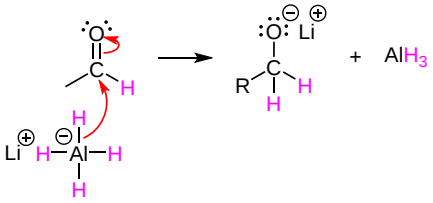
Dialkoxide Complex

3) Leaving group removal

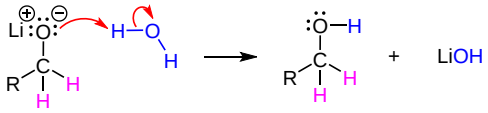


Aldehyde

4) Nucleopilic attack by a hydride anion



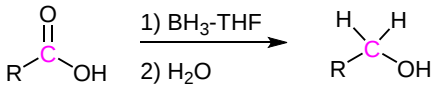
5) Alkoxide protonation



1° Alcohol

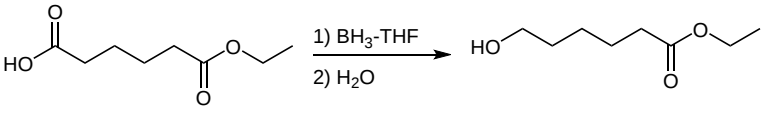
BORANE TETRAHYDROFURAN COMPLEX

Solutions of a borane tetrahydrofuran complex (BH_3-THF) rapidly reduce carboxylic acids at room temperature with often high yields. The borane tetrahydrofuran complex offers a safer and easier alternative to $LiAlH_4$ reductions.



Carboxylic Acid **1° Alcohol**

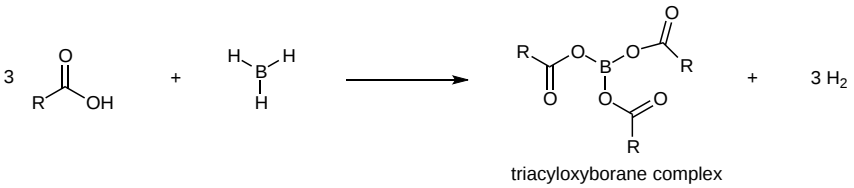
EXAMPLE



Adipic acid monoethyl ester **Ethyl 6-hydroxyhexanoate, (88% Yield)**

The acidic hydrogen of carboxylic acids allows them react faster with the borane tetrahydrofuran complex faster than any other functional group, allowing them to be selectively reduced in the presence of other carbonyls. In the first step of the reduction mechanism, which is rate

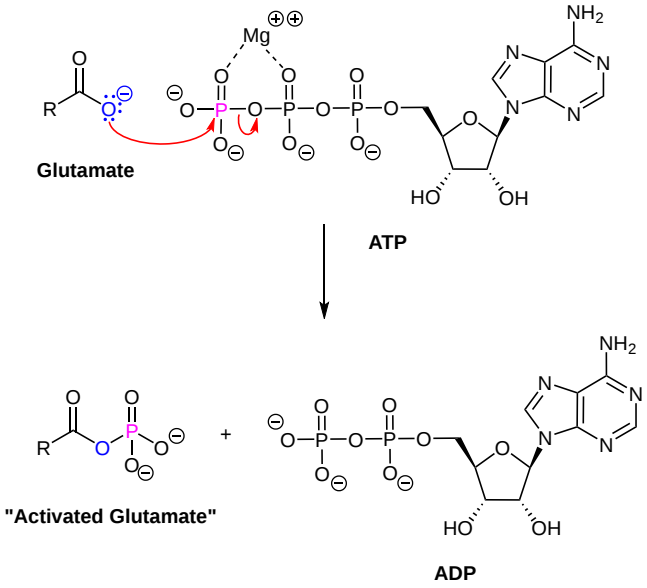
determining, the acidic hydrogens of three carboxylic acids along with the three hydrogens from BH_3 are rapidly removed to form hydrogen gas (H_2) and a triacyloxyborane complex. A subsequent aqueous work-up converts the complex into a primary alcohol as shown in the general reaction above.



triacyloxyborane complex

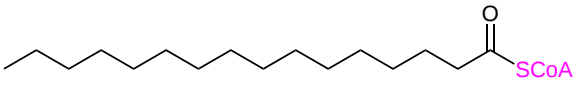
BIOLOGIC CONVERSION OF CARBOXYLIC ACIDS

In biological chemistry direct conversion of a carboxylic acid to an acyl derivative by nucleophilic acyl substitution does not occur. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.



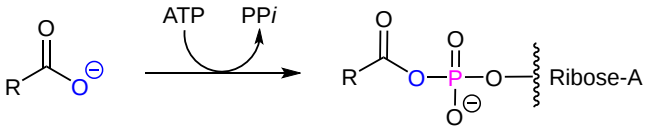
Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

An excellent example of biological activated carboxylic acids is seed in the biosynthesis of fatty acids. In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



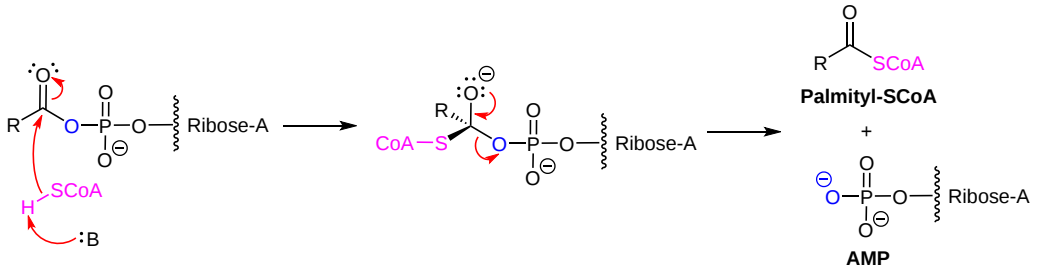
Palmityl-SCoA

Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction (section 12.2B).



Palmitate **Palmityl-AMP**

The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.

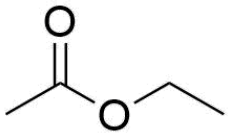


EXERCISES

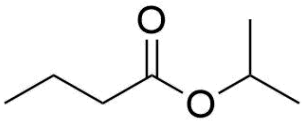
Q21.3.1

How would you create the following esters from the corresponding acids?

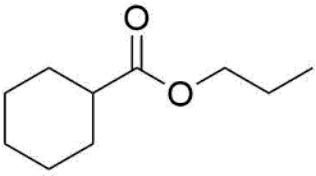
(a)



(b)

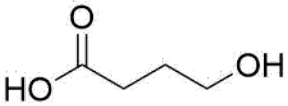


(c)



Q21.3.2

The following molecule is treated with acid and undergoes an intramolecular Fischer Esterification. Draw the product.

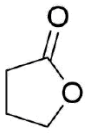


SOLUTIONS

S21.3.1

a. Acetic acid + ethanol
b. Butanoic acid + isopropanol
c. Cyclohexanecarboxylic acid + propanol

S21.3.2



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21.4: CHEMISTRY OF ACID HALIDES

OBJECTIVES

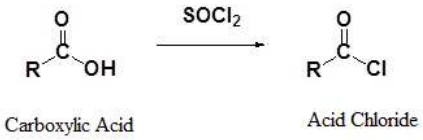
After completing this section, you should be able to

1. identify the reagent normally used to convert a carboxylic acid to an acid bromide.
2. write equations to show how an acid halide may be converted into each of the following: a carboxylic acid, an ester, an amide.
3. write a detailed mechanisms for the reaction of an acid halide with each of the following: water, an alcohol, ammonia, a primary or secondary amine.
4. identify the product formed when a given acid halide reacts with any of the following reagents: water, an alcohol, a primary or secondary amine.
5. identify the acid halide, the reagents, or both, needed to prepare a given carboxylic acid, ester or amide.
6. identify the product formed when a given acid halide reacts with water, a given alcohol, ammonia, or a given primary or secondary amine.
7. identify lithium aluminum hydride as a reagent for reducing acid halides to primary alcohols, and explain the limited practical value of this reaction.
8. identify the partial reduction of an acid halide using lithium tri-*tert*-butoxyaluminum to form an aldehyde.
9. write an equation to describe the formation of a tertiary alcohol by the reaction of an acid halide with a Grignard reagent.
10. write a detailed mechanism for the reaction of an acid halide with a Grignard reagent.
11. identify the product formed from the reaction of a given acid halide with a given Grignard reagent.
12. identify the acid halide, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
13. write an equation to illustrate the reaction of an acid halide with a lithium diorganocopper reagent.
14. identify the product formed from the reaction of a given acid halide with a given lithium diorganocopper reagent.
15. identify the acid halide, the lithium diorganocopper reagent, or both, that must be used to prepare a given ketone.

Acid halides are highly reactive carboxylic acid derivatives. As such they are able to be used to synthesize many other carboxylic acid derivatives.

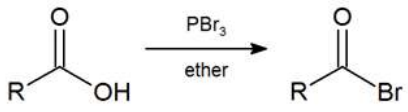
FORMATION OF ACID HALIDES

Carboxylic acids react with thionyl chloride ($SOCl_2$) to form acid chlorides. A nucleophilic acyl substitution allows for the replacement of the carboxylic acid –OH with a chloride atom.



Carboxylic Acid Acid Chloride

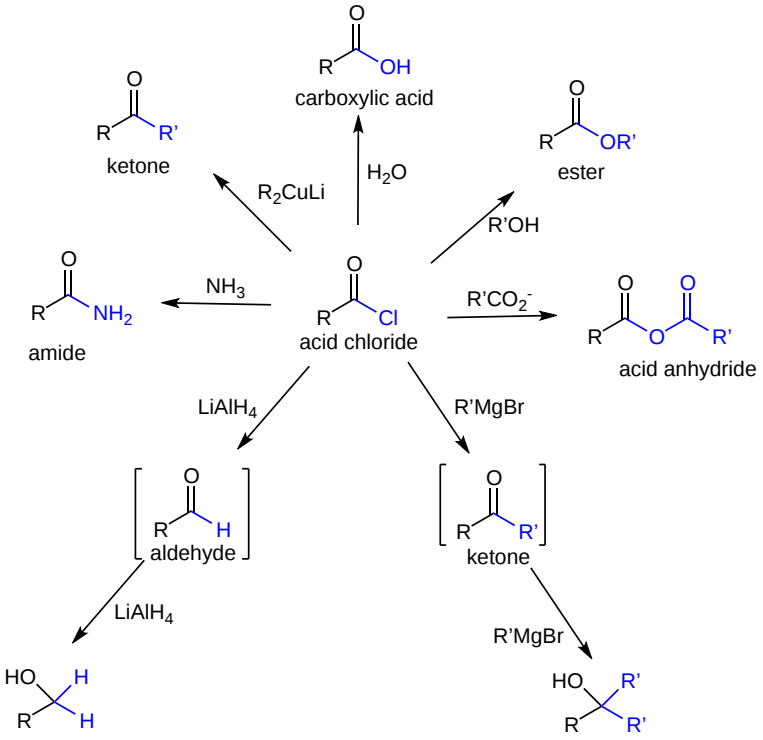
Earlier (Section 10.5), we saw that primary and secondary alcohols react with phosphorous tribromide (PBr_3) to afford the corresponding alkyl bromide. In a similar fashion, acid bromides can be formed from the corresponding carboxylic acid by reaction with PBr_3.



Carboxylic Acid Acid Bromide

REACTIONS OF ACID HALIDES

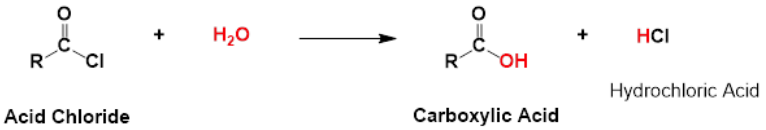
The high reactivity of acid halides allows them to be easily converted into other acyl compound through nucleophilic acyl substitution. Depending on the nucleophilic reagent applied, acid halides can be used to create carboxylic acids, anhydrides, esters, amides, or ketones. Also, acid halides undergo a double nucleophilic addition with LiAlH4 to produce primary alcohols and Grignard reagents to produce tertiary alcohols. Although this section will only represent reactions with acid chlorides, other acid halides undergo similar reactions.



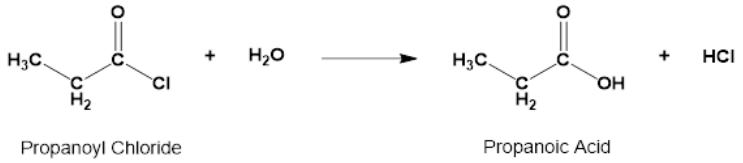
CONVERSION OF ACID CHLORIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Acid chlorides are converted into carboxylic acids through a nucleophic acyl substitution with water. This reaction follows the typical mechanism where a water nucleophile attacks the electrophilic carbonyl carbon to form a tetrahedral alkoxide intermediate. The carbonyl bond is reformed and Cl- is eliminated as a leaving group. Because water is a neutral nucleophile, an oxonium intermediate in produced. The oxonium intermediate is deprotonated by the chloride anion to produce a neutral carboxylic acid and HCl. The HCl is commonly removed from the reaction mixture by a basic work-up.

GENERAL REACTION

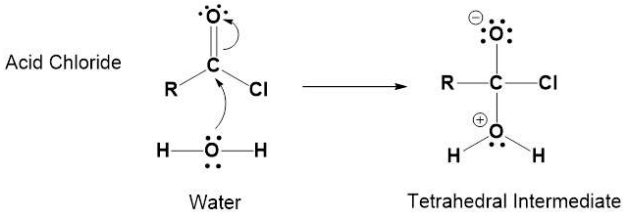


EXAMPLE

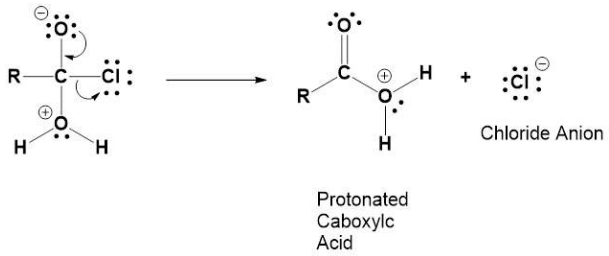


MECHANISM

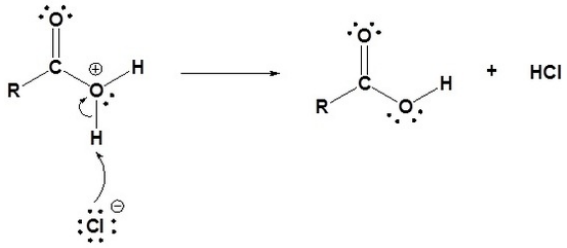
1) Nucleophilic attack by water



2) Leaving group is removed



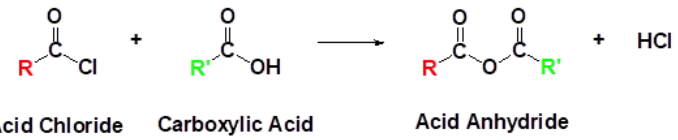
3) Deprotonation



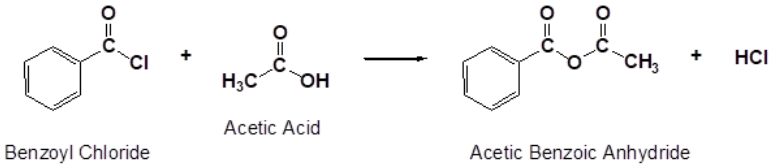
CONVERSION OF ACID CHLORIDES TO ANHYDRIDES

Acid chlorides react with carboxylic acids to form anhydrides through a nucleophilic acyl substitution. Because the carboxylic acid nucleophile is neutral, HCl is produced as a side-product during the reaction and is typically removed as part of a basic work-up. Both symmetrical and asymmetrical anhydrides can be created using this reaction. Carboxylates can also be used to form anhydrides in a similar reaction under basic conditions.

GENERAL REACTION

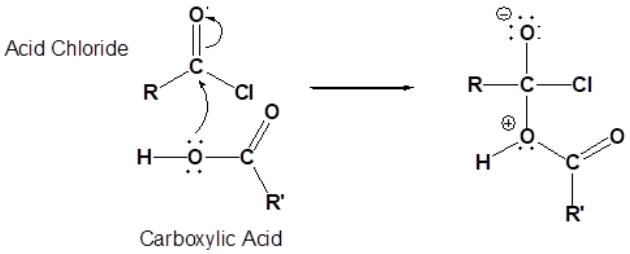


EXAMPLE

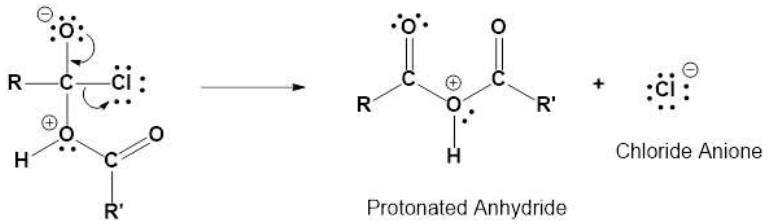


MECHANISM

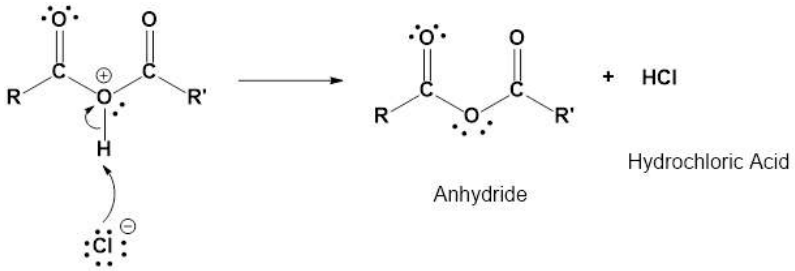
1) Nucleophilic attack by a carboxylic acid



2) Leaving group removal



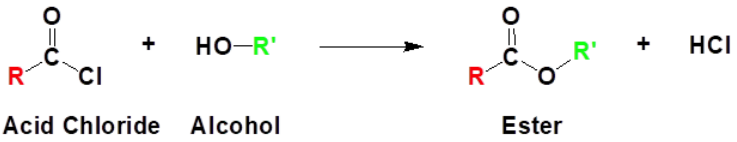
3) Deprotonation



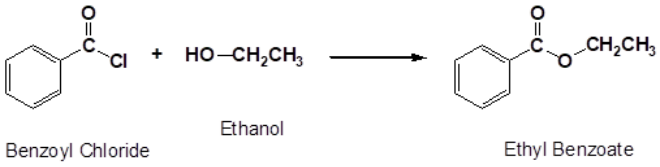
CONVERSION OF ACID CHLORIDES TO ESTERS: ALCOHOLYSIS

Acid chlorides react with alcohol nucleophiles to produce esters. This reaction is the preferred method for preparing esters. Pryidine is often added to the reaction mixture to remove the HCl produced.

GENERAL REACTION

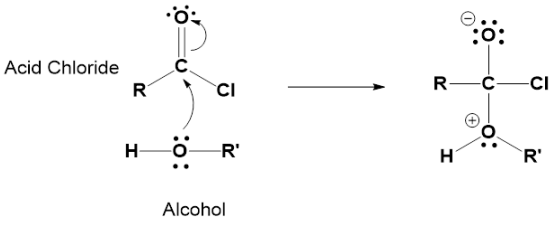


EXAMPLE

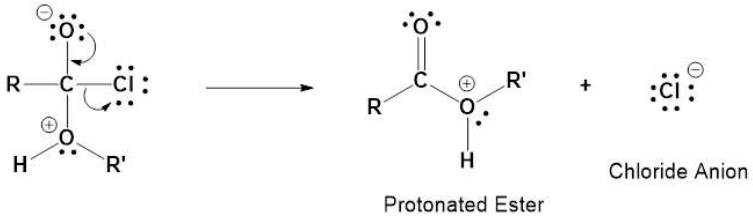


MECHANISM

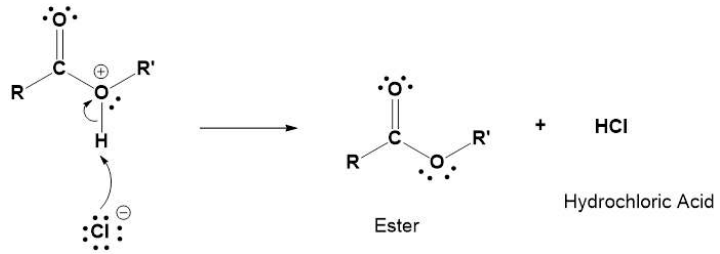
1) Nucleophilic attack by an alcohol



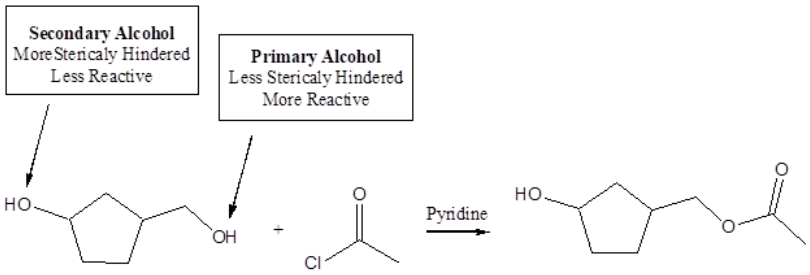
2) Leaving group removal



3) Deprotonation

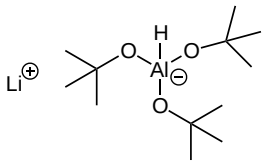


This reaction is particularly affected by steric hindrance so bulky alkyl groups on either the acid chloride or the alcohol significantly decrease the rate. For a given acid chloride there is a reactivity order among alcohols of primary > secondary > tertiary. If a compound has multiple alcohols the less hindered one will be selectively esterified.

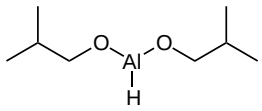


CONVERSION OF ACID CHLORIDES TO ALDEHYDES: REDUCTION

Acid chlorides can be converted to aldehydes using a hindered reducing agent such as lithium tri-tert-butoxyaluminum hydride $LiAlH(Ot\text{-}Bu)_3$ or diisobutylaluminum hydride (DIBALH). These hydride sources are weaker reducing agents than lithium aluminum hydride in part because they are sterically hindered. Also, they have only one equivalent of hydride which makes stoichiometric control of hydride addition much easier.



lithium tri-tert-butoxyaluminum hydride

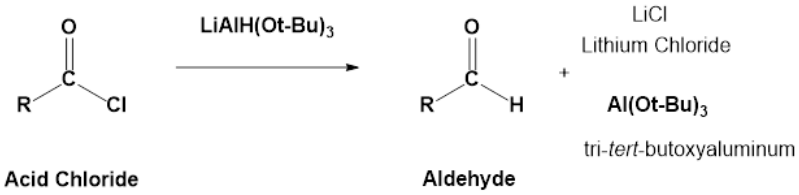


diisobutylaluminum hydride

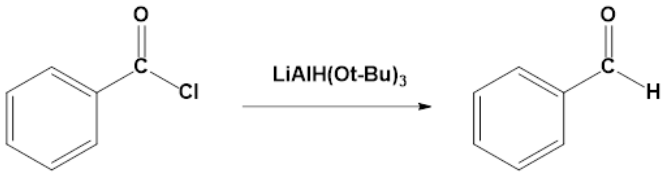
The mechanism of this reaction is analogous to the hydride reduction of carboxylic acids. We have previously seen that $LiAlH_4$ will reduce carboxylic acids to 1° alcohols thorough an aldehyde intermediate. In that case, the aldehyde intermediate was actually more reactive to hydride reduction than the carboxylic starting material. This prevented the isolation of the aldehyde intermediate because of it quick conversion to the 1° alcohol. $LiAlH_4$ would also convert acid chlorides to 1° alcohols but this reaction would be inefficient because it would be easier to perform the reaction on the corresponding carboxylic acid.

Because acid chlorides are highly activated, they will still react with the weaker hydride sources, to form an aldehyde. Once formed, the aldehyde competes with the remaining acid chloride for the remaining hydride reagent. However, acid chlorides are more reactive towards nucleophilic attack than aldehydes. The acid chloride starting material is quickly consumed by hydride reduction before the aldehyde has a chance to react allowing for isolation of the resulting aldehyde. Using a reaction temperature of -78 ºC also helps to isolate the aldehyde as the product by further slowing the aldehyde reduction reaction.

GENERAL REACTION



EXAMPLE



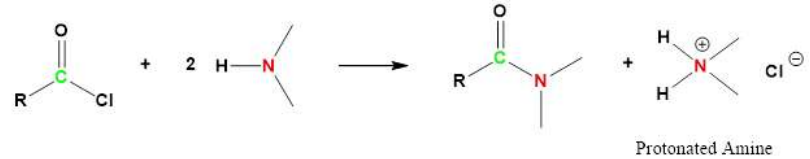
Benzoyl Chloride — Benzaldehyde

CONVERSION OF ACID CHLORIDES TO AMIDES: AMINOLYSIS

Ammonia, 1º amines, and 2º amines react with acid chlorides to form 1º, 2º, and 3º amides respectively. These reactions typically take place rapidly at room temperature and provides high reaction yields.

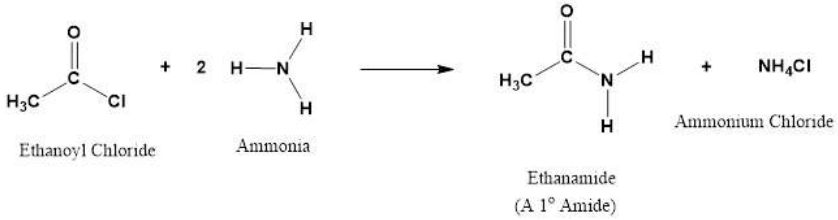
The reaction is commonly run with an excess of the amine starting material. Without the excess the amine reactant would eventually become protonated by the HCl produced by the reaction to form a non-nucleophilic ammonium compound. If the amine is not readily available, the reaction is usually run with a base, such as NaOH or pyridine, to neutralize the HCl produced.

GENERAL REACTION

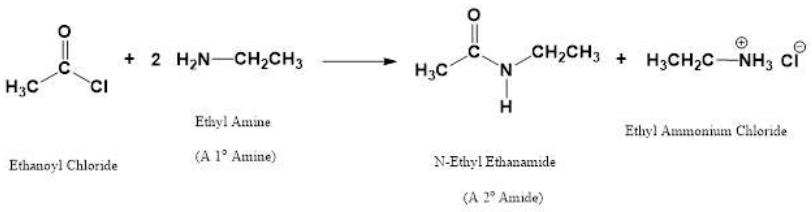


Acid Chloride — Amine — Amide — Protonated Amine

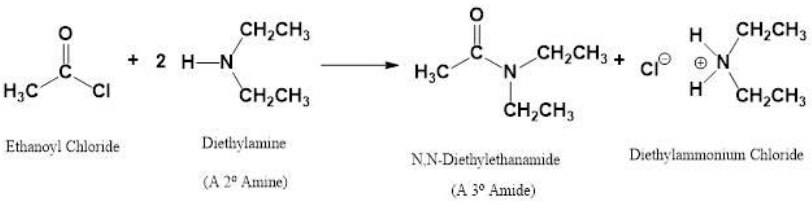
EXAMPLES



Ethanoyl Chloride — Ammonia — Ethanamide (A 1° Amide) — Ammonium Chloride



Ethanoyl Chloride — Ethyl Amine (A 1° Amine) — N-Ethyl Ethanamide (A 2° Amide) — Ethyl Ammonium Chloride

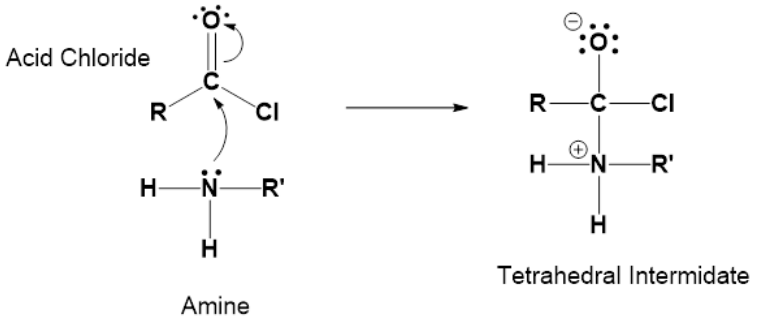


Ethanoyl Chloride — Diethylamine (A 2° Amine) — N,N-Diethylethanamide (A 3° Amide) — Diethylammonium Chloride

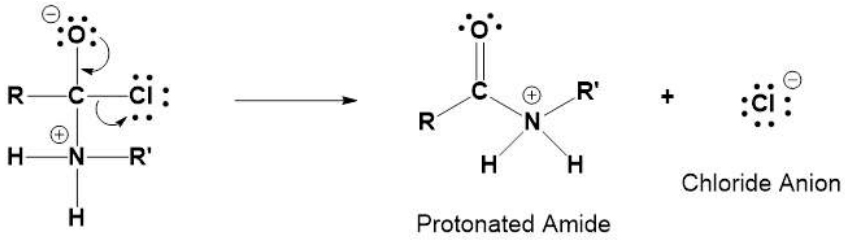
MECHANISM

The mechanism of aminolysis follows a typical nucleophilic acyl substitution. The amine nucleophile attacks the carbonyl carbon of the acid chloride forming an alkoxide tetrahedral intermediate. The -Cl leaving group is eliminated, allowing the carbonyl bond to be reformed. Because amines are neutral nuleophiles a protonated amide is produced after this step. In the last step of the mechanism, a second amine acts as a base, removing a proton, and allowing for the amide product to be formed.

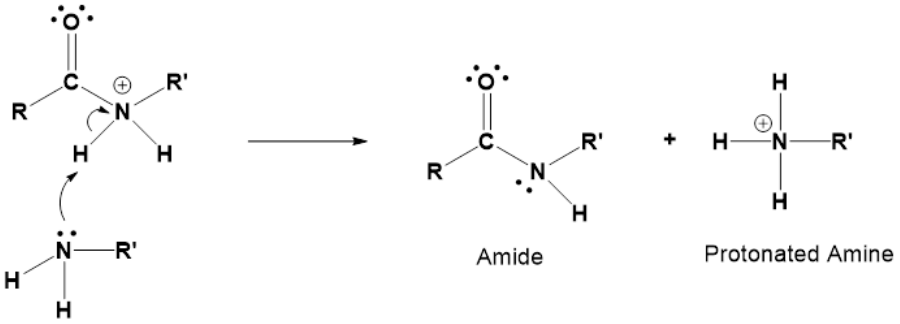
1) Nucleophilic attack by an amine



2) Leaving group removal

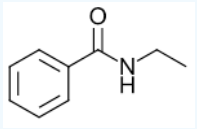


3) Deprotonation



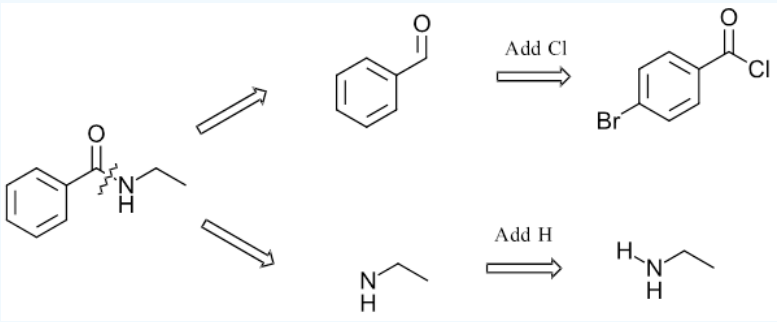
EXAMPLE 21.4.1

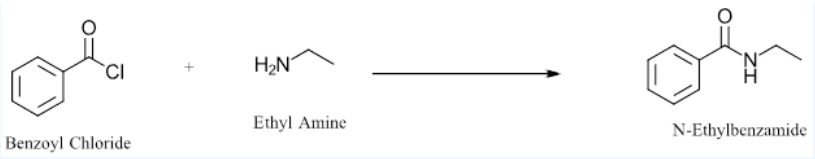
How could the following molecule be synthsized using an aminolysis of an acid chloride?



Solution

The key bond formed during this reaction is the C-N sigma bond between the carbonyl carbon and the nitrogen. Breaking this bond separated the target molecule into the two required starting materials. The carbonyl carbon gains an –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1° amine. The acid chloride and the 1° amine can then be joined to form the product.

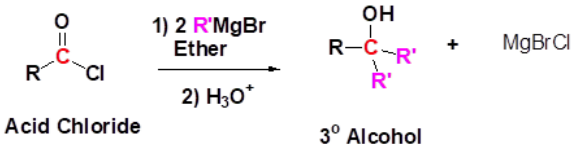




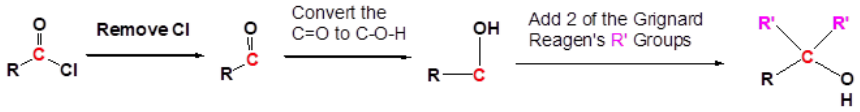
CONVERSION OF ACID CHLORIDES TO 3° ALCOHOLS: GRIGNARD REAGENTS

Addition of Grignard reagents converts acid halides to 3° alcohols while forming two C-C bonds. The Grignard reagent adds to the carbonyl carbon twice during this reaction. First, as part of a nucleophilic acyl substitution to form a ketone intermediate. Then as part of a nucleophilic addition to the ketone to form a 3° alcohol.

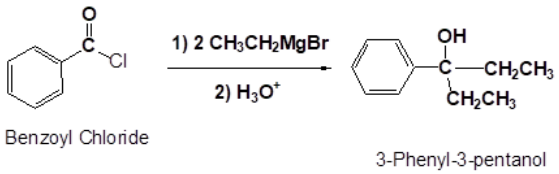
GENERAL REACTION



PREDICTING THE PRODUCT OF A GRIGNARD REACTION

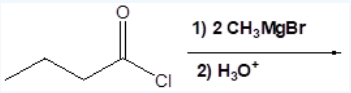


EXAMPLE



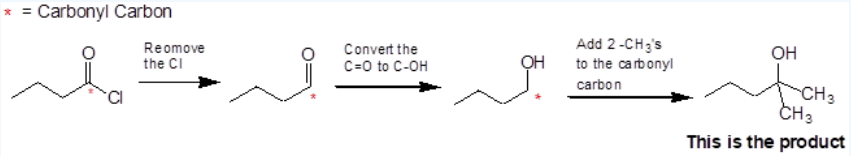
✔ EXAMPLE 21.4.2

Draw the products of the following reaction.



Solution

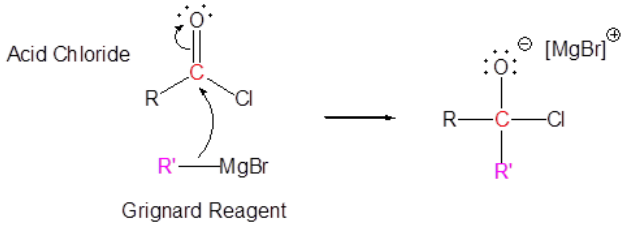
The carbanion nucleophile from the Grignard reagent is added to the carbonyl carbon twice. Once as part of a nucleophilic acyl substitution which eliminates the Cl leaving group. Then again as part of a nucleophilic addition which converts the carbonyl C=O into an alcohol OH. These steps are combined to form a 3° alcohol.



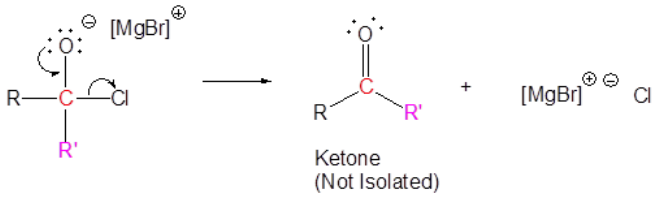
MECHANISM

The mechanism starts with the Grignard reagent's carbanion nucleophile adding to the acid halide carbonyl to form a tetrahedral alkoxide intermediate. The chloride leaving group is then eliminated, reforming the carbonyl to create a ketone intermediate. Once formed, the ketone is in competition with the acid chloride for the Grignard reagent remaining. Although acid chlorides are more reactive toward nucleophilic addition than ketones, the high reactivity of Grignard reagents makes isolating the ketone intermediate difficult. The reaction mechanism continues with the addition of a second carbanion nucleophile to the ketone to form another tetrahedral alkoxide intermediate. Protonation of the alkoxide as part of an acidic work-up creates the 3° alcohol product.

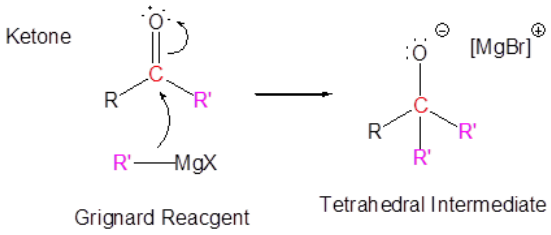
1) Nucleophilic attack



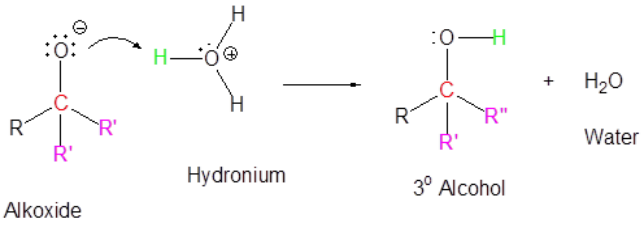
2) Leaving group removal



3) Nucleophilic attack



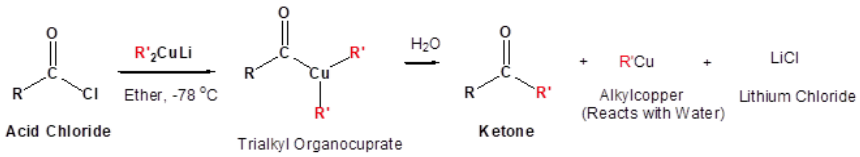
4) Protonation



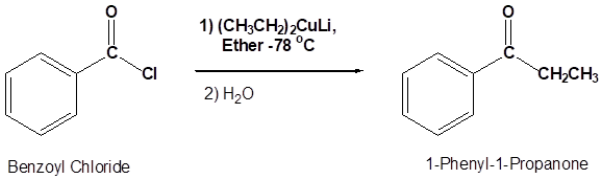
CONVERSION OF ACID CHLORIDES TO KETONES: GILMAN REAGENTS

When acid chlorides are reacted with Grignard reagents the ketone intermediate is difficult to isolate because the addition of a second equivalent of the highly reactive Grignard reagent rapidly occurs. Organocuprates however are significantly less reactive than organolithium and organomagnesium reagents and when an acid chloride is reacted with a diorganocuprate (Gillman) reagent (R_2CuLi), a ketone product is produced in excellent yields.

GENERAL REACTION



EXAMPLE

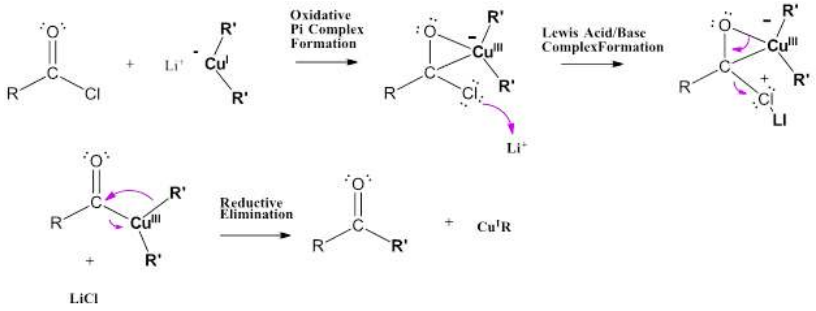


MECHANISM

The copper atom in organocuprate reagents radically changes the reaction mechanism for their nucleophilic addition to acid chlorides. Computational studies suggest that the reaction mechanism is more complicated than the typical “addition-elimination” sequence seen in nucleophilic acyl substitutions but rather involves multiple mechanistic steps involving complexation with copper and lithium.

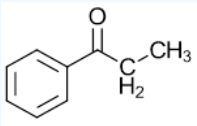
The mechanism starts with an oxidative pi-complex formation between the Cu atom in Gilman reagents and the C=O carbonyl bond in acid chlorides. Next, the chloride atom is activated toward elimination through formation of a Lewis Acid/Base complex with a lithium cation. The subsequent elimination of the –Cl leaving cleaves the C-Cl bond and forms a Cu-C bond creating a triorganocopper(III) intermediate. A ketone product is formed when reductive elimination breaks the Cu^{III}-C bond of the intermediate and forms a C-C bond between the carbonyl carbon and an alkyl group from the organocuprate reagent. During the reduction step, copper gains two electrons forming an alkylcopper (CuR) compound as a side product.

This mechanism, in part, explains the selectivity of organocuprates for acid chlorides. Acid chlorides are promoted for this reaction due to the strong electrostatic interaction between chlorine and the lithium cation present. Most other carbonyls compounds, such as ketones, carboxylic acids, esters, acid anhydrides, or amides lack this Cl-Li interaction and react with organocuprate reagents either very slowly or not at all. Because ketones do not react with organocuprate reagents, they are not subject to further nucleophilic additions and are easily isolated as the product of this reaction.



EXAMPLE 21.4.3

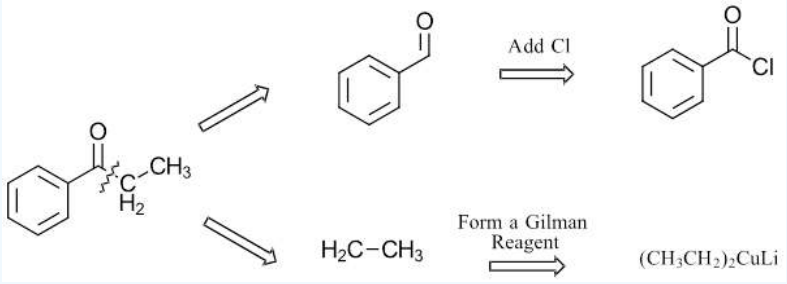
How could the following molecule be synthesized using a Gilman reagent and an acid chloride?



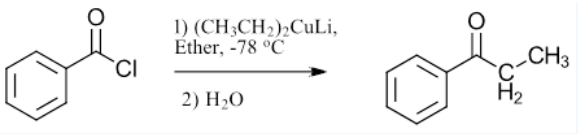
Solution

The key bond formed during this reaction is the C-C sigma bond between the carbonyl carbon and an alpha carbon. Breaking this bond separated the target molecule into two possible two starting materials. The carbonyl carbon gains an –Cl to become an acid chloride and the alkyl fragment becomes part of a Gilman Reagent R_2CuLi. The required alkyl fragment becomes the R group in the Gilman reagent. Remember that the Gilman reagent has contains two of the alkyl fragment. Because ketones have two alpha carbons there should be two possible acid chloride/Gilman reagent combinations to make this molecule.

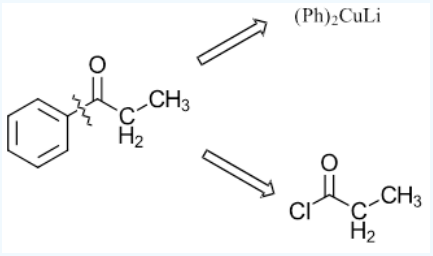
Pathway 1



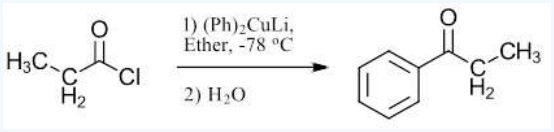
Solution 1



Pathway 2



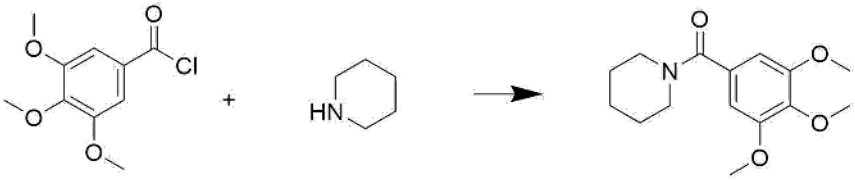
Solution 2



EXERCISES

Q21.4.1

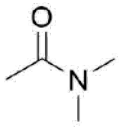
Draw the mechanism for the following reaction



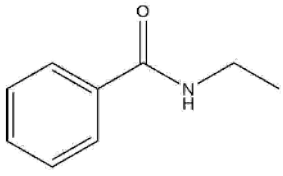
Q21.4.2

Propose a synthesis of the following molecules from an acid chloride and an amide.

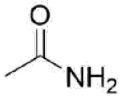
(a)



(b)

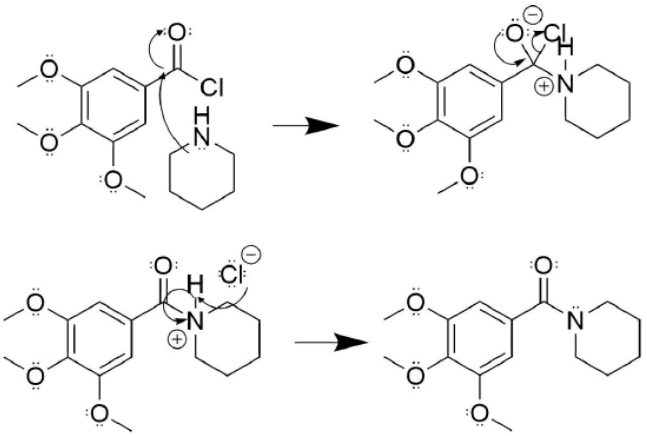


(c)



SOLUTIONS

S21.4.1



S21.4.2

a. Acetyl chloride and dimethylamine
b. Benzoyl chloride and ethylamine
c. Acetyl chloride and ammonia

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21.5: CHEMISTRY OF ACID ANHYDRIDES

OBJECTIVES

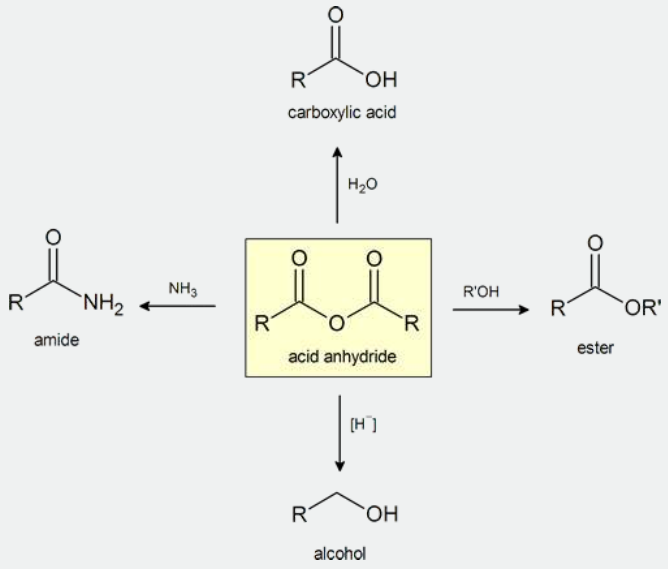
After completing this section, you should be able to

1. write an equation to illustrate the preparation of an acid anhydride from an acid halide and the sodium salt of a carboxylic acid.
2. identify the product formed from the reaction of a given acid halide with the sodium salt of a given carboxylic acid.
3. identify the acid halide, carboxylate salt, or both, required to prepare a given acid anhydride.
4. write an equation to describe the reaction of an acid anhydride with each of the following: water, alcohol, ammonia, a primary or secondary amine, lithium aluminum hydride.
5. identify the product formed when a given acid anhydride is reacted with any of the reagents listed in Objective 4, above.
6. write a detailed mechanism for the reaction of an acid anhydride with any of the reagents listed in Objective 4, above.
7. identify the acid anhydride, the nucleophilic reagent, or both, needed to prepare a specified carboxylic acid, ester, amide, or primary alcohol.

STUDY NOTES

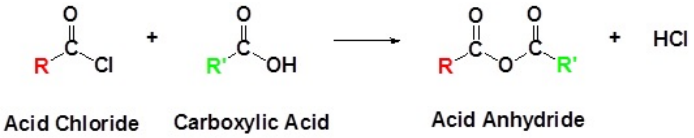
The reactions described in this section are, in principle, identical to those discussed in Section 21.4. Once you have understood the mechanism of nucleophilic acyl substitution, these reactions should not present you with any great difficulty, and memorization can be kept to a minimum.

This figure provides a convenient general summary of a few of the reactions described in Section 21.5. Note that from a synthetic perspective the ester- and amide-forming reactions are the most common, so they are the focus of this section.



PREPARATION OF ACID ANHYDRIDES

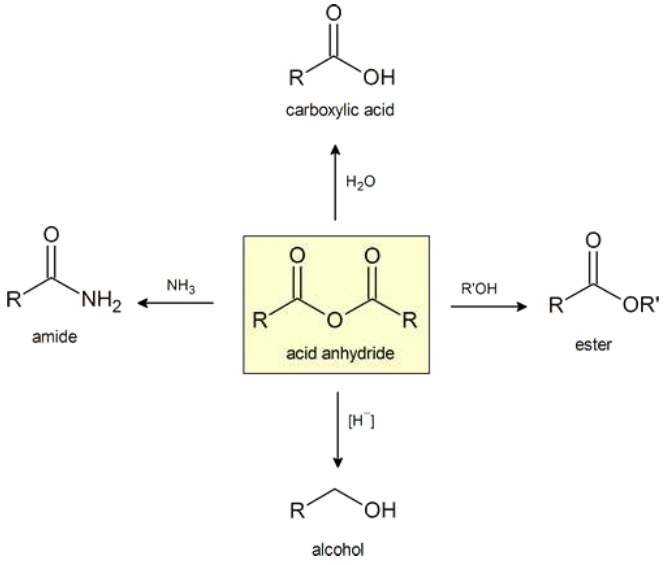
As show in Section 21.4, acid anhydrides are generally made using a nucleophilic acyl substitution reaction of an acid chloride with a carboxylic acid or a carboxylate anion.



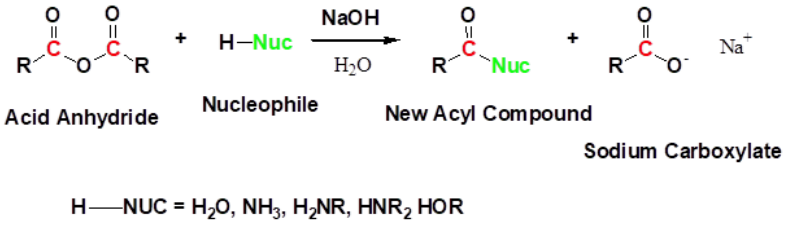
CHEMISTRY OF ANHYDRIDES

Anhydrides are highly reactive to nucleophilic attack and undergo many of the same reactions as acid chlorides that were explored in section 21.4. Although slower reacting than acid chlorides, anhydrides react with water to form carboxylic acids, with alcohols to form

esters, and with amines to form amides. Anhydrides can also be reduced to 1º alcohols by hydride reduction. Because many anhydrides are made from the coupling of two carboxylic acids, reactions using anyhydrides waste one equivalent of the carboxylic acid as a leaving group. As a consequence, reactions are only commonly performed with inexpensive, readily available anhydrides, such as acetic anhydride or benzoic anhydride. Anydrides have the advantage of being easier to work with than acid chlorides.



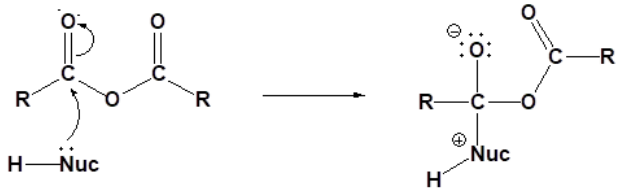
GENERIC REACTION WITH AN ANHYDRIDE



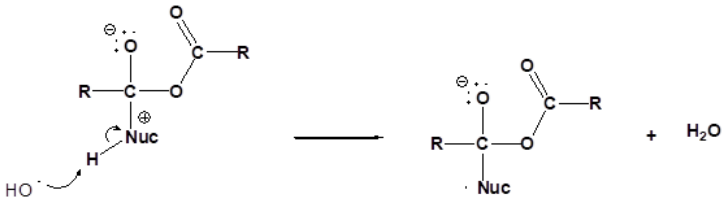
GENERIC MECHANISM OF NUCLEOPHILIC ACYL SUBSTITUTION USING AN ANHYDRIDE

The following nucleophilic acyl substitution reactions are all similar and can be represented by one generic mechanism. The nuceophile (water, ammonia, amine, or alcohol) adds to one of the carbonyl carbons in the anhydride forming a tetrahedral alkoxide intermediate. The reforming of the carbonyl C=O bond eliminates a carboxylate leaving group. Because the nucleophile is neutral, a protonated intermediate is formed. A base deprotonates the intermediate to form the neutral carboxylic acid derivative product (carboxylic acid, ester, amide).

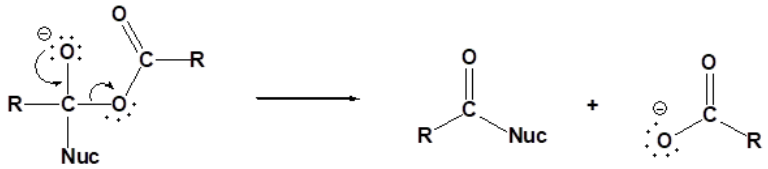
1) Nucleophilic attack



2) Deprotonation

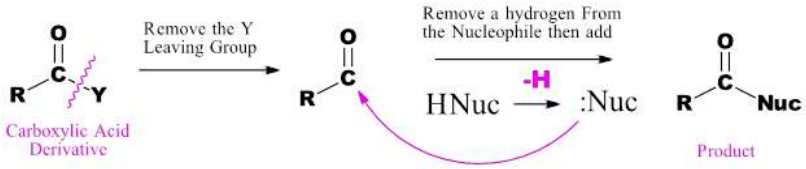


3) Leaving group removal



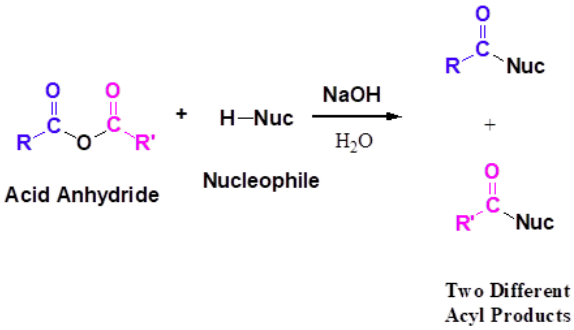
PREDICTING THE PRODUCTS OF AN ANHYDRIDE REACTION

An anhydride and a neutral nucleophile react to form a new acyl compound through nucleophilic acyl substitution. During this reaction there are three changes in bonding. The leaving group is removed from the anhydride. The neutral nucleophile loses a hydrogen. A C-Nuc bond is formed between the nucleophile and the anhydride's electrophilic carbonyl carbon.



REACTIONS WITH ASYMMETRICAL ANHYDRIDES

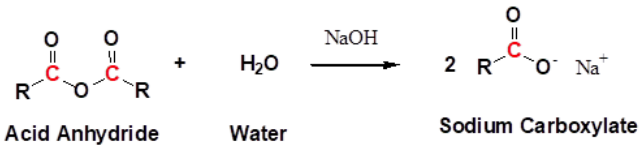
Asymmetrical anhydrides are typically not used in the formation of esters and amides because they have the possibility of forming two different products. This is not the case when symmetrical anhydrides are used.



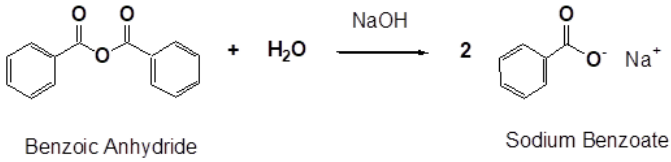
CONVERSION OF ACID ANHYDRIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Anhydrides react rapidly with water to form two carboxylic acids compounds. Because anhydrides are often prepared from carboxylic acids this reaction serves little synthetic value. However, this reaction serves as a reminder to prevent the exposure of anhydrides to moisture because they will become contaminated with the corresponding carboxylic acids.

GENERAL REACTION



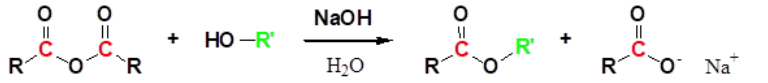
EXAMPLE



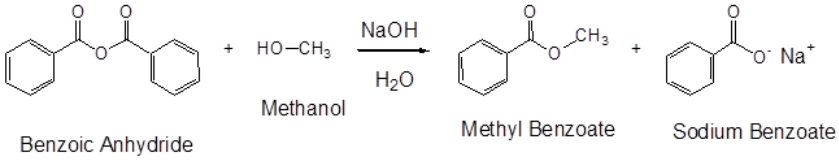
CONVERSION OF ACID ANHYDRIDES TO ESTERS: ALCOHOLYSIS

Anhydrides react with alcohols to form esters as the main product and a carboxylate as a side product. The reaction is typically run with a base, such as NaOH or pyridine, to remove any acid produced. Notice that one acyl group from the anhydride is incorporated into the ester and the other acyl group forms a carboxylate.

GENERAL REACTION

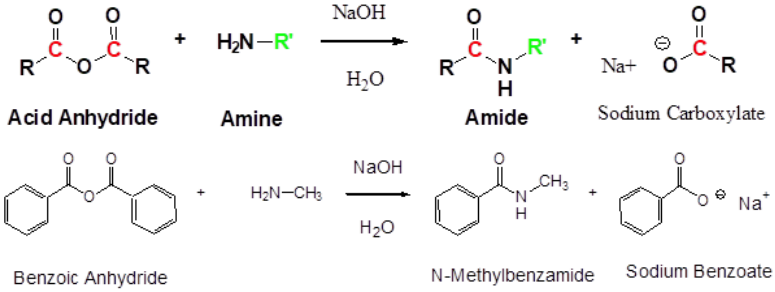


EXAMPLE



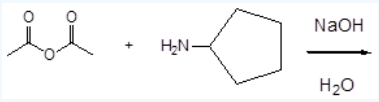
CONVERSION OF ACID ANHYDRIDES TO AMIDES: AMINOLYSIS

Acid anhydrides react with ammonia, 1º, or 2º amines to form the corresponding amides. Two molar equivalents of amine are required. It is important to run this reaction with a base to neutralize the acid produced otherwise the amine reactant would be become protonated to form a non-nucleophilic ammonium compound. During the reaction, one acyl group from the anhydride becomes part of the amide while the other acyl group becomes a carboxylate.



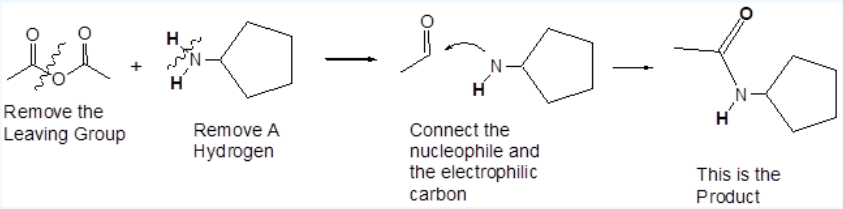
✔ EXAMPLE 21.5.1

Draw the products of the following reaction:



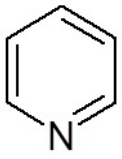
Solution

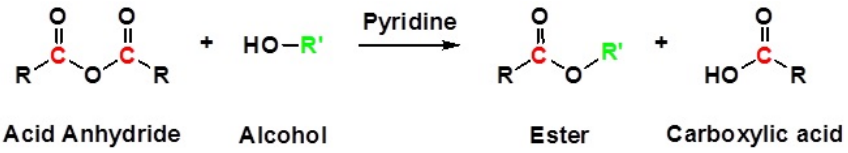
The reaction of an anhydride and an amine form an amide through nucleophilic acyl substitution. During this reaction three changes in bonding occur. The leaving group is removed from the anhydride. The amine loses a hydrogen. A C-N bond is formed between the amine and the electrophilic carbonyl carbon.



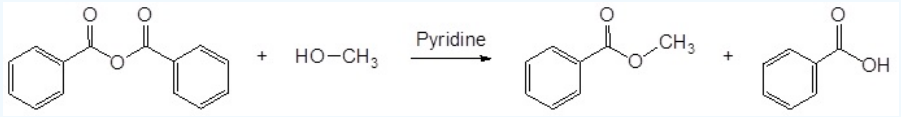
ACID ANHYDRIDES REACT WITH ALCOHOLS TO FORM ESTERS

Reactions of anhydrides use Pyridine as a solvent



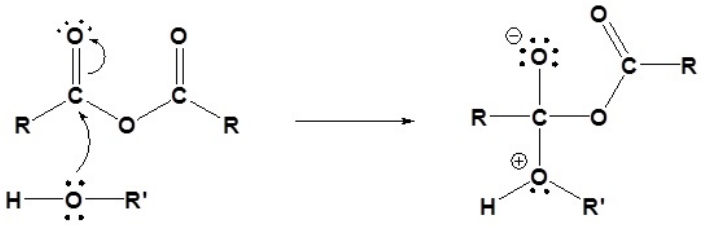


EXAMPLE 21.5.1

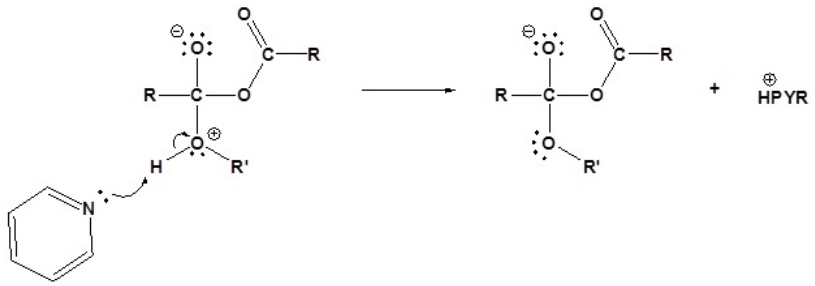


MECHANISM

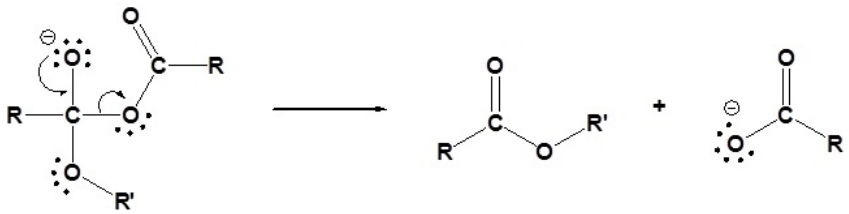
1) Nucleophilic Attack by the Alcohol



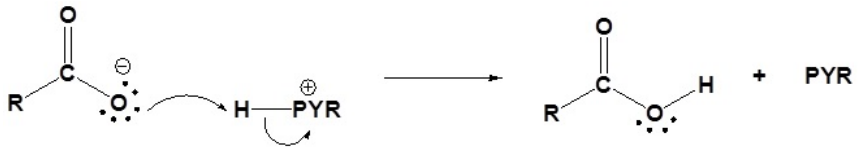
2) Deprotonation by pyridine



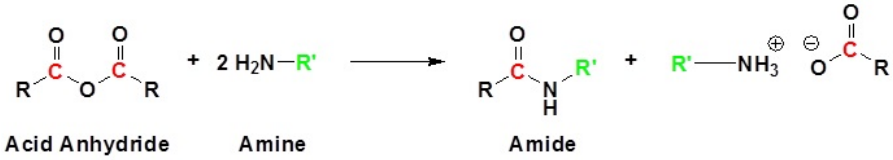
3) Leaving group removal



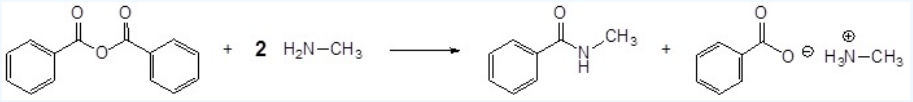
4) Protonation of the carboxylate



ACID ANHYDRIDES REACT WITH AMINES TO FORM AMIDES

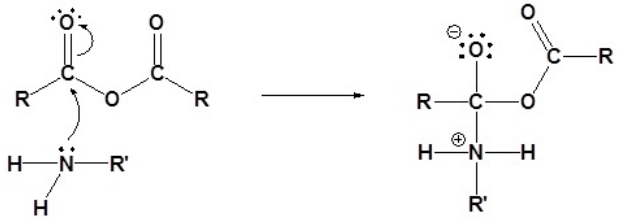


EXAMPLE 21.5.2

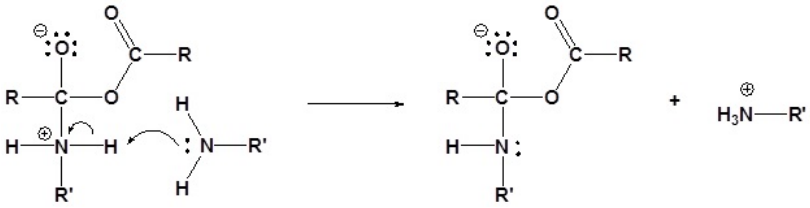


MECHANISM

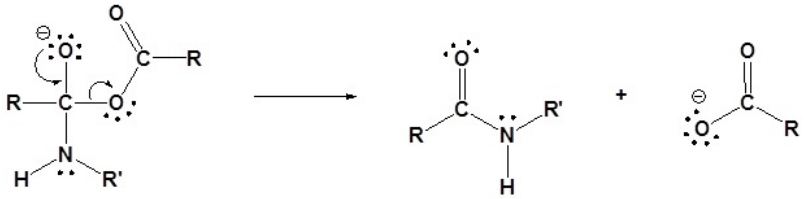
1) Nucleophilic Attack by the Amine



2) Deprotonation by the amine



3) Leaving group removal

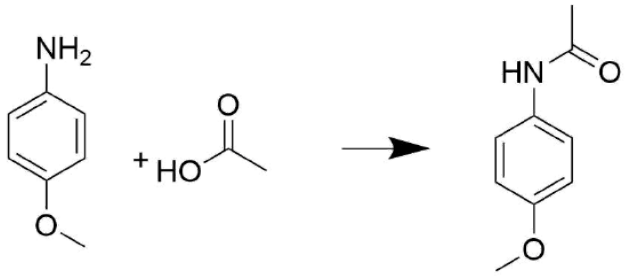


EXERCISES

QUESTIONS

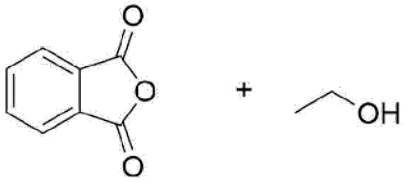
Q21.5.1

Draw out the mechanism for the following reaction.



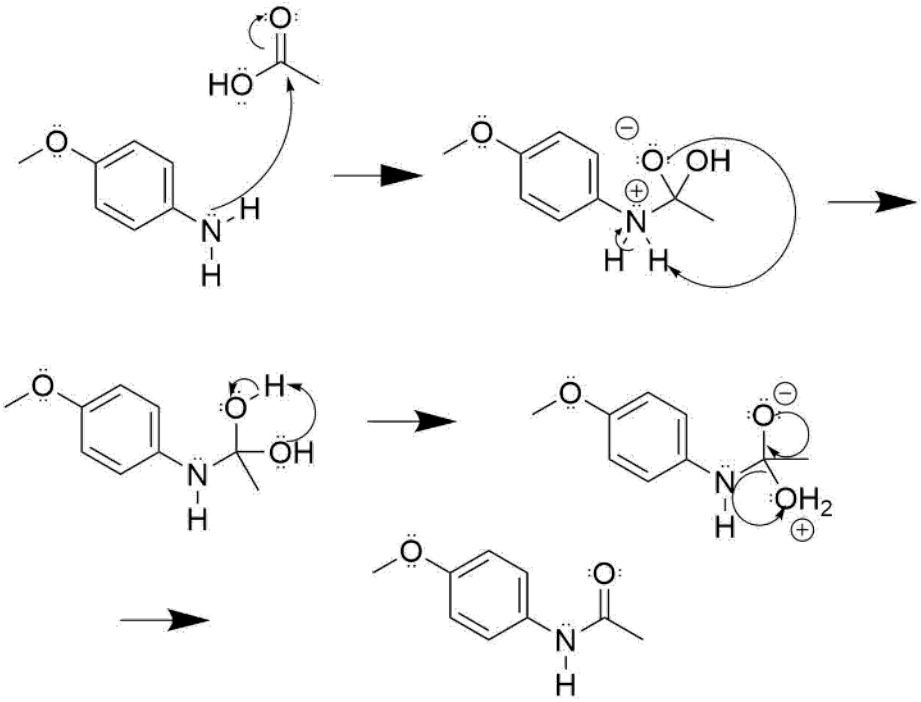
Q21.5.2

Draw the product of the reaction between these two molecules.

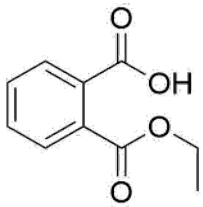


SOLUTIONS

S21.5.1



S21.5.1



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21.6: CHEMISTRY OF ESTERS

OBJECTIVES

After completing this section, you should be able to

1. discuss the wide occurrence of esters in nature, and their important commercial uses, giving one example of an ester linkage in nature, and one example of a commercially important ester.
2. write an equation to describe the hydrolysis of an ester under acidic or basic conditions.
3. identify the products formed from the hydrolysis of an given ester.
4. identify the reagents that can be used to bring about ester hydrolysis.
5. identify the structure of an unknown ester, given the products of its hydrolysis.
6. write the mechanism of alkaline ester hydrolysis.
7. write the mechanism of acidic ester hydrolysis.
8. write an equation to describe the reduction of an ester with lithium aluminum hydride.
9. identify the product formed from the reduction of a given ester (or lactone) with lithium aluminum hydride.
10. identify the ester, the reagents, or both, that should be used to prepare a given primary alcohol.
11. write a detailed mechanism for the reduction of an ester by lithium aluminum hydride.
12. identify diisobutylaluminum hydride as a reagent for reducing an ester to an aldehyde, and write an equation for such a reaction.
13. write an equation to describe the reaction of an ester with a Grignard reagent.
14. identify the product formed from the reaction of a given ester with a given Grignard reagent.
15. identify the ester, the Grignard reagent, or both, needed to prepare a given tertiary alcohol.
16. write a detailed mechanism for the reaction of an ester with a Grignard reagent.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- lactone
- saponification

STUDY NOTES

Many esters have characteristic aromas and flavours. Some examples are listed below.

Basic structure:

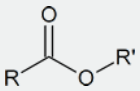
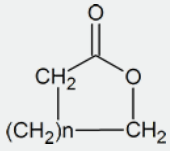


Table 21.1 Structures and characteristic odours of selected esters

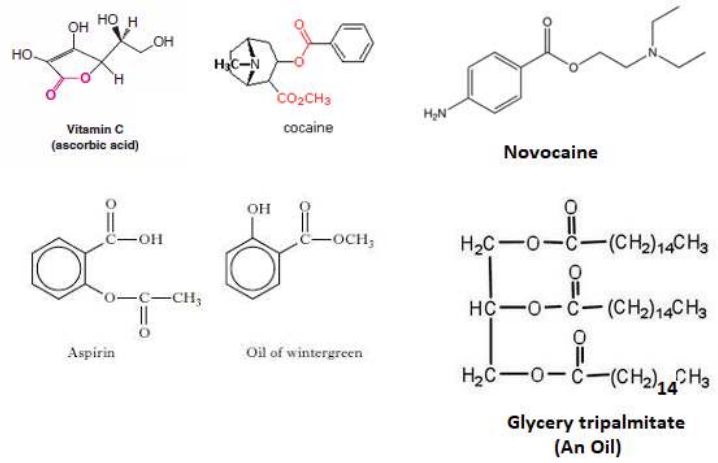
IUPAC name	R	R′	Aroma
octyl ethanoate	CH_3	$CH_3(CH_2)_6CH_2$	orange
propyl ethanoate	CH_3	$CH_3CH_2\ CH_2$	pear
2-methylpropyl propanoate	CH_3CH_2	$(CH_3)_2CHCH_2$	rum
methyl butanoate	$CH_3CH_2CH_2$	CH_3	apple
ethyl butanoate	$CH_3CH_2CH_2$	CH_3CH_2	pineapple

A “lactone” is a cyclic ester and has the general structure

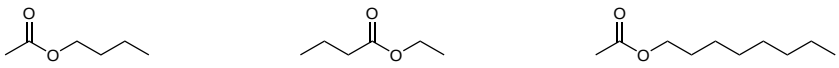


By recognizing that the steps in the acidic hydrolysis of an ester are exactly the same as those in a Fischer esterification (but in the reverse order!), you can again minimize the amount of memorization that you must undertake. The details of both mechanisms can be deduced from the knowledge that both reactions are acid-catalyzed nucleophilic acyl substitutions.

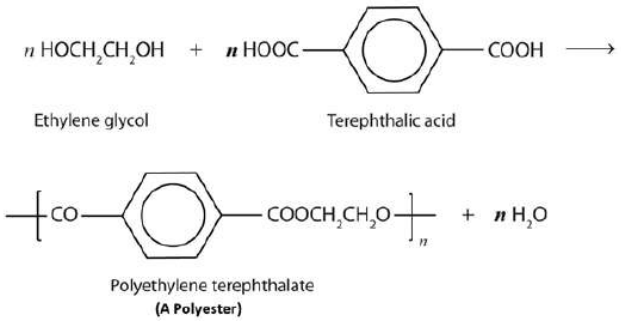
Esters are present in a many biologically important molecules, which have a wide range of effects including fats, waxes, Vitamin C, Cocaine, Novacaine, oil of wintergreen, and aspirin.



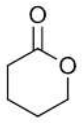
Esters compounds are often the source of the pleasant aromas of many fruits.



Esters are also present in a number of important commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers. PET is used to make bottles for water and other beverages. It is also formed into films called Mylar which is used in balloons. Synthetic arteries can be made from PET, polytetrafluoroethylene (PTFE), and other polymers.



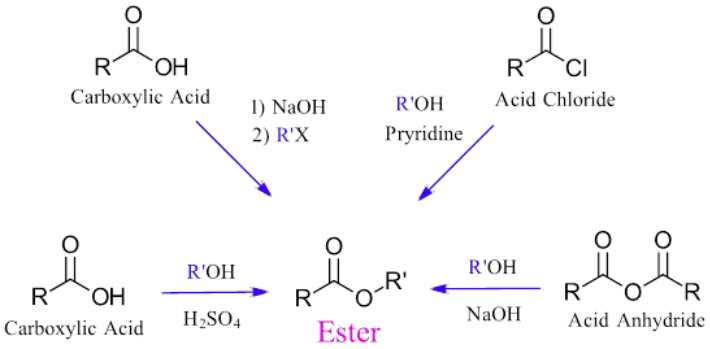
Lactones, cyclic esters, have similar reactivity as acyclic esters.



PREPARATION OF ESTERS

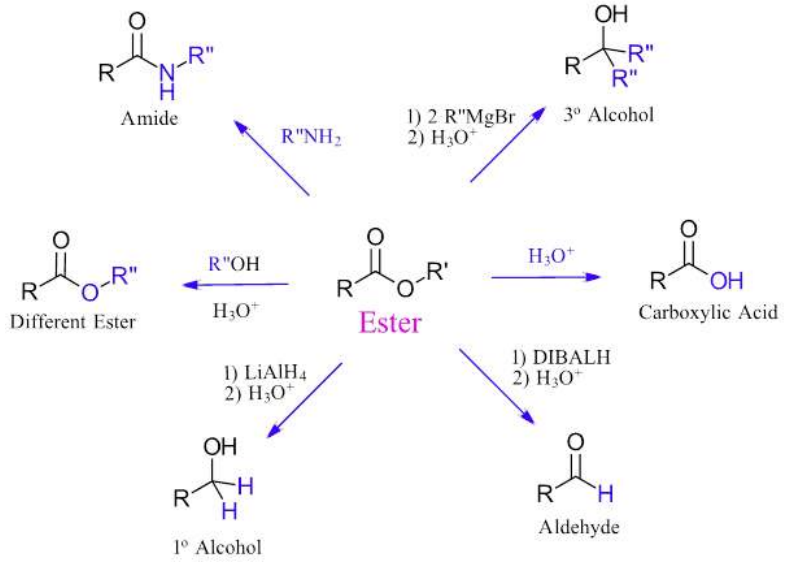
The most versatile method for the preparations of esters is the nucleophilic acyl substitution of of an acid chloride with an alcohol. Acid ahydrides and carboxylic acids can also react with alcohols to form esters but both reactions are limited to formation of simple esters. Esters

can also be formed by deprotonating a carboxylic acid to form a carboxylate and then reacting it with a primary alkyl halide using an S_N2 reaction.



REACTIONS OF ESTERS

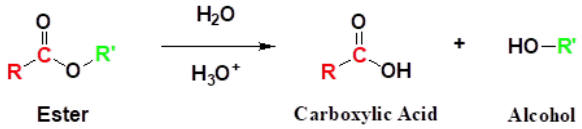
Esters are one of the more useful functional groups. Their low reactivity makes the easy to work with and they are stable enough to be used as a solvent in organic reactions (ex. ethyl acetate). Esters are still reactive enough to undergo hydrolysis to form carboxylic acids, alcoholysis, to form different esters, and aminolysis to form amides. Also, they can react with Grignard reagents to form 3° alcohols and hydride reagents to form 1° alcohols or aldehydes.



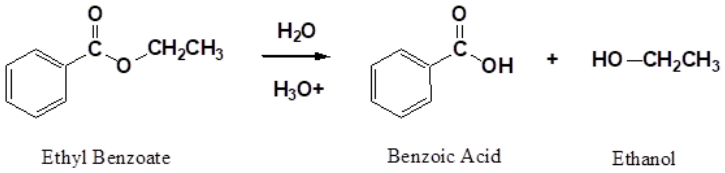
CONVERSION OF ESTERS TO CARBOXYLIC ACIDS: HYDROLYSIS

Esters can be cleaved back into a carboxylic acid and an alcohol through reaction with water and a catalytic amount of strong acid. This reaction represents the reverse of the acid catalyzed esterification of a carboxylic acid and an alcohol discussed in Section 21.3. Both the ester formation and cleavage reactions are part of an equilibrium which can be manipulated using Le Chatelier's principle. For ester hydrolysis, the equilibrium is shifted toward carboxylic acid formation by using a large excess of water in the reaction.

GENERAL REACTION



EXAMPLE

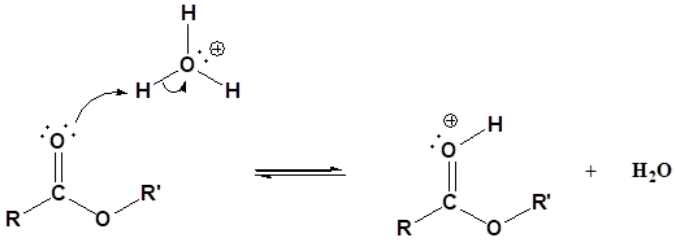


Ethyl Benzoate | Benzoic Acid | Ethanol

MECHANISM

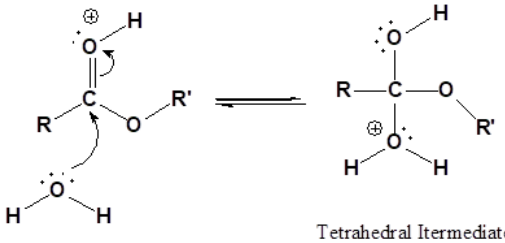
Acid catalysis is required during ester hydrolysis due to water being a weak nucleophile. Protonation of the ester carbonyl increases the partial positive charge on the carbonyl carbon increasing its electrophilicity. After protonation, water adds to the carbonyl carbon causing the formation of a tetrahedral alkoxide intermediate. Then a proton transfers to the –OR group, increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an alcohol (HOR) as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, water acts as a base, removing a hydrogen, to form a carboxylic acid and regenerating the acid catalyst.

1) Protonation of the carbonyl



Ester | Protonated Ester

2) Nucleophilic attack by water

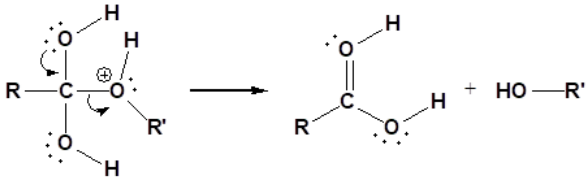


Tetrahedral Itermediate

3) Proton transfer

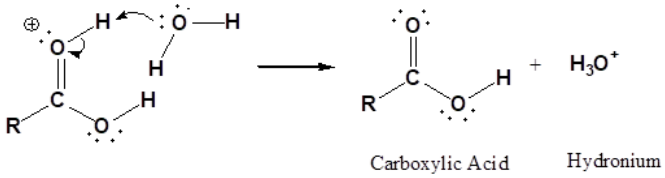


4) Leaving group removal



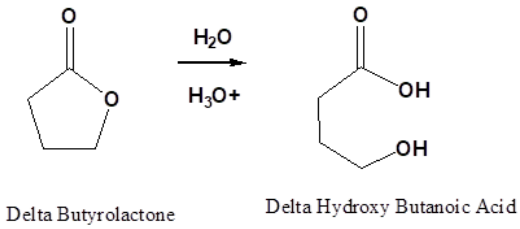
Protonated Carboxylic Acid | Alcohol

5) Deprotonation



HYDROLYSIS OF LACTONES

Lactones (Cyclic esters) undergo typical reactions of esters including hydrolysis. Hydrolysis of the lactone under acidic conditions creates a hydroxyacid.

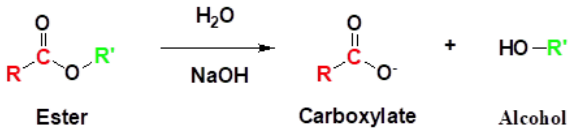


CONVERSION OF ESTERS TO CARBOXYLIC ACIDS: SAPONIFICATION

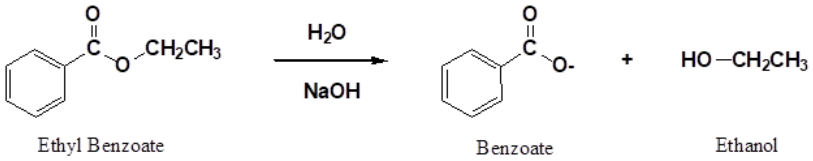
Esters can also be cleaved into a carboxylate and an alcohol through reaction with water and a base. The reaction is commonly called a saponification from the Latin sapo which means soap. This name comes from the fact that soap used to me made by the ester hydrolysis of fats.

Saponification reaction utilize a better nucleophile (hydroxide) and are typically faster than an acid catalyzed hydrolysis. The carboxylation ions produced by saponification are negatively charged and very unreactive toward further nucleophilic substitution which makes the reaction irreversible.

GENERAL REACTION



EXAMPLE

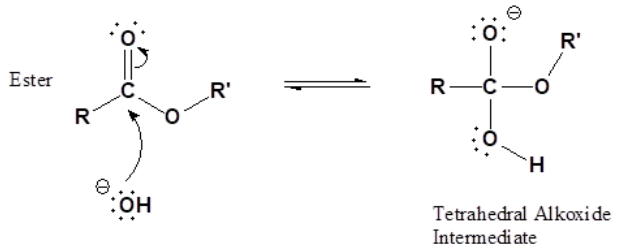


MECHANISM

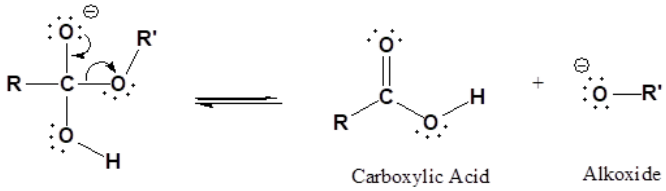
The base-promoted hydrolysis of an ester follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of ester saponification begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon to give a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an alkoxide (-OR) leaving group yielding a carboxylic acid. The alkoxide base deprotonates the carboxylic acid to for a carboxylate salt and an alcohol as products.

The last deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the saponification towards completion. Because the carboxylic acid is no longer part of the equilibrium the reaction is effectively irreversible.

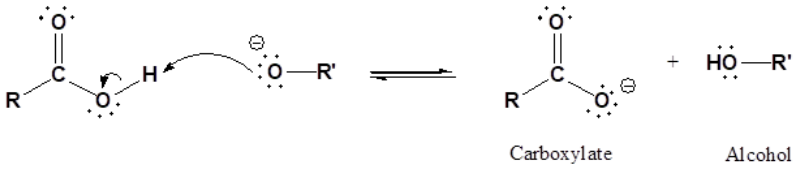
1) Nucleophilic attack by hydroxide



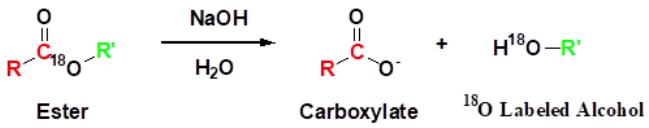
2) Leaving group removal



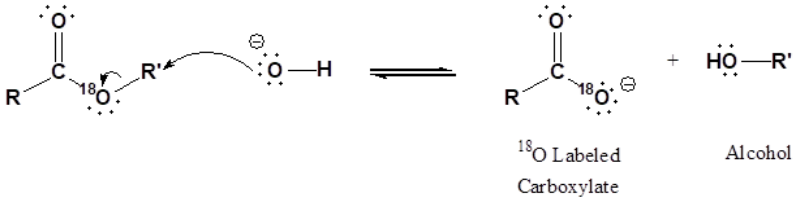
3) Deprotonation



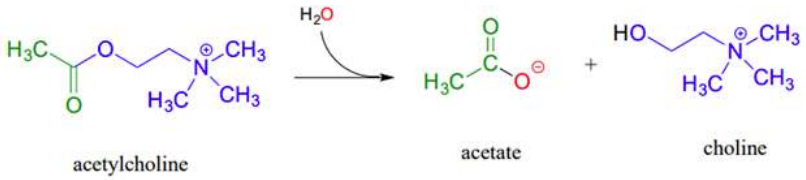
This mechanism is supported by experiments performed using isotopically labeled esters. When the ether-type oxygen of the ester was labeled with ^{18}O, the labeled oxygen showed up in the alcohol product after hydrolysis.



An alternative mechanism would be if the hydroxide participated in an S_N2 reaction to create the carboxylate product. If this were to happen the alcohol reaction product would not contain the labeled oxygen.



Ester saponification in biological systems, called hydrolytic acyl substitution reactions, are common. In particular, acetylcholinesterase, an enzyme present in the synapse, catalyzes hydrolysis of the ester group in acetylcholine which is a neurotransmitter that triggers muscle contraction. Like many other hydrolytic enzymes, the acetylcholinesterase reaction proceeds in two phases: first, a covalent enzyme-substrate intermediate is formed when the acyl group of acetylcholine is transferred to an active-site serine on the enzyme (a transesterification reaction). A water nucleophile then attacks this ester, driving off acetate and completing the hydrolysis

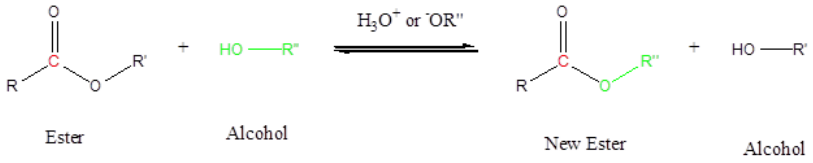


CONVERSION OF ESTERS TO DIFFERENT ESTERS: TRANSESTERIFICATION

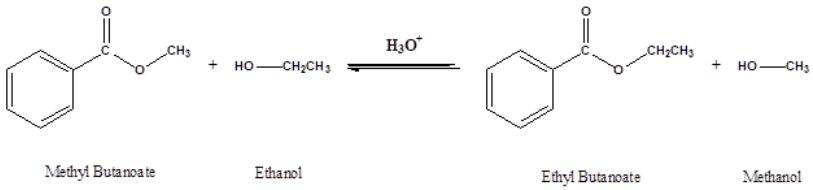
Transesterification is a reaction where an ester is converted to a different ester through reaction with an alcohol. Because there is typically very little difference in stability between both esters, the equilibrium constant of this reaction is usually near one. Using a large excess of the reactant alcohol or removing the alcohol side-product can push the reaction equilibrium towards the products by Le Chatelier's principal.

Transesterifications also shows that great care should be taken when an ester containing compound is used in a reaction involving an alcohol.

GENERAL REACTION



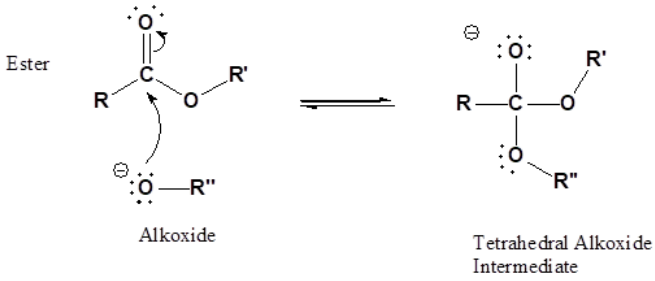
EXAMPLE



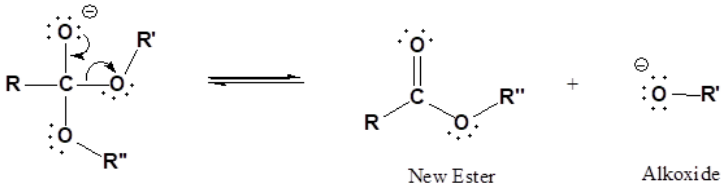
MECHANISM IN BASIC CONDITIONS

The reaction follows the basic mechanism of a nucleophilic acyl substitution. The alkoxide leaving group of the ester is replace by an incoming alkoxide nucleophile creating a different ester.

1) Nucleophilic attack by an alkoxide



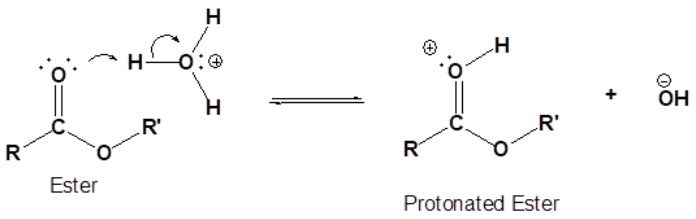
2) Leaving group removal



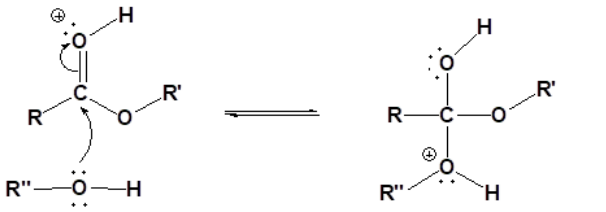
MECHANISM IN ACIDIC CONDITIONS

Protonation allows the alcohol reactant to add to the ester carbonyl. Proton transfer to the ester's alkoxy group increases it ability to act as a leaving group. Reforming the C=O carbonyl bond removes the leaving group and subsequent deprotonation by water forms the ester product.

1) Protonation of the carbonyl



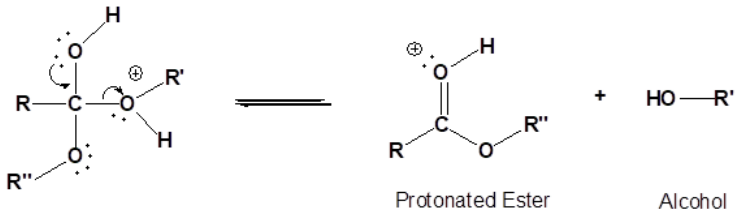
2) Nucleophilic attack on the carbonyl



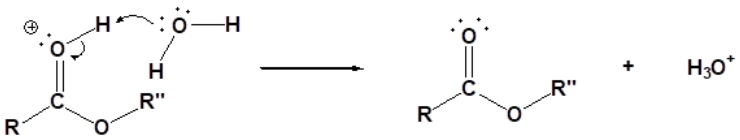
3) Proton transfer



4) Removal of the leaving group

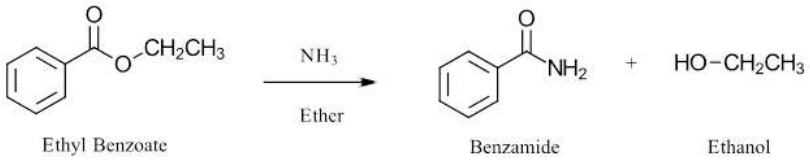


5) Deprotonation



CONVERSION OF ESTER TO AMIDES: AMINOLYSIS

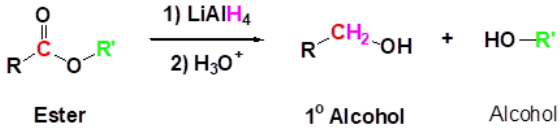
It is possible to convert esters to amides through direct reaction with ammonia or amines. However, these reactions are not commonly used because the formation of an amide using an acid chloride is a much simpler reaction.



CONVERSION OF ESTERS TO 1^{O} ALCOHOLS: HYDRIDE REDUCTION

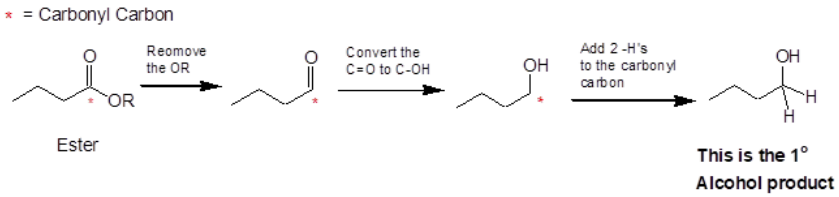
Esters can undergo hydride reduction with $LiAlH_4$ to form two alcohols. The alcohol derived from the acyl group of the ester will be 1° and is typically considered the main product of the reaction. The other alcohol is derived from the ester's alkoxy group and is typically considered a side-product of the reaction. Note! Sodium borohydride ($NaBH_4$) is not a reactive enough hydride agent to reduce esters or carboxylic acids. In fact, $NaBH_4$ can selectively reduce aldehydes and ketones in the presence of ester functional groups.

GENERAL REACTION

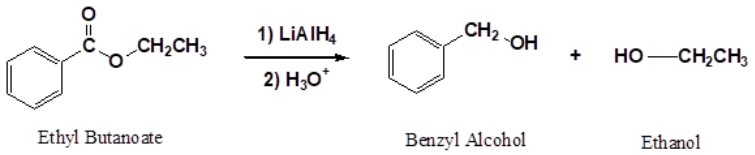


PREDICTING THE PRODUCTS OF A HYDRIDE REDUCTION

There are three major changes in bonding during this reaction: 1) The –OR leaving group is removed from the ester. 2) The C=O carbonyl bond is converted to a C-O-H, an alcohol. 3) Two C-H bonds are formed as two of the hydride nucleophiles are added to the original carbonyl carbon of the ester.



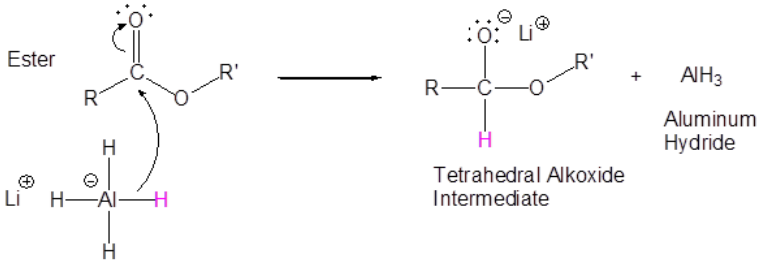
EXAMPLE



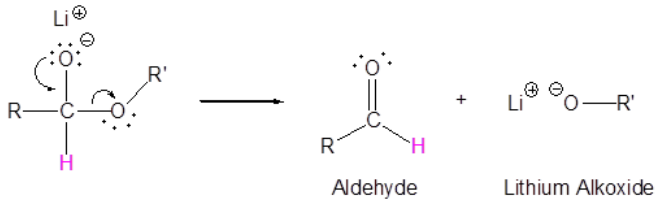
MECHANISM

The mechanisms for the hydride reduction of esters is analogous to the hydride reduction of carboxylic acids. Nucleophilic acyl substitution replaces the –OR leaving group in ester with a hydride nucleophile to form an aldehyde intermediate. Because aldehydes are more reactive than esters, they rapidly undergo a second nucleophilic hydride addition to form a tetrahedral alkoxide intermediate. An acid work-up protonates the alkoxide to create a 1º alcohol.

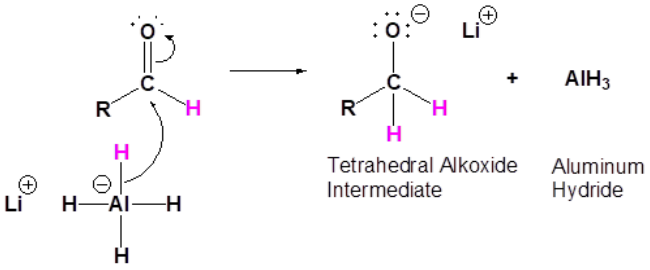
1) Nucleophilic attack by the hydride



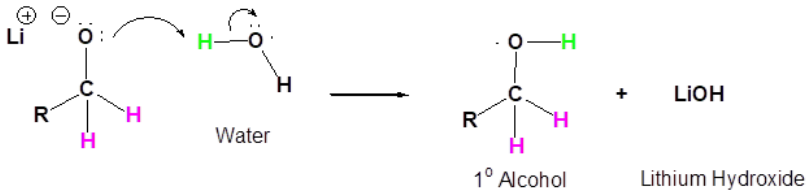
2) Leaving Group Removal



3) Nucleopilic attack by the hydride anion



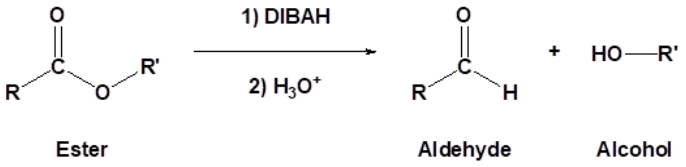
4) The alkoxide is protonated



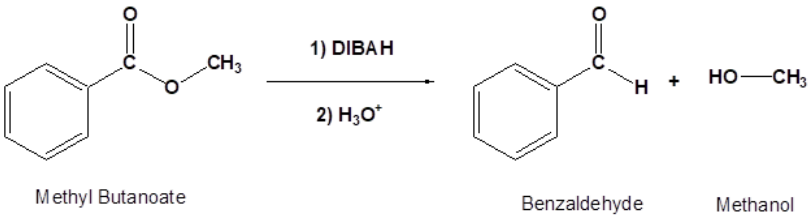
CONVERSION OF ESTERS TO ALDEHYDES: HYDRIDE REDUCTION

Much like acid chlorides, esters can be converted to aldehydes using the weaker reducing reagent diisobutylaluminum hydride (DIBALH). As shown above, an aldehyde intermediate is produced after an ester undergoes nucleophilic acyl substitution with a hydride. When DIBALH is used as the hydride source, the aldehyde does not react further and is isolated as the product of the reaction. The reaction is usually carried out at -78 ^{o}C to help isolate the aldehyde product.

GENERAL REACTION



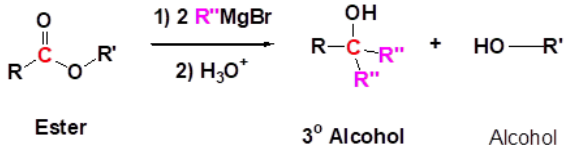
EXAMPLE



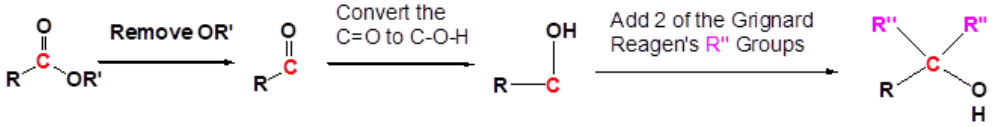
CONVERSION OF ESTERS TO 3° ALCOHOLS: GRIGNARD REAGENTS

Addition of Grignard reagents converts esters to two alcohols, one 3° alcohols (main product) and one 1° alcohol (considered a side product). The Grignard reagent adds to the ester twice, once during a nucleophilic acyl substitution to form a ketone intermediate then again during a nucleophilic addition to form the 3° alcohol product. Overall, during this reaction two C-C bonds are formed on the ester's original carbonyl carbon.

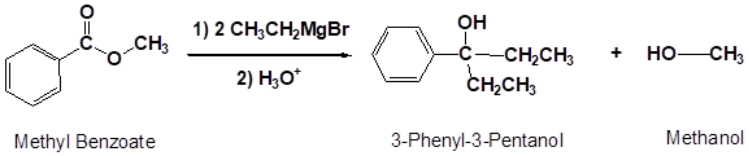
GENERAL REACTION



PREDICTING THE PRODUCTS OF A GRIGNARD REACTION



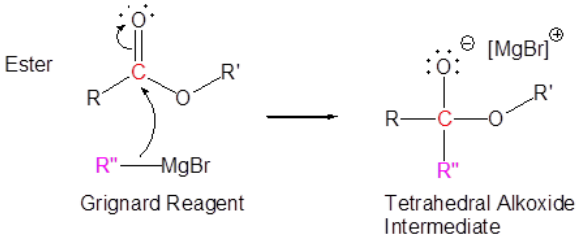
EXAMPLE



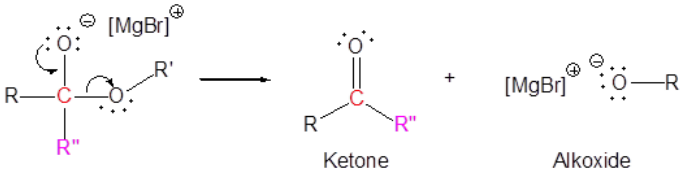
MECHANISM

In the first two steps of the mechanism, the OR leaving group from the ester is replaced by the R group from the Grignard reagent through a nucleophilic acyl substitution. This forms a ketone intermediate which is not isolated because ketones, which are more reactive than esters, rapidly undergo nucleophilic addition with a second equivalent of the Grignard reagent to form an alkoxide intermediate. An acid work-up protonates the alkoxide to form the 3° alcohol product.

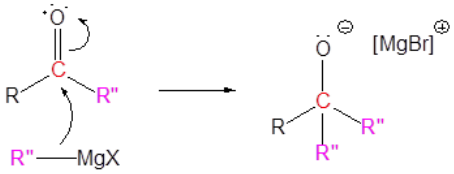
1) Nucleophilic Attack



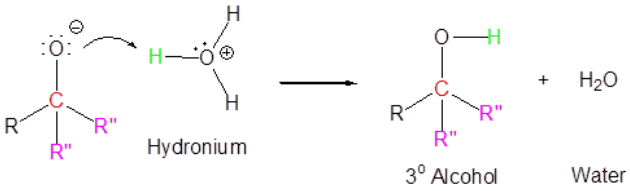
2) Leaving group removal



3) Nucleophilic attack

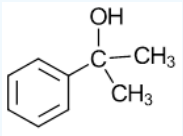


4) Protonation



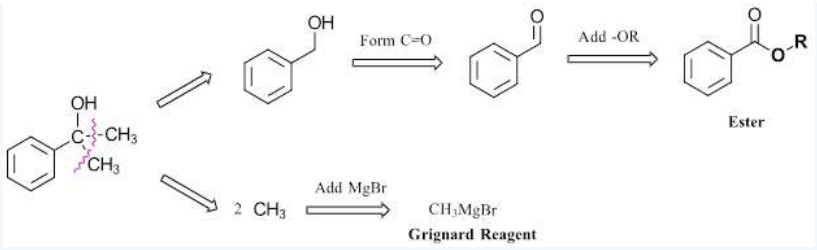
EXAMPLE 21.6.1

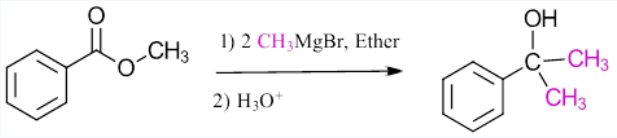
How could the following molecule be made using a Grignard reagent and an ester?



Solution

The key bond breaks for this example are two C-C sigma bonds between the carbonyl carbon and two alpha carbons. Reactions with esters involve a double addition of the Grignard reagent so the fragments removed must be the same. In this example, the C-C bonds involving the two methyl groups are broken. Breaking these bonds separate the target molecule into the required starting materials. The fragment which contains the alcohol carbon forms a C=O carbonyl bond and gains an –OR to become an ester. The R group of the ester is largely unimportant to the overall reaction and is typically a methyl or ethyl group. The alkyl fragments gain MgBr to form a Grignard reagent. Remember that the Grignard reagent only contains one alkyl fragment.

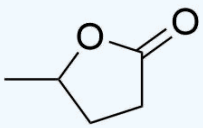




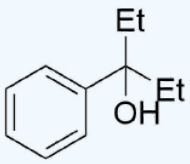
EXERCISES 21.6.1

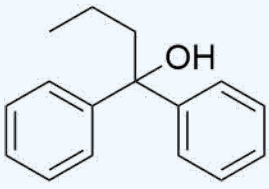
1) Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

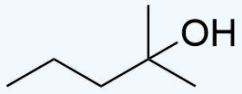
2) Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.



3) How might you Prepare the following molecules from esters and Grignard reagents?

(a)


(b)


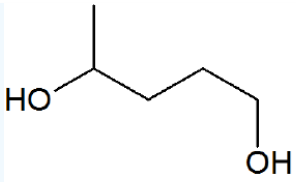
(c)


Answers

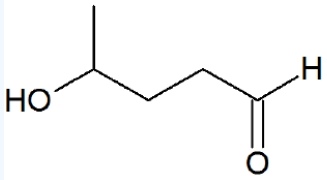
1) The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

2)

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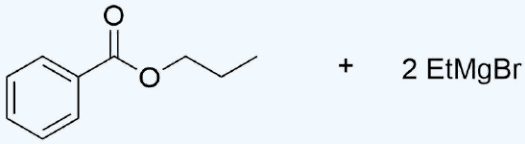
($LiAlH_4$)



(DIBAH)

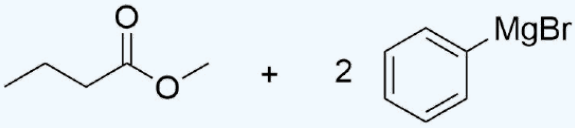
3)

(a)



+ 2 EtMgBr

(b)



(c)

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21.7: CHEMISTRY OF AMIDES

OBJECTIVES

After completing this section, you should be able to

1. write an equation to describe the preparation of an amide from an acid chloride.
2. identify the amide linkage as the basic unit from which all proteins are made, and hence recognize the importance of the amide linkage to biologists and biochemists.
3. write detailed mechanisms for the acidic and basic hydrolysis of amides.
4. write an equation to describe the reduction of an amide to an amine.
5. write a detailed mechanism for the reduction of an amide to an amine.
6. identify the product formed when a given amide is reduced with lithium aluminum hydride.
7. identify the amide, the reagents, or both, necessary to prepare a given amine by direct reduction.
8. identify lactams as being cyclic amides which undergo hydrolysis and reduction in a manner analogous to that of their acyclic counterparts.

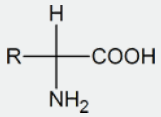
KEY TERMS

Make certain that you can define, and use in context, the key term below.

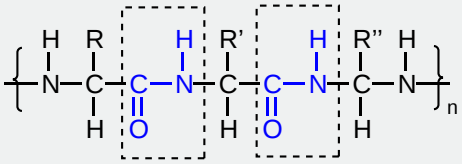
- lactam

STUDY NOTES

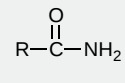
When we talk about amino acids, we are generally referring to *α*-amino acids; that is, compounds in which an amino (NH_2) group and a carboxyl group are attached to the same carbon atom:



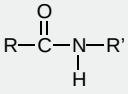
Notice that such compounds contain a chiral carbon atom (unless R = H, which is glycine). Proteins can be considered to consist of amino acid residues joined by amide (or peptide) links. These peptide links consist of exactly the same structural units that we find in *N*-substituted primary amides.



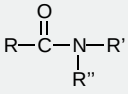
peptide (amide) links



primary amide

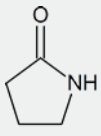


N—substituted primary amide

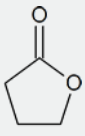


N, *N*—disubstituted primary amide

A lactam is a cyclic amide, in the same way that a lactone is a cyclic ester:

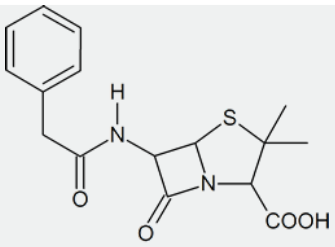


a lactam



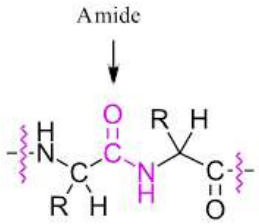
a lactone

Among the most important molecules that contain lactam rings are the penicillins:



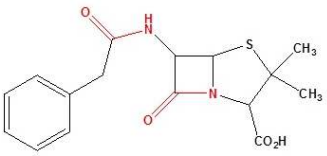
penicillin G (benzylpenicillin)

The amide functional group is extremely important for biological molecules because amides make up the backbone of proteins. Proteins are actually polymers of amino acids, linked by amide groups known as peptide bonds. Proteins (polymers of ~40 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. The individual amino acids within a peptide or protein are called **amino acid residues**.

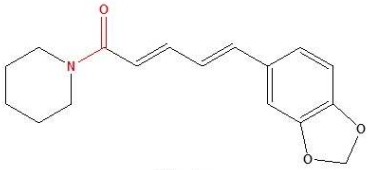


Protein Backbone

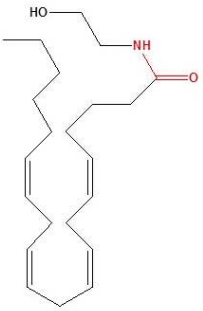
Compounds containing amides have a wide range of biological activity and include penicillin G an antibiotic, piperine which is responsible for the pungent flavor of black pepper, and anandamide which provides some of the pleasurable sensations gained from eating chocolate.



Penicillin G
(An Antibiotic)



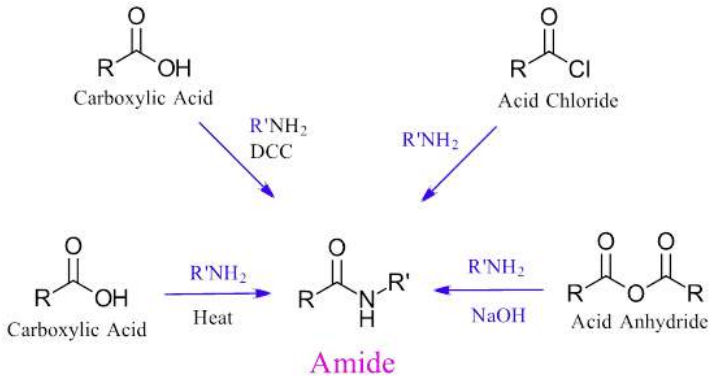
Piperine
(From Black Pepper)



Anandamide
(From Chocolate)

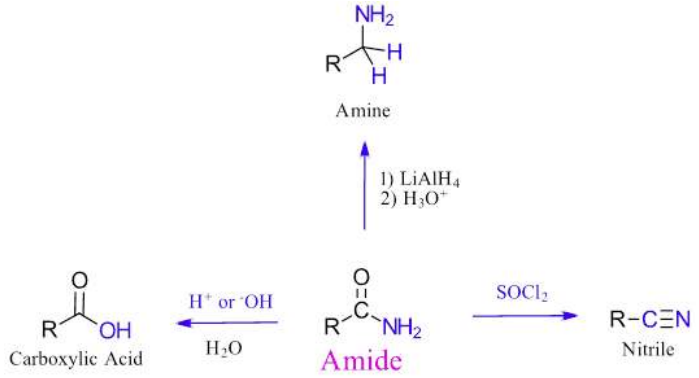
PREPARATION OF AMIDES

Amides are most commonly prepared though the reaction of an acid chloride with ammonia, a 1° amine, or 2° amine. In an analogous reaction, an amide can be prepared through the reaction of a carboxylic acid and an amine using a coupling agent such as DCC. Simple amides can be prepared by reacting an acid anhydride with an amine. Lastly, amides can be formed through the direct reaction of a carboxylic acid and an amine. However, this reaction is rarely used because the conditions are relatively severe.



REACTIONS OF AMIDES

Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group. Despite this, amides can react with water under acidic or basic conditions to create a carboxylic acid through nucleophilic acyl substitution. Reaction of primary amides with thionyl chloride ($SOCl_2$) creates nitriles. Hydride reduction using $LiAlH_4$ causes the carbonyl oxygen of the amide to eliminate as a leaving group creating the corresponding amine.



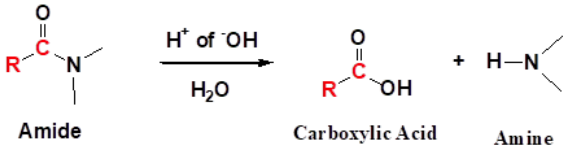
Lactams, cyclic amides, are affected by these reactions in the same fashion as acyclic amides.



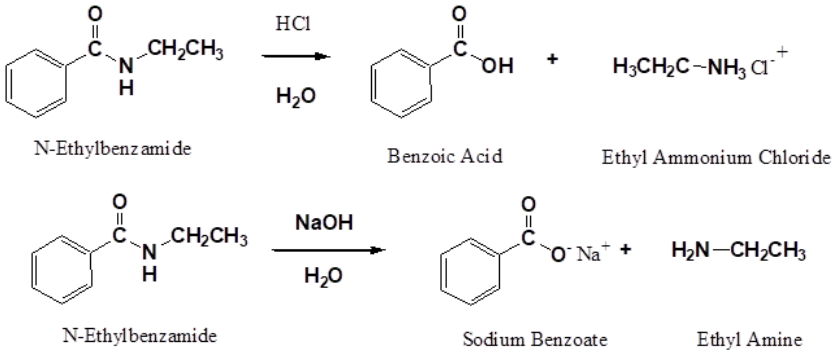
CONVERSION OF AMIDES TO CARBOXYLIC ACIDS: HYDROLYSIS

Amides can be hydrolyzed into a carboxylic acid and ammonia or an amine by heating in an acidic or basic aqueous solution. In both cases, acid-base reactions occurring with the products make the overall reaction irreversible. Under acidic conditions the amine produced by the reaction is protonated to form a non-nucleophilic ammonium compound. Under basic conditions the carboxylic acid produced by the reaction is deprotonated to a non-electrophilic carboxylate.

GENERAL REACTION



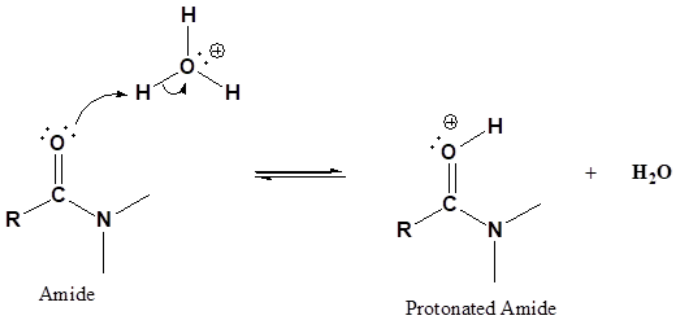
EXAMPLES



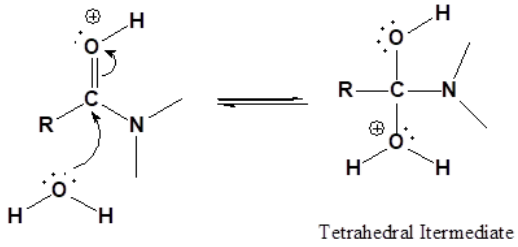
MECHANISM UNDER ACIDIC CONDITIONS

Protonation of the amide increases the electrophilicity of the carbonyl carbon allowing water to add causing formation of a tetrahedral oxonium intermediate. Next a proton is transferred to the amide nitrogen giving it a positive charge and increasing its ability to act as a leaving group. Reforming the carbonyl double bond causes the elimination of an amine as a leaving group, creating a protonated carboxylic acid. In the last step of the mechanism, the produced amine acts as a base, removing a hydrogen, to form a carboxylic acid and an ammonium compound. This final deprotonation step essentially removes the amine from the equilibrium which drives the reaction towards completion. Since the amine is no longer part of the equilibrium, the reaction is effectively irreversible.

1) Protonation of the carbonyl



2) Nucleophilic attack by water

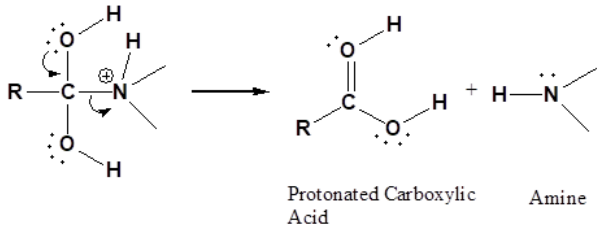


3) Proton transfer

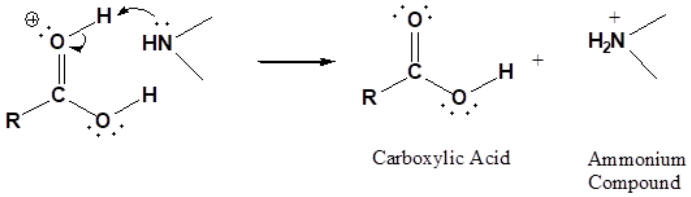


4) Leaving group removal

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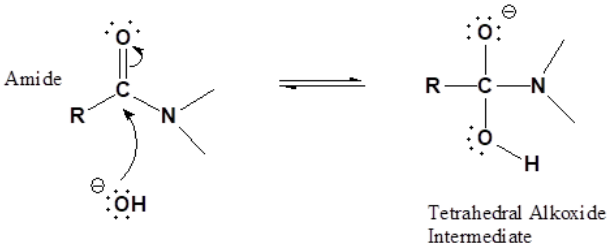
5) Deprotonation



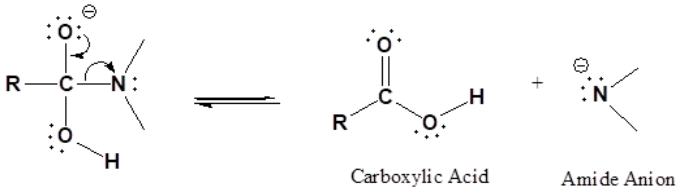
MECHANISM UNDER BASIC CONDITIONS

The base-promoted hydrolysis of an amide follows the typical nucleophilic acyl substitution mechanism. A full equivalent of hydroxide anion is used, so the reaction is called base-promoted and not base catalyzed. The mechanism of basic amide hydrolysis begins with the nucleophilic addition of a hydroxide ion at the carbonyl carbon creating a tetrahedral alkoxide intermediate. The carbonyl bond is reformed along with the elimination of an amide ion (-NHR) leaving group (note this is a different use of the word amide meaning an amine anion), forming a carboxylic acid. In the last step, the amide ion deprotonates the carboxylic acid to form a carboxylate salt and an amine as products. This final deprotonation step essentially removes the carboxylic acid from the equilibrium which drives the reaction towards completion. Since the carboxylic acid is no longer part of the equilibrium, the reaction is effectively irreversible.

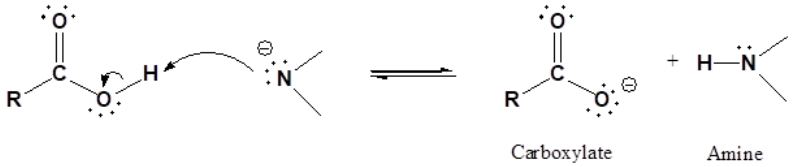
1) Nucleophilic attack by hydroxide



2) Leaving group removal

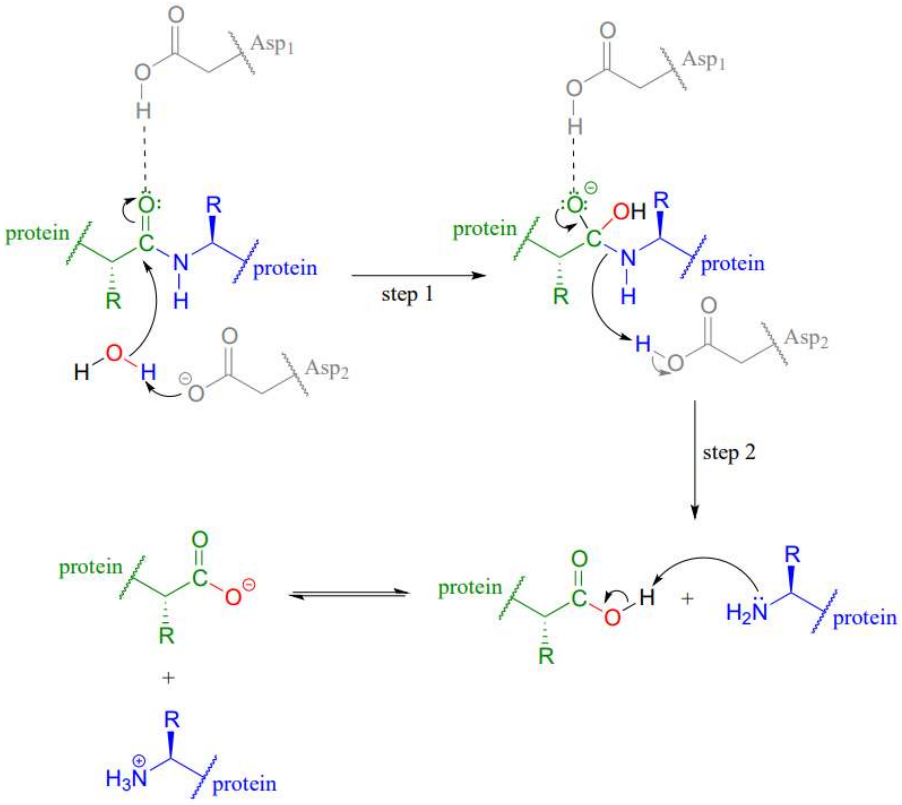


3) Deprotonation



HYDROLYSIS OF PROTEINS

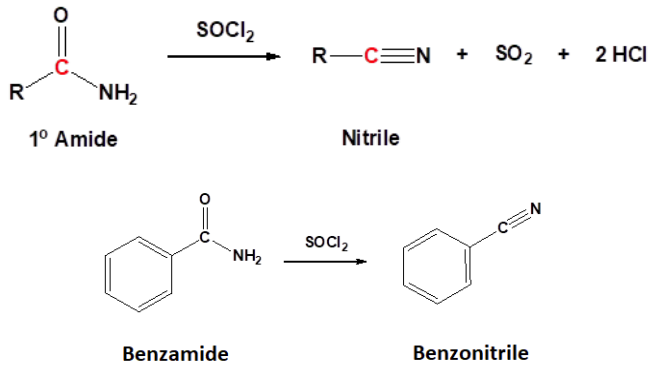
Hydrolysis of amide bonds is the first step in the metabolism of dietary proteins. Protein hydrolysis is catalyzed by protease enzymes (abbreviated Asp_1 and Asp_2 in the figure below). The mechanisms starts with the nucleophilic acyl substitution by water while breaking the amide C-N bond. This produces a protein fragment with an amine and another with a carboxylic acid. The amine fragment will deprotonate the carboxylic acid forming the carboxylate and ammonium fragments.



CONVERSION OF 1^{O} AMIDES TO NITRILES: DEHYDRATION

1° Amides can be converted into a nitrile through reaction with thionyl chloride ($SOCl_2$). Sulfurdioxide (SO_2) and hydrochloric acid are produced as byproducts.

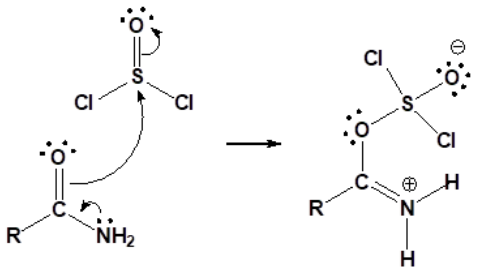
GENERAL REACTION



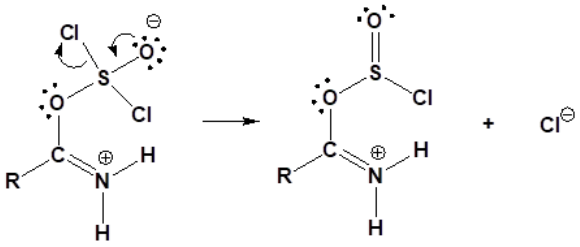
MECHANISM FOR THE CONVERSION OF A 1^{O} AMIDE TO A NITRILE

During the first step of the mechanism, the amide acts as a nucleophile and attacks the electrophilic sulfur of thionyl chloride, pushing the pi electrons of the S=O bond onto oxygen. Removal of a chloride anion as a leaving group allows the sulfoxide S=O bond to reform creating a protonated imine chlorosulfite. Deprotonation forms an imine chlorosulfite intermediate. A second deprotonation eliminates the chlorosulfite leaving group as sulfur dioxide and a chloride anion and forms the C-N triple bond of the nitrile product.

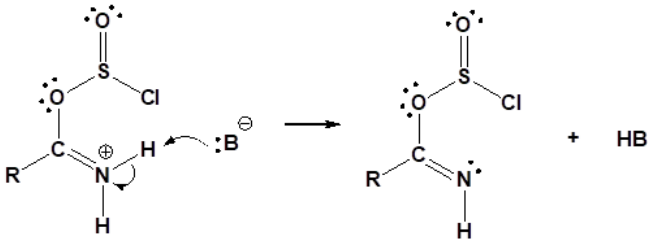
1) Nucleophilic attach on thionyl chloride



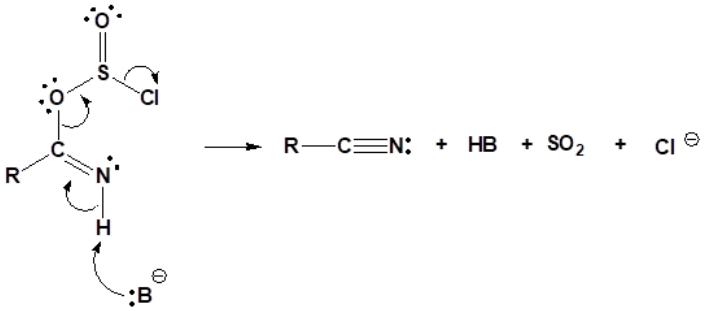
2) Leaving group removal



3) Deprotonation



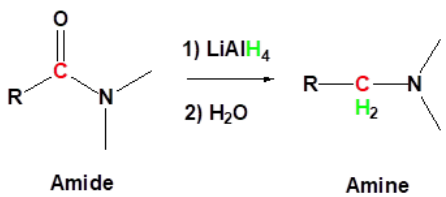
4) Leaving group removal



CONVERSION OF AMIDES TO 1^{O}, 2^{O} OR 3° AMINES: HYDRIDE REDUCTION

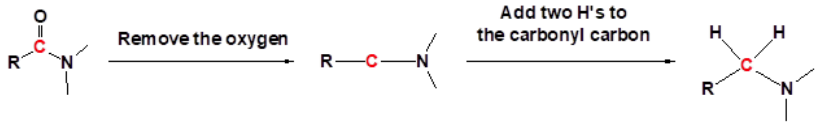
Amides are reduced to amines by treatment with $LiAlH_4$, and this has proven to be one of the most general methods for preparing all classes of amines (1º, 2º & 3º). Due to the nitrogen in the Y group of amides, the outcome of $LiAlH_4$ reductions is distinctly different than for esters since amide anions are poorer leaving groups than alkoxide anions. Furthermore, oxygen forms especially strong bonds to aluminum. During this reaction the carbonyl oxygen of the amide is removed as a leaving group and not the nitrogen containing Y group. Removal of the leaving group allows for a formation of a C=N iminium bond which can accept a second addition of a hydride nucleophile to form the amine.

GENERAL REACTION

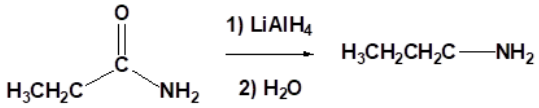


PREDICTING THE PRODUCTS OF A HYDRIDE REDUCTION

There are two major changes in bonding during this reaction: 1) The C=O carbonyl is removed from the starting material 2) Two hydride nucleophiles are added to what was the carbonyl carbon of the amide.

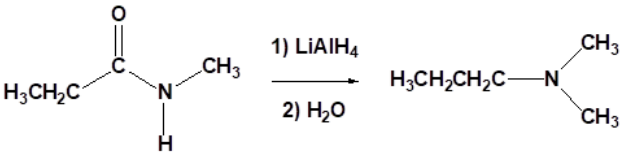


EXAMPLE

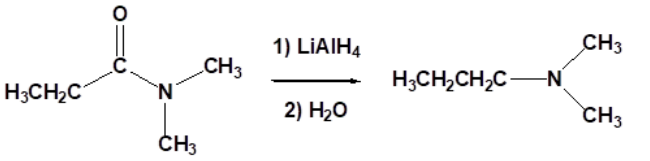


Propanamide — Propyl Amine

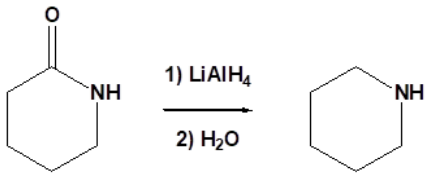
Alkyl groups attached to the nitrogen do not affect the reaction.



N-Methylpropanamide — N-Methylpropylamine



N,N-Dimethylpropanamide — N,N-Dimethylpropylamine

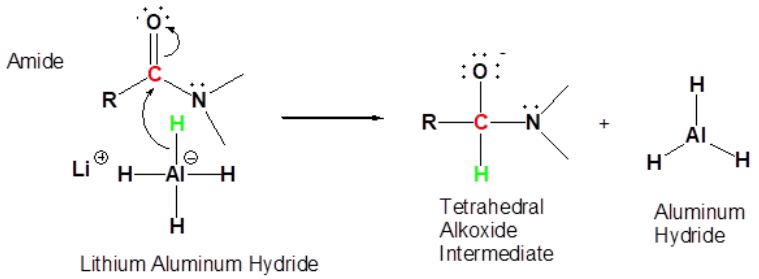


δ-Valerolactam — Piperidine

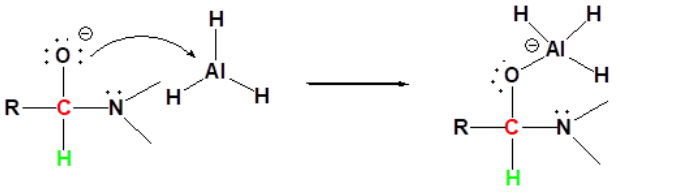
MECHANISM FOR THE HYDRIDE REDUCTION OF AN AMIDE TO FORM AN AMINE

Addition of a hydride nucleophile to the carbonyl carbon of the amide produces a tetrahedral alkoxide intermediate. A Lewis acid-base interaction occurs between the alkoxide (Lewis Base) and AlH_3 (Lewis acid) forming a complex with an O-Al bond. The nitrogen lone pair forms a double bond with the previous carbonyl carbon ejecting a metal oxide species (e.g. $[H3Al–O]^{2-}$) as a leaving group, and while forming an iminium double bond. Addition of a second equivalent of hydride nucleophile to the iminium carbon produces an amine.

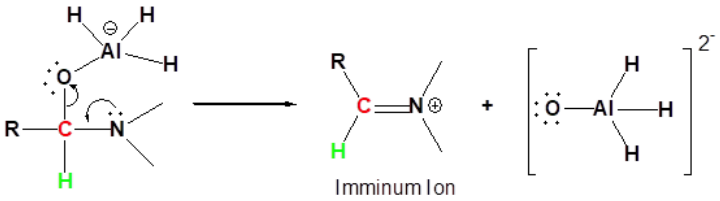
1) Nucleophilic attack by the hydride



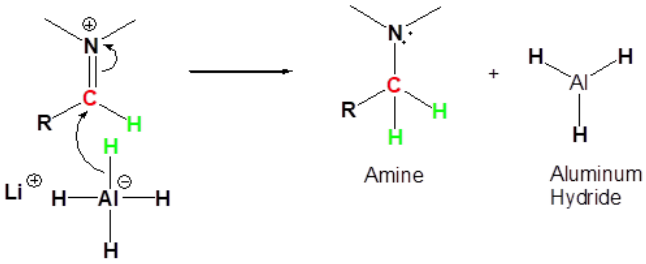
2) Complex formation



3) Leaving group removal

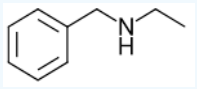


4) Nucleophilic attach by the hydride



? EXAMPLE 21.7.1

How could the following molecule be synthesized using an aminolysis of an acid chloride?



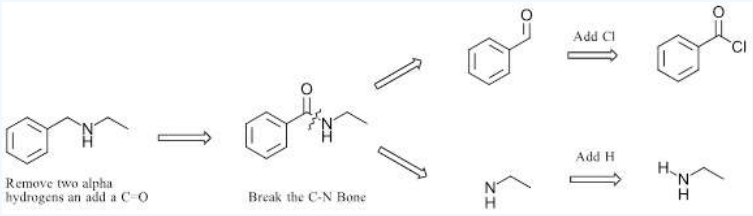
Answer

One of the preferred methods for making amines is through a nucleophilic acyl substitution using an acid chloride and amine to form an amide. The amide is then reduced to the amine during a hydride reduction with $LiAlH_4$.

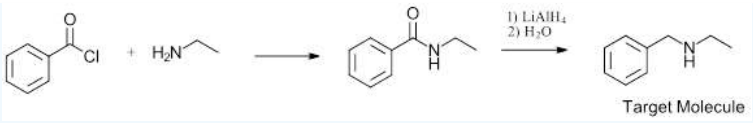
In the first step of retrosynthetic analysis, one of the carbons alpha to the amine nitrogen is converted to a carbonyl thus creating an amide intermediate. The key bond formed during this pathway is the C-N sigma bond between the carbonyl carbon and the nitrogen created during amide formation. Breaking this bond separated the target molecule into the two starting materials for the pathway. The carbonyl carbon gains a –Cl to become an acid chloride and the nitrogen fragment gains an H to become a 1º amine. In the forward reaction pathway, the acid chloride and the 1º amine are linked to from an amide in the first step of the reaction. Subsequent hydride reduction of the amide using $LiAlH_4$ produces the amine target molecule.

The target molecule has two alpha carbons which could possibly be converted to a carbonyl. This allows there to be two possible synthetic pathways.

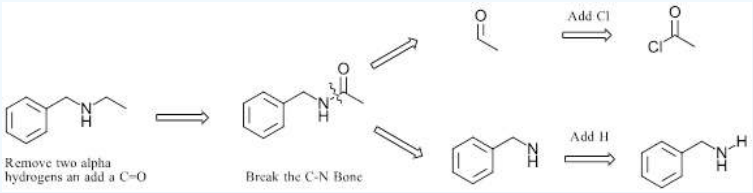
Pathway 1



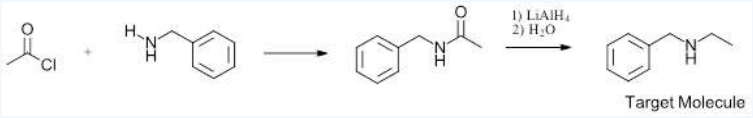
Solution 1



Pathway 2



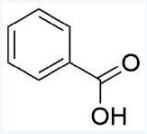
Solution 2



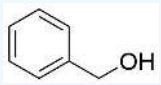
EXERCISE 21.7.1

1) How would you prepare the following compounds from N-Propypl benzamide?

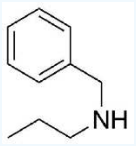
(a)



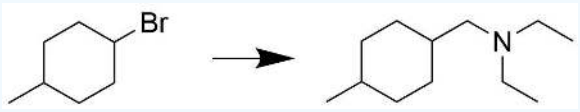
(b)



(c)



2) Propose a synthesis pathway for the following conversion:



Answer

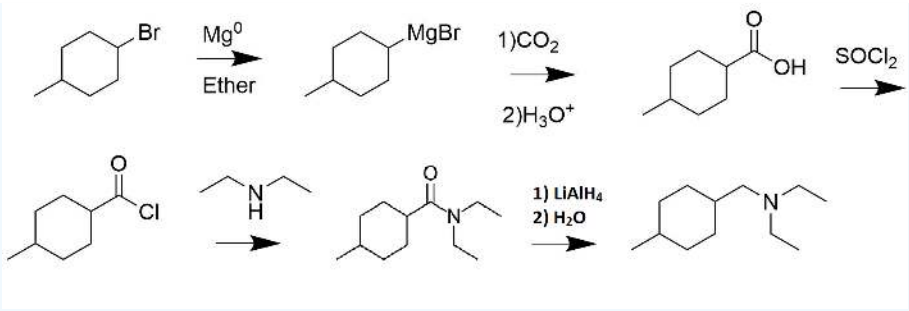
1) (a) NaOH, H_2O

(b) NaOH, H_2O, then $LiAlH_4$

(c) $LiAlH_4$

2)

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21.8: CHEMISTRY OF THIOESTERS AND ACYL PHOSPHATES - BIOLOGICAL CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

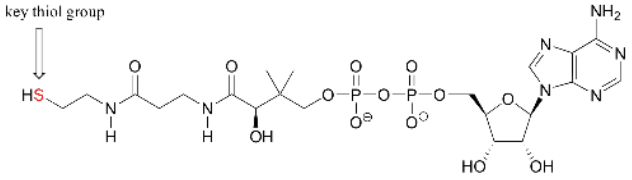
After completing this section, you should be able to

1. discuss, briefly, the role played in nature by acetylating agents, such as acetyl coenzyme A, and explain what is happening in reactions such as the acetylation in biological systems, without necessarily being able to write a detailed equation.
2. rank the reactivity of thioesters and acyl phosphates towards nucleophiles compared with other carboxylic acid derivatives.

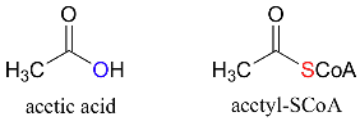
INTRODUCTION TO THIOESTERS AND COENZYME A

Acyl phosphates and acyl adenosine phosphates are not the only activated forms of carboxylate groups in biochemical reactions. Slightly lower on the reactivity scale are thioesters. In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

The 'acyl X group' in a thioester is a thiol. The most important thiol compound used to make thioesters is called coenzyme A, which has the following structure:

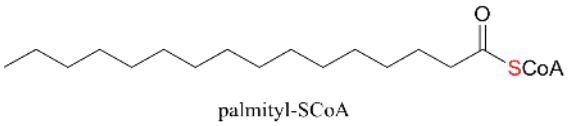


Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:

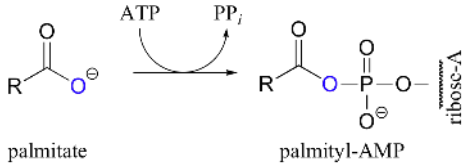


ACTIVATION OF FATTY ACIDS BY COENZYME A: A THIOESTERIFICATION REACTION

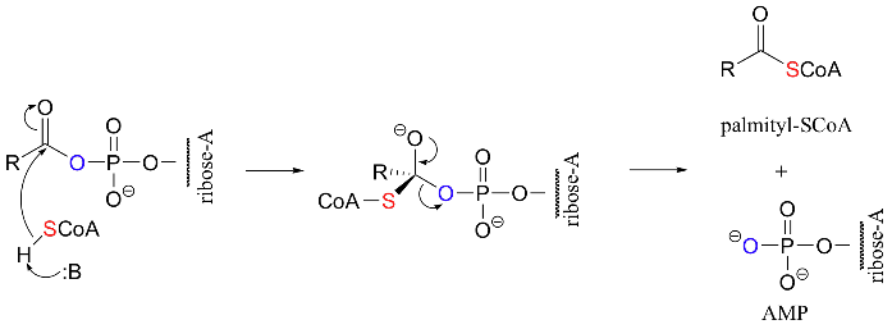
In the biologically active form of fatty acids, the carboxylate groups have been converted to thioesters using coenzyme A. For example, the activated form of the C_{16} fatty acid palmitate is:



Let's take a look at how this activation takes place, in a reaction catalyzed by an enzyme called acyl CoA synthetase. You already know that carboxylates are not themselves good substrates for acyl substitution reactions, and must be activated. Thus, you might predict that the first step of this reaction requires ATP to make a high-energy acyl phosphate intermediate. In fact, the activated carboxylate in this case is an acyl-AMP, formed in the same way as the acyl-AMP intermediate in the asparagine synthetase reaction (section 12.2B).

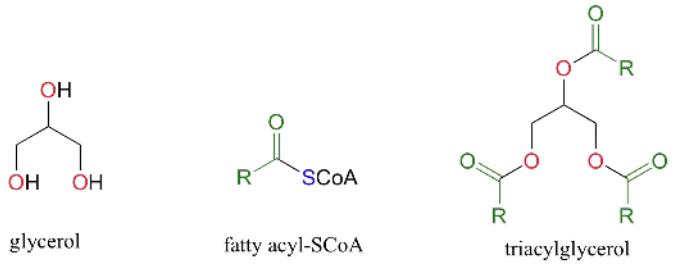


The activated acyl-AMP intermediate is then attacked by the thiol sulfur of coenzyme A, and the AMP group is expelled to form the fatty acyl CoA.

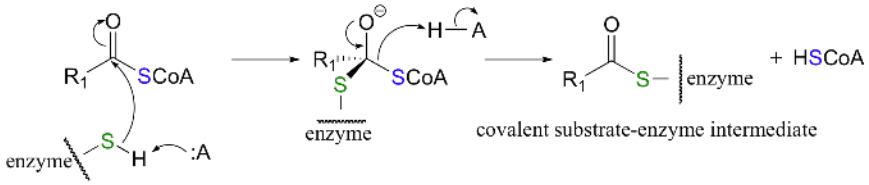


TRANSFER OF FATTY ACYL GROUPS TO GLYCEROL: A THIOESTER TO ESTER SUBSTITUTION

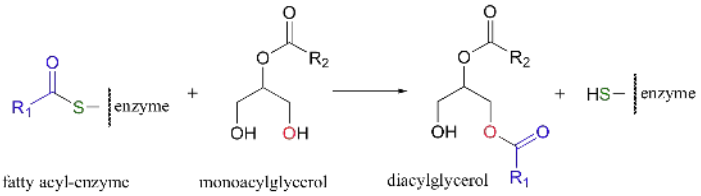
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall (section 12.1B) that triacylglycerol is composed of a glycerol 'backbone' connected to three fatty acid groups through ester linkages.



The reaction in which a fatty acid acyl group is linked to glycerol represents the conversion of a thioester (fatty acyl CoA) to an ester. First, however, a **transthioesterification** reaction occurs. A transthioesterification is merely the conversion of one thioester to another. In the case of monoacylglycerolacyltransferase, the fatty acyl group first trades its thioester link to coenzyme A for another thioester link to a cysteine residue in the active site of the enzyme. It is a common strategy for enzymes to first form a covalent link to one substrate before catalyzing the principle chemical reaction.



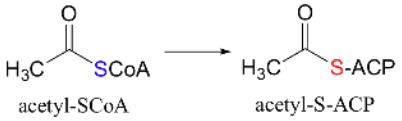
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.

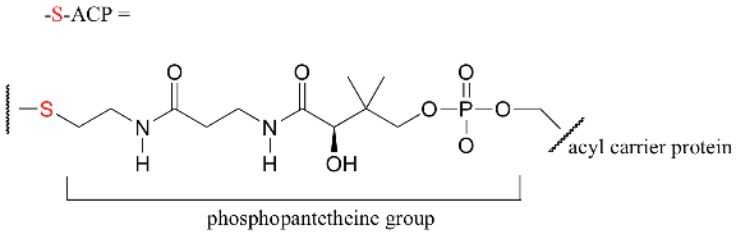


Because esters are more stable than thioesters, this is an energetically downhill reaction.

TRANSTHIOESTERIFICATION REACTIONS

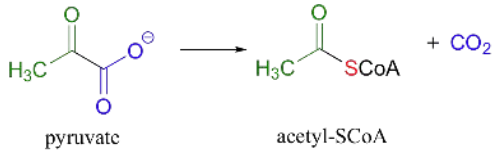
In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, acetyl CoA must first be linked to a so-called 'acyl carrier protein' (ACP). The acetyl group is linked to the acyl carrier protein *via* a thiol group on a carrier molecule that is covalently attached to the protein.



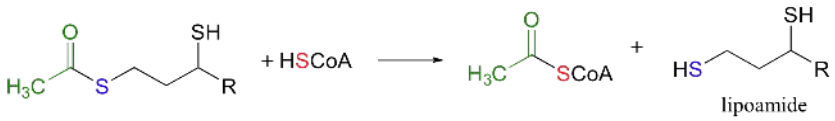


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow. We will study these important carbon-carbon bond forming reactions in section 13.4.

Finally, a transthioesterification is the final step in one of the most important and well-studied reactions in animal metabolism: the conversion of pyruvate to acetyl CoA by a cluster of enzymes called the pyruvate dehydrogenase complex.



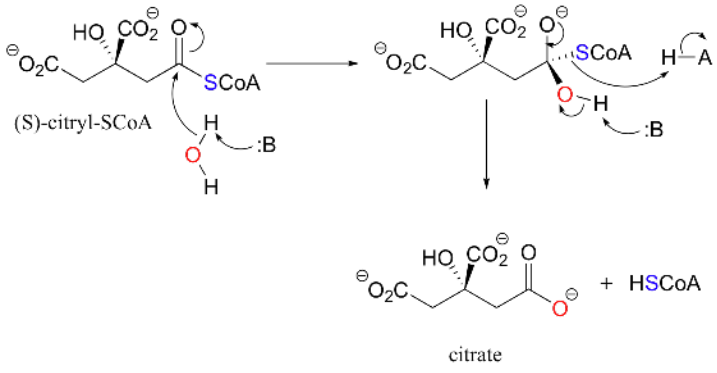
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

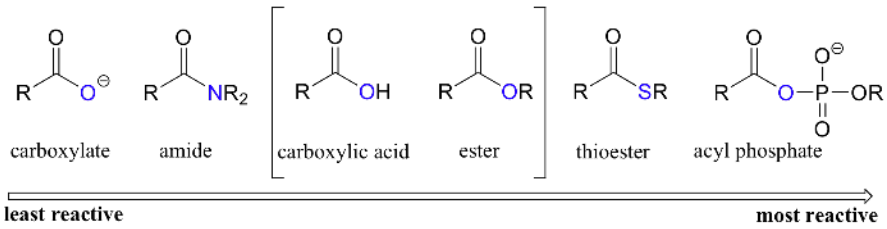
HYDROLYSIS OF THIOESTERS

The acyl group of a thioester can be transferred to a water molecule in a hydrolysis reaction, resulting in a carboxylate. An example of thioester hydrolysis is the conversion of (S)-citryl CoA to citrate in the citric acid cycle (also known as the Krebs cycle).



REACTIVITY OF THIOESTERS AND ACYL PHOSPHATES

Recall from Section 21.2 that thioesters and acyl phosphates are the most reactive among the biologically relevant acyl groups. However, neither is as reactive as an acid chloride or acid anhydride.



Relative reactivity of biologically relevant acyl groups

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21.9: POLYAMIDES AND POLYESTERS - STEP-GROWTH POLYMERS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the formation of nylon 66 from adipic acid and hexamethylenediamine.
2. write an equation to represent the formation of nylon 6 from caprolactam.
3. predict the structure of the step-growth polymer formed from the reaction of two given monomers.
4. identify the monomers needed to prepare a step-growth polymer of a given structure.
5. write an equation to describe the formation of a polyester, such as poly(ethylene terephthalate), from a given diol and diester.
6. write an equation to describe the formation of a polycarbonate from a carbonate and a bisphenol.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- chain-growth polymer
- polyamide
- polyester
- step-growth polymer

STUDY NOTES

You may wish to review chain-growth polymerization in Section 8.10 and Section 14.6. In this section we discuss another important class of polymerization kknow as step-growth polymerization.

As you can see from the equation given in the discussion on forming condensation polymers, Dacron is formed from two monomers, one of which possesses two carboxylate groups and the other two hydroxyl groups.

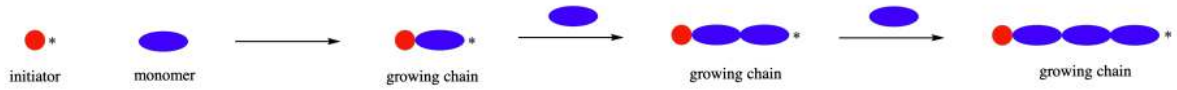
It is also possible to form a polyester using two monomers that each possesse one carboxyl group and one hydroxyl group. An example is the polymer formed between lactic acid and glycolic acid. This polymer has been used to produce absorbable staples that provide surgeons with a convenient method of closing incisions made during operations on the bladder or intestines, or during hysterectomies. Two advantages of this polyester in such applications are, first, that it begins to hydrolyze in the body after six to eight weeks, and then, that the products of the hydrolysis are both compounds normally present in the body.

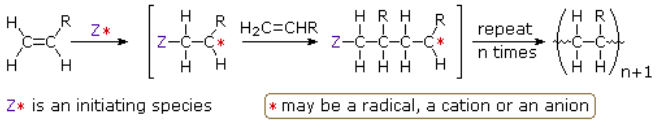


lactic acid (2-hydroxypropanoic acid) + glycolic acid (2-hydroxyethanoic acid)

STEP-GROWTH POLYMERIZATIONS

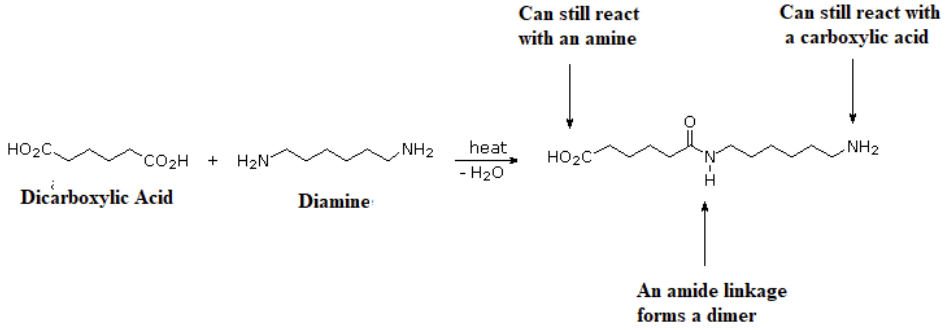
Step-growth and chain-growth are two broad classes of polymerization methods. Sections 8.11 and 14.7 discussed how chain-growth polymers usually start with a single alkene containing monomer, which is unreactive until an initiator is added. The initiator converts one monomer molecule into a reactive intermediate (radical, cation, anion) which is capable of reacting with another monomer forming a C-C bond and creating a new reactive intermediate. This reactive intermediate reacts with another monomer and the process is repeated as a chain reaction to form a polymer.



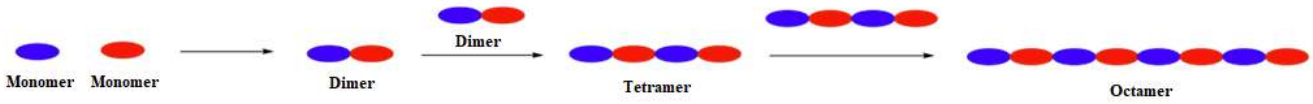


A Chain-Growth Polymerization

The process of step-growth polymerizations are fundamentally different than in chain-growth. In step-growth polymerizations, monomers are generally linked by a carbon-heteroatom bond (C-O & C-N) formed in non-sequential steps. Often, the reactions used to link these monomers include multiple nucleophilic acyl substitutions. Step-growth polymerizations usually use two different monomers, neither of which would undergo polymerization on its own. The two monomers are multifuntional and complementary to each other, such that each provides the other with a reactive partner. In this section, we will be focusing on monomers which are **difunctional**, meaning they contain two of the same reactive functional group. A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer. Because both monomers were difunctional, each retains a reactive group and can react with additional complementary monomers.

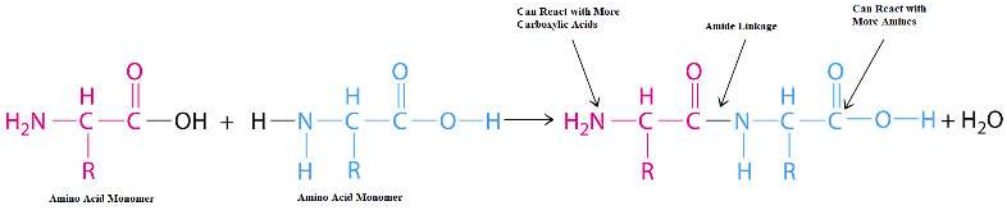


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another dimer and form a tetramer. Then when the tetramer goes to react again it will most likely find another tetramer and form an octamer. This process is repeated allowing the polymer to grow in two directions at the same time.



The Step-Growth Polymerization Process

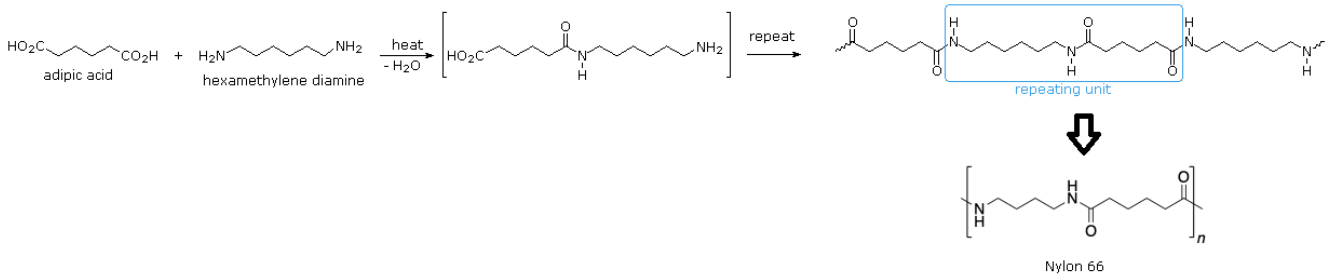
Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.



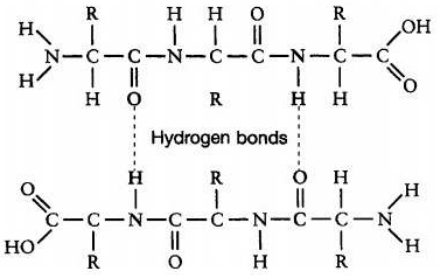
POLYAMIDES

The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins in silk. Nylon-6,6 was created by first reacting 1,6-hexanedioic acid (adipic acid) and 1,6-hexanediamine

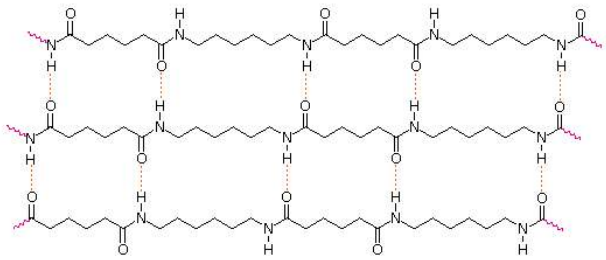
to give a salt which was then heated creating multiple amide bonds through nucleophilic acyl substitution. The product of this particular reaction is a polyamide called nylon-6,6. The numbers of the name indicate how many carbons are contained in each monomer. The first “6” stands for the number of carbons in the diamine monomer while the second number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. Known for their high strength and abrasion resistance, nylons can be molded into blocks for use in electrical equipment, gears, bearings, and valves. The strength of nylon fibers comes, in part, from their ability to form strong hydrogen bonding intermolecular forces with each other in much the same fashion as proteins.



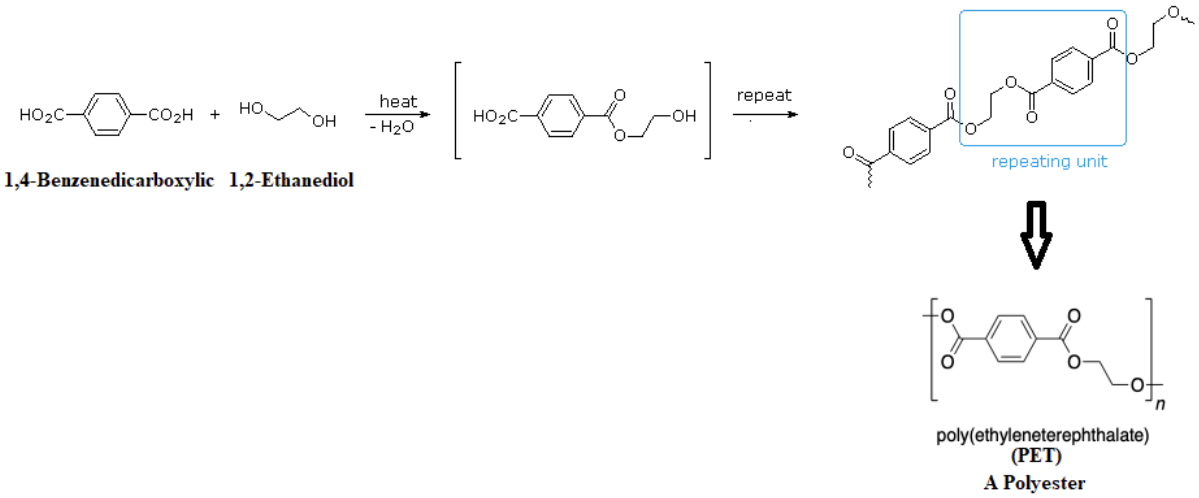
The Hydrogen Bonding between Proteins



The Hydrogen Bonding between Nylon Polyamides

POLYESTERS

Esterfication, via nucleophilic acyl substitutions, can also be used to form the primary linkages in step-growth polymers. A polyester is typically produced when a dicarboxylic acid and a diol are reacted together. After the initial reaction, the ester product contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other. Further esterification using a step-growth polymerization, produces a polyester. The most important polyester, polyethylene terephthalate (PET), is made from the reaction of 1,4-benzenedicarboxylic (terephthalic acid) and 1,2-ethanediol (ethylene glycol) monomers.



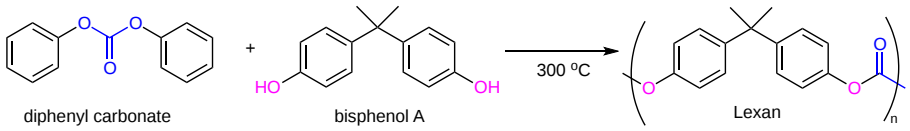
Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

POLYCARBONATES

Beyond carboxylic acid derivatives, virtually any reaction which involves reactive species on two different molecules can be used to perform a step-growth polymerization. A variation involves using a monomer containing a carbonate functional group. A carbonate acts like a double ester and can undergo a type of double transesterification reaction with two alcohols to form a new carbonate containing compound.

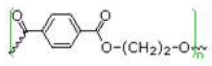
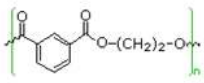
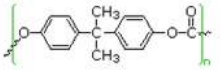
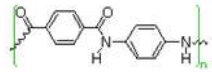
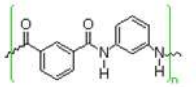


In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



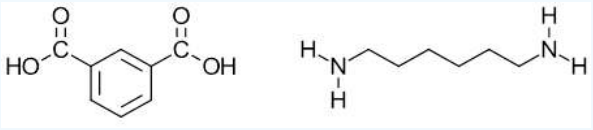
Polycarbonates used in engineering are strong, tough materials, and some grades are optically transparent. They are easily worked, molded, and thermoformed. Because of these properties, polycarbonates find many applications. One major application of polycarbonates is the production of compact discs, DVDs, and Blu-ray discs.

Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern about trace amounts of BPA leaching from the containers and being ingested. A study conducted in 2003 and 2004 by the Center for Disease Control and Prevention found trace amounts BPA in the tissues of 93% of people in the United States. Consequently, this has led to many beverage companies switching to non-polycarbonate polymers.

Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH$_2$)$_4$CO-OCH$_2$CH$_2$O]$_n$~	polyester	HO$_2$C-(CH$_2$)$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	< 0	50
	polyester Dacron, Mylar	para HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	70	265
	polyester	meta HO$_2$C-C$_6$H$_4$-CO$_2$H HO-CH$_2$CH$_2$-OH	50	240
	polycarbonate Lexan	(HO-C$_6$H$_4$-)$_2$C(CH$_3$)$_2$ (Bisphenol A) X$_2$C=O (X = OCH$_3$ or Cl)	150	267
~[CO(CH$_2$)$_4$CO-NH(CH$_2$)$_6$NH]$_n$~	polyamide Nylon 66	HO$_2$C-(CH$_2$)$_4$-CO$_2$H H$_2$N-(CH$_2$)$_6$-NH$_2$	45	265
~[CO(CH$_2$)$_5$NH]$_n$~	polyamide Nylon 6 Perlon		53	223
	polyamide Kevlar	para HO$_2$C-C$_6$H$_4$-CO$_2$H para H$_2$N-C$_6$H$_4$-NH$_2$	---	500
	polyamide Nomex	meta HO$_2$C-C$_6$H$_4$-CO$_2$H meta H$_2$N-C$_6$H$_4$-NH$_2$	273	390

EXAMPLE 21.9.1

Provide the structure of the polyamide made from the monomers as indicated. Please use bracketed notation.

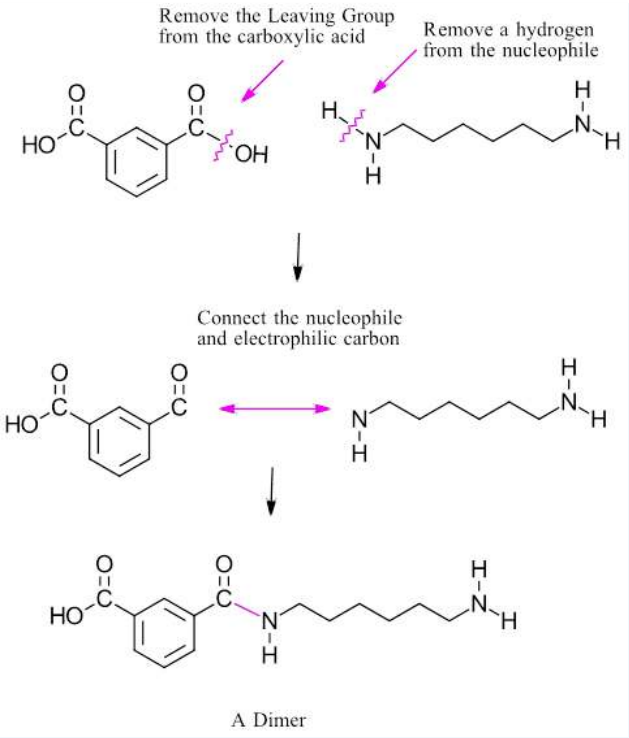


Solution

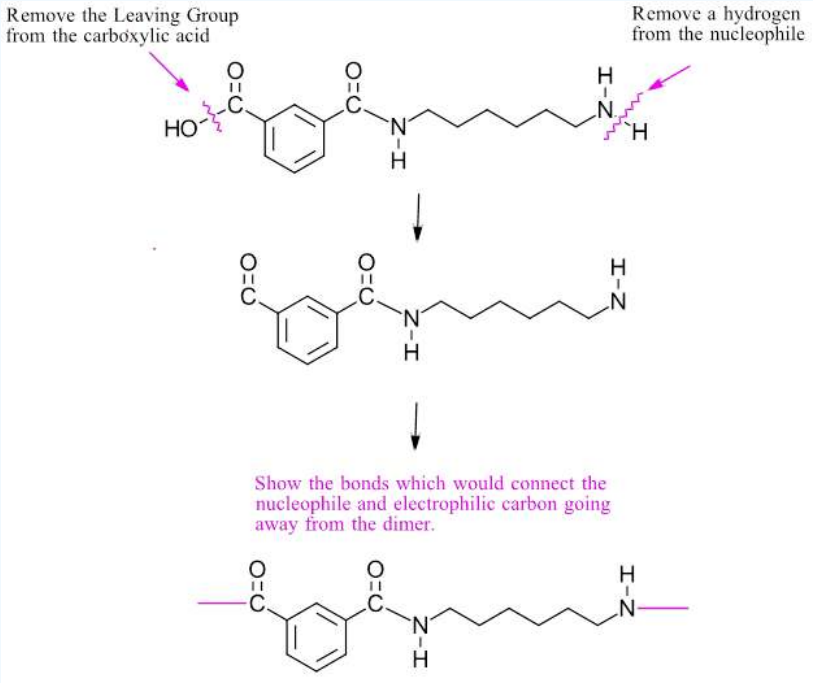
When drawing the polymer product of a step-growth polymerization, it is important to first identify the reaction which forms the repetitive linkage between monomers. In this case, the reaction is anucleophilic acyl substitution btween a carboxylic acid and an amine to form an amide. In total, the bracket structure of a polymer shows two versions of the linkage formation. The first is clearly shows connecting the monomers to form the dimer making up the repeating unit in the polymer. The second version involves bonds going out of the bracket and represents how the linkage repeats throughout the polymer.

1) The connect two monomers to make a dimer using the indicated reaction.

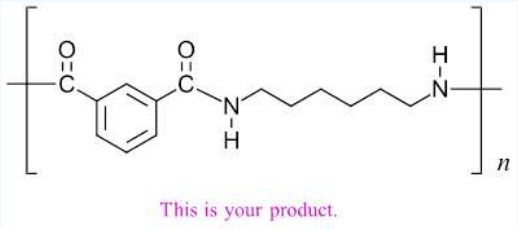
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2) Beak the same bonds as before ecepptt the bonds for the final connection will be shown going away from the dimer.

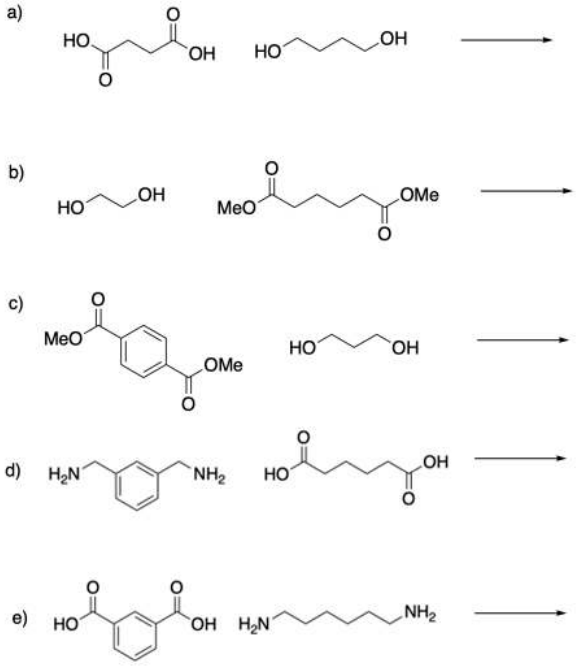


3) Place brackets around the dimer and put an italicized lower case "n" in the lower right.

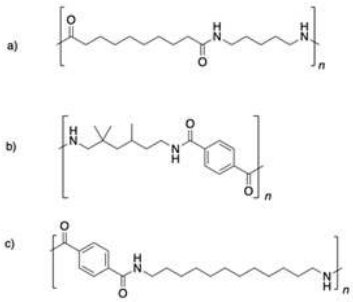


EXERCISES

1) Provide structures of the polyesters made from the monomers as indicated.



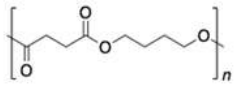
2) Identify the monomers that would be used to produce these polymers.

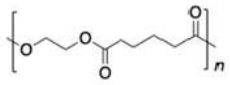


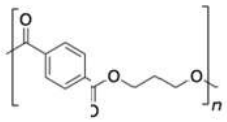
SOLUTIONS

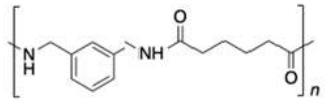
1)

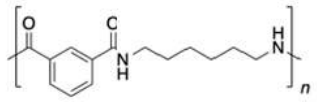
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a) 

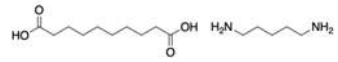
b) 

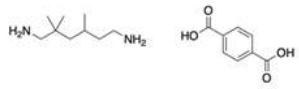
c) 

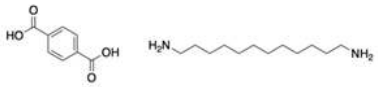
d) 

e) 

2)

a) 

b) 

c) 

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21.10: SPECTROSCOPY OF CARBOXYLIC ACID DERIVATIVES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum in which absorptions resulting from the carbonyl group of carboxylic acid derivatives occur.
2. identify the characteristic features of the infrared spectra of acid anhydrides and nitriles that allow us to use infrared spectroscopy to distinguish between these compounds and the others discussed in this unit.
3. use a table of characteristic infrared absorptions to interpret the infrared spectra of carbonyl-containing compounds.
4. use infrared spectroscopy and ^{1}H NMR spectroscopy in the deduction of the structure of an unknown compound.

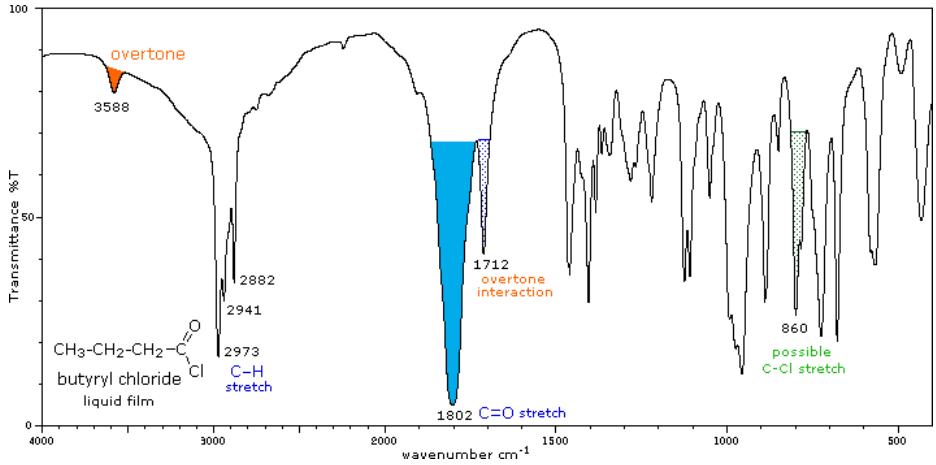
STUDY NOTES

Note: You should recognize that protons on carbon atoms next to carbonyl groups are slightly deshielded, and absorb near 2 δ in the ^{1}H NMR spectrum.

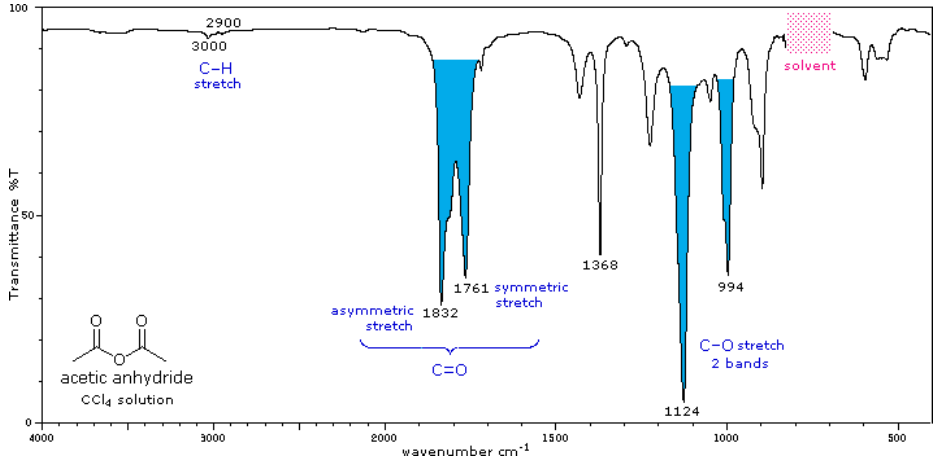
The influence of heteroatom substituents on the reactivity of carbonyl functions toward nucleophiles was discussed earlier with respect to carboxylic acid derivatives. A useful relationship exists between the reactivity of these derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher than ketones, whereas the relatively unreactive amides absorb at lower frequencies. These characteristics are listed below.

Infrared spectra of many carboxylic acid derivatives will be displayed in the figure below the table by clicking the appropriate buttons presented there.

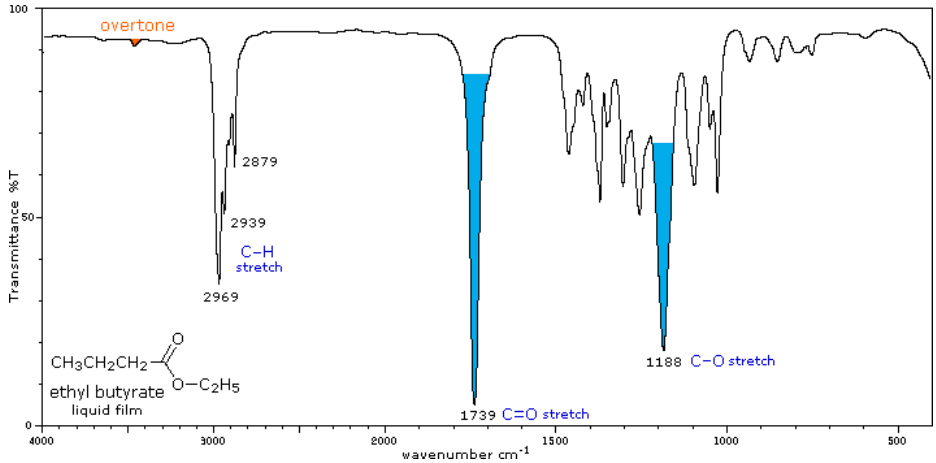
Carbonyl Derivative	Carbonyl Absorption	Comments
Acyl Halides (RCOX) X = F X = Cl X = Br	**C=O stretch** 1860 ± 20 cm^{-1} 1800 ± 15 1800 ± 15	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. In acyl chlorides a lower intensity shoulder or peak near 1740 cm^{-1} is due to an overtone interaction.
Acid Anhydride, $(RCO)_2O$ acyclic 6-membered ring 5-membered ring	**C=O stretch** (2 bands) 1750 & 1820 cm^{-1} 1750 &1820 1785 & 1865	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones. The two stretching bands are separated by 60 ± 30 cm^{-1}, and for acyclic anhydrides the higher frequency (asymmetric stretching) band is stronger than the lower frequency (symmetric) absorption. Cyclic anhydrides also display two carbonyl stretching absorptions, but the lower frequency band is the strongest. One or two -CO-O-CO- stretching bands are observed in the 1000 to 1300 cm^{-1} region.
Esters & Lactones (RCOOR') esters 6-membered lactone 5-membered lactone 4-membered lactone	**C=O stretch** 1740 cm ± 10 cm^{-1} 1740 cm ± 10 1765 cm± 5 1840 cm ± 5	Conjugation lowers the C=O frequencies reported here, as with aldehydes & ketones Strong CO-O stretching absorptions (one ot two) are found from 1150 to 1250 cm^{-1}
Amides & Lactams ($RCONR_2$) 1° & 2°-amides 3°-amides 6-membered lactams 5-membered lactams 4-membered lactams	**C=O bands** 1510 to 1700 cm^{-1} (2 bands) 1650± 15 (one band) 1670 ± 10 (one band) 1700 ± 15 1745 ± 15	The effect of conjugation is much less than for aldehydes & ketones. The higher frequency absorption (1665± 30) is called the **Amide I band**. The lower frequency **Amide II band** (1620± 30 in 1° amides & 1530± 30 in 2° amides) is largely due to N-H bending trans to the carbonyl oxygen. In concentrated samples this absorption is often obscured by the stronger amide I absorption. Hydrogen bonded association shifts some of these absorptions, as well as the prominent N-H stretching absorptions. **N-H stretch**: 3170 to 3500 cm^{-1}. Two bands for 1°-amides, one for 2°-amides.



IR - Carbonyl peak of an acid halide

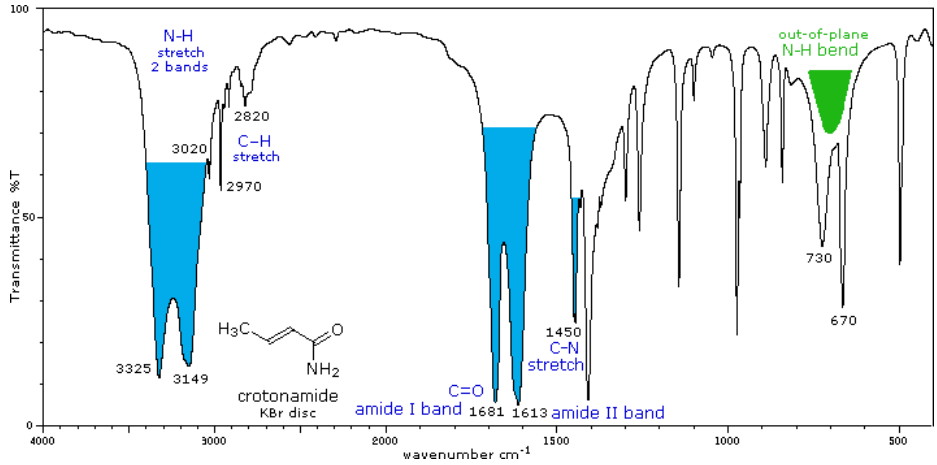


IR - Carbonyl and carbon-oxygen single bond peaks of an acid anhydride



IR - Carbonyl and carbon-oxygen single bond peaks of an ester

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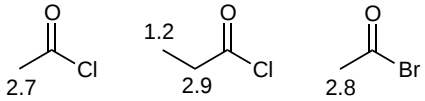
IR - Carbonyl, carbon-nitrogen and nitrogen-hydrogen bond peaks of an amide

^{1}H NUCLEAR MAGNETIC SPECTROSCOPY

Alpha protons of carboxylic acid derivatives, due to the presence of a carbonyl, resonate in the 2.0-3.0 ppm region of a ^{1}H NMR spectra. The downfield shift occurs from deshielding due to higher electronegativity of the sp^2 hybridized carbonyl carbon relative to the sp^3 hybridized alpha carbons. This effect is reduced for protons which are further from the carbonyl group as seen in the figure below.

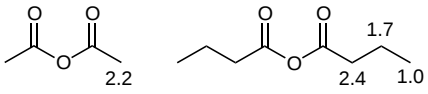
ACID HALIDES

The X groups of acid halides do not contain additional protons and thus do not provide any distinctive ^{1}H NMR peaks. The protons on carbon adjacent to the carbonyl appear at similar chemical shift to other carbonyl containing compounds (2-3 ppm).



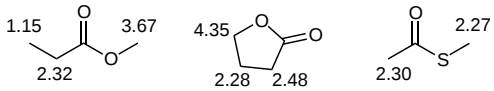
ACID ANHYDRIDES

Many anhydrides used in organic chemistry are symmetrical, therefore the alkyl chains on either side of the carbonyls produce equivalent protons.



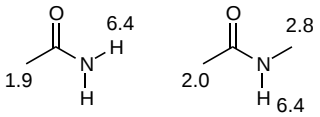
ESTERS AND THIOESTERS

The Y groups of esters, and thioesters have alkyl groups attached to their heteroatom which provide additional ^{1}H NMR peaks. Protons on carbons attached to the alkoxide oxygen in esters show up in the 3.5-4.5 ppm region while those attached to the sulfur in thioesters show up in the 2.0-3.0 ppm region. The downfield shift in these protons is attributable to the deshielding caused by the electronegativity of oxygen and sulfur.

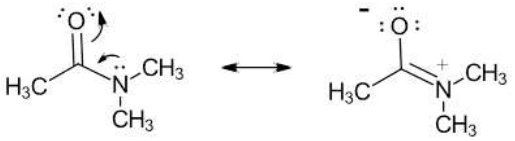


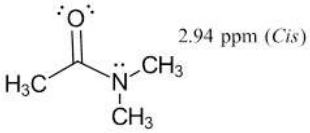
AMIDES

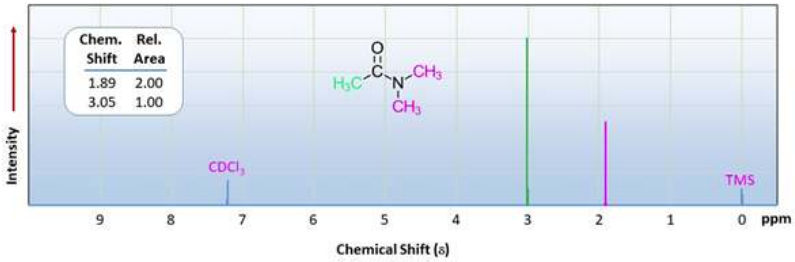
Amides have the possibility of alkyl groups or hydrogens attached to their Y group both of which provide distinctive ^{1}H NMR peaks. Resonances from protons directly attached to the carbon bonded to nitrogen in an amide tend to resonate in the 2.0-3.0 ppm region of an NMR spectra. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions. Like other hydrogen bonding protons, these NH proton peaks appear broad and can be washed out by the hydrogen-deuterium exchange created by D_2O addition.



An interesting facet of amide structure is shown when looking at the ^{1}H NMR spectra of N,N-dimethylacetamide. The two N-methyl groups are in fact non-equivalent and appear as two singlets with difference chemical shifts. Resonance in the amide bond provides a significant amount of double bond character reducing the rate of rotation about the OC-N bond. The rotation is slow enough that on the time scale of an NMR experiment the two methyl appears to be frozen as if it is part of a double bond. This causes the N-methyl groups to have different chemical shifts because one appears to be cis to the carbonyl oxygen and the other trans during an NMR experiment.

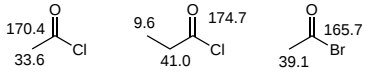




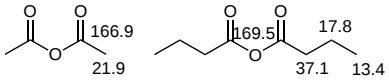


^{13}C NUCLEAR MAGNETIC SPECTROSCOPY

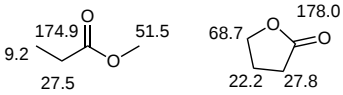
The carbonyl carbons of carboxylic acid derivatives are strongly deshielded (160-180 ppm) due to the close presence (due to the double bond) of a highly electronegative oxygen. However, they are not as deshielded as the carbonyl carbon of an aldehyde or ketone (180-220 ppm) due to the electron donating effects of the Y group. Carbons attached to the alkoxide oxygen of esters appear in the range of 50-90 ppm. Carbons attached to the nitrogen of an amide appear in the 20-65 ppm range and those attached to the sulfur of thioesters appear at 20-45 ppm.



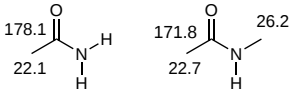
Acid halide ^{13}C NMR chemical shifts (ppm)



Anhydride ^{13}C NMR chemical shifts (ppm)



Ester ^{13}C NMR chemical shifts (ppm)

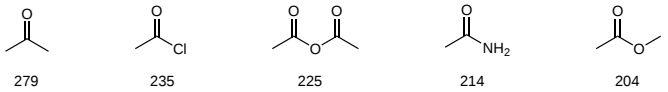


Amide ^{13}C NMR chemical shifts (ppm)

UV/VIS SPECTROSCOPY

Carboxylic acid derivatives show the n→π* absorption typical for carbonyl containing compounds. The Y group of acid derivatives give a hypsochromic shift (wavelength lowering) to the absorption due to the inductive effect of the electronegative oxygen, nitrogen, and

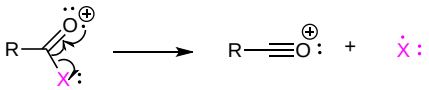
halogens present. Electrons are inductively removed from the carbonyl carbon which causes the lone pair electrons on the carbonyl oxygen to be held more firmly. This causes them to require higher energy photons to transition which corresponds to a lower wavelength λ_{max} when compared to other carbonyls such as a ketone.



UV-Visible absorption of carbonyl compounds (showing λ_{max} in nm)

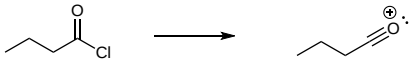
MASS SPECTROMETRY

In the mass spectra of most carboxylic acid derivatives, the base peak is due to the cleavage of C-Y bond to form an acylium ion ($R\text{-}CO^+$). Other than the molecular ion peak, the acylium ion is one of the only major peaks present in the mass spectra of acid halides and thioesters. Amide and ester often show additional fragmentations.



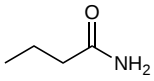
Acid halides

The molecular ion peak of acid chlorides is often not seen. When they do occur, acid chlorides and acid bromides would have an important M + 2 peak due to the two isotopic forms of the halogens. The base peak fragmentation involves the alpha cleavage of C-X bond to from an acylium ion. In butanoyl chloride this peak shows up at m/z = 72.

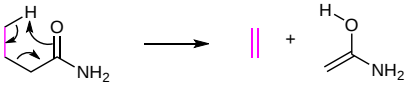


Amide

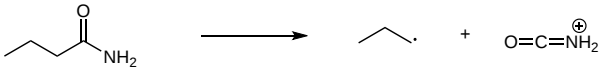
Amides, like other compounds containing nitrogen, follow the Nitrogen Rule. This means that a compound with an odd number of nitrogen atoms will also have an odd-numbered molecular weight. This is shown in butanamide (C_4H_9NO) which has the odd-numbered molecular weight of 87.12 g/mol.



Primary amides show a base peak due to the McLafferty rearrangement which appears at m/z = 59. Secondary and tertiary amides give analogous peaks at higher m/z values.

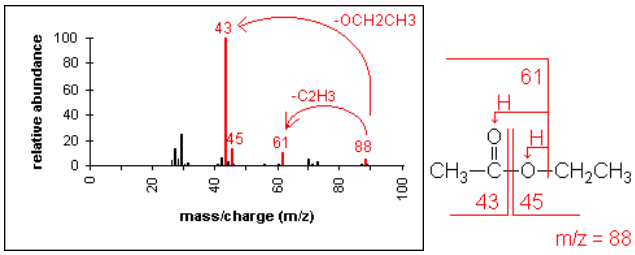


Amides can also cleave the alkyl group attached to the carbonyl forming an amide stabilized acelium ion. For butanamide, like other primary amines, this peak shows up at m/z = 44.



Ester

Esters have multiple fragmentation pathways which are often dependent on the overall size of the ester. The most important fragmentation appears due to alpha-cleavage bond of the C-O to produce the corresponding acylium ion RCO^+. In the mass spectra of ethyl acetate the acylium ion peak appears at 43 m/z and the alkoxy ion peak (RO^+) shows up a 45 m/z. Other important fragments include the loss or the alkyl group (R^+) from the acyl side and the alkoxy side of the ester. Loss of the alkyl group on the alkyoxy side of ethyl acetate ($^+CH_2CH_3$) produces a peak at m/z 61.



SDBSWeb : https://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, date of access

NIST Chemistry WebBook: https://webbook.nist.gov/chemistry/ (National Insitute of Standards and Technology)

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21.S: CARBOXYLIC ACID DERIVATIVES (SUMMARY)

CONCEPTS & VOCABULARY

21.0 Chapter Objectives and Introduction to Carboxylic Acid Derivatives

- Carboxylic acid derivatives formed when the hydroxyl group of the carboxylic acid is replaced by a different group.
- Carboxylic acid derivatives are also known as acyl derivatives.
- Many types of carboxylic acid derivatives, the chapter focused on acid halides (acyl halides), anhydrides, esters, amides, thioesters, and acylphosphates.
- Cyclic esters are referred to as lactones and cyclic amides are referred to as lactams.
- Nucleophilic acyl substitution reactions convert the carboxylic acid to one of the derivatives.

21.1 Naming Carboxylic Acid Derivatives

- Acid halide are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and the halide ending in an -ide.
- Anhydrides are named following the IUPAC rules with the carboxylic acid ending -acid being replaced by -anhydride.
- Esters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -ate and the alkoxy alkyl chain as a substituent.
- Thioesters are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -thioate and the sulfide alkyl chain as a substituent.
- Primary amides are named following the IUPAC rules with the carboxylic acid ending with -oic acid being replaced by -amide.
- Secondary or tertiary amides are named as primary amides are, but in additon an upper case N is used to designate the alkyl groups attached to the nitrogen atom, which are names as substituents.
- Cyclic amides (lactams) use a Greek letter to identify the location of the nitrogen in relation the carbonyl group.
- Acyl phosphates are named following the IUPAC rules with the carboxylic acid ending with -oyl or -yl and -phosphate.

21.2 Nucleophilic Acyl Substitution Reactions

- Carboxylic acid derivatives contain an electronegative heteroatom (typically oxygen, nitrogen, sulfur, or phosphorus) bonded directly to the carbonyl carbon represented by the symbol Y.
- The acyl group is the remainder of the molecule, which includes the carbonyl and the attached alkyl group.
- The Y group acts as a leaving group during the nucleophilic acyl substitution reaction.
- Stability of the negative charge on the Y group can be guaged by the pK_a of its corresponding acid (HY).
- Carboxylic acid derivatives undergo a reaction called nucleophilic acyl substitution.
- The electrophile is the carbon of the carbonyl, which undergoes an attack by a nucelophile followed by the elimination of the Y group in the carboxylic acid derivative.
- The Y group is substituted for the nucleophile.
- The reactivity of the carboxylic acid derivatives depends on the stability of the carbonyl and the effectiveness of the leaving group.
- Stabilization of the carbonyl reduces the electrophilic character of the carbonyl group.
- The ability of the leaving group to stabilize negative charge creates a more effective leaving group.
- More reactive carboxylic acid derivatives can be used to make less reactive carboxylic acid derivatives.

21.3 Nucleophilic Acyl Substitution Reactions of Carboxylic Acids

- The hydroxyl of a carboxylic acid is a poor leaving group, but activating the carbonyl and converting the hydroxyl to a better leaving group allow for reactions to occur.
- Carboxylic acids can be converted to acid chlorides using thionyl chloride ($SOCl_2$).
- Carboxylic acids can be converted into anhydrides by condensing two carboxylic acids together and the loss of water.
- Carboxylic acids can be converted into esters in two ways.
  - Using the carboxylate in an SN_2 mechanism.
  - The Fischer Esterification
    - Acid catalyzed
    - Pushing equilibrium in the forward direction using Le Chatelier's principle
- Carboxylic acids can be converted into amides in two ways.
  - Direct conversion by heating ammonium carboxylate salts
  - Using a coupling agent like dicyclohexylcarbodiimide (DCC)

- Carboxylic acids can be reduced to primary alcohols using lithium aluminum hydride or borane tetrahydrofurane (THF).
- In biological chemistry, carboxylate anions are converted to an acyl phosphate, which requires phosphrylation using TAP as the phosphate donor or thioesters using coenzyme A.

21.4 Chemistry of Acid Halides

- Carboxylic acids react with thionyl chloride to form acid chlorides.
- Carboxylic acids react with phosphorus tribromide to form acid bromides.
- Acid chlorides are the most reactive carboxylic acid derivative, which allows them to easily convert to other acyl compounds.
- Acid chlorides undergo hydrolysis to form carboxylic acids.
- Acid chlorides react with carboxylic acid to from anhydrides through a nucleophilic acyl substitution.
- Acid chlorides react with alcohol nucleophiles to produce esters with pyridine being used to neutralize the HCl produced.
- Acid chlorides can be reduced to aldehydes using hindered reducing agents that have only one equivalent of hydride.
- Acid chlorides react with amines to form amides, usually an excess of amine is used to neutralize the HCl produced.
- Acid chlorides react with Grignard reagents to from tertiary alcohols.
- Acid chlorides react with Gillman reagents to produce ketones.

21.5 Chemistry of Acid Anhydrides

- Anhydrides generally made by nucleophlic acyl substitution reactions using an acid chloride and a carboxylic acid or carboxylate anion.
- Anhydrides are not as reactive as acid chlorides, but still undergo many of the same reactions.
- Asymmetrical anhydrides not used to make amides or esters since multiple products can be formed.
- Anhydrides undergo hydrolysis to form carboxylic acids.
- Anhydrides react with alcohol nucleophiles to produce esters.
- Anhydrides can react with amines to form the corresponding amides.

21.6 Chemistry of Esters

- Esters are present in many biologically important molecules.
- Esters are often the sources of pleasant aromas of many fruits and perfumes.
- Esters are also present in commercial and synthetic applications.
- Esters are prepared
  - most often using nucleophilic acyl substitution using an acid chloride and an alcohol
  - using nucleophilic acyl substitution using an anhydride and an alcohol
  - using nucleophilic acyl substitution using a carboxylic acid and an alcohol
  - deprotonating a carboxlylic acid for an SN_2 reaction
- Esters can be converted to a carboxylic acid through a reaction witt water and a catalytic amount of strong acid.
- Saponification is the reaction between an ester and water under basic conditions to produce a carboxylate anion.
- Esters can be inter-converted using a transesterfication reaction.
- Esters can be converted into amides using an ester and a large excess of amine.
- Esters can be reduced to primary alcohols using lithium aluminum hydride.
- Like acid chlorides, esters can be reduced to aldehydes using weak, bulky reducing agents.
- Esters can react with Grignard reagents to form tertiary alcohols.

21.7 Chemistry of Amides

- Amides make up the backbone of proteins when the amino group of one amino acid reacts with the carboxylate carbon of another amino acid and from an amide linkage (peptide bond).
- Amides are most commonly prepared through the reaction of an acid chloride and amine.
- Amides are relatively unreactive towards nucleophilic acyl substitutions due to the poor leaving group ability of its nitrogen containing Y group.
- Amides can be hydrolzyed to a carboxylic acid and ammonia or amine by heating the reaction under acidic or basic aqueous solutions.
- Hydrolysis of amines is the first step in metabolism of dietary proteins.
- Primary amines can be converted into a nitrile through a reaction with thionyl chloride.
- Amides are reduced to amines by treatment with lithium aluminum hydride.

21.8 Chemistry of Thioesters and Acyl Phosphates - Biological Carboxylic Acid Derivatives

- Acyl phosphates, acyl adenosine phosphophates, and thioesters are all activated forms of carboxylate groups in biochemical reactions.
- Carboxylate groups of fatty acids are converted to thioesters using coenzyme A

- Thioesters are a good substrate for a number of metabolic transformations.
- Thioesters can be hydrolyzed, resulting back to a carboxylate anion.
- Thioesters and acyl phosphates are the most reactive biologically relevant acyl groups, but not as reactive as an acid chloride or anhydride.

21.9 Polyamides and Polyesters - Step-Growth Polymers

- Step-growth is one of two broad classes of polymerization methods.
- Step-growth polymerizations are linked by a carbon-heteroatom bond formed in non-sequential steps.
- A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer.
- Using a difunctional monomer, allows step-growth polymers to grow in two directions at once.
- Fibers are made from some form of polymer.
- Nylon
  - First successful fully synthetic polymer was nylon-6,6 in 1938 by the company DuPont, which is a polyamide.
  - Nylons are widely used synthetic fibers, which are found in commercial products such as rope, sails, clothing, and more.
- Esterfication
  - Can also be used to form primary linkages in step-growth polymers.
  - Polyester is typically produced when a dicarboxylic acid and a diol react together.
  - The most important polyester is polyethylene terephthalate (PET), which is used to make bottles for soda.
  - Polyesters are fibers often used in many fabrics.
- Polycarbonates
  - Monomer is a carbonate, which acts like a double ester and can undergo a type of double transesterification reaction with two alcohols.
  - A carbonate is difunctional and can react with a diol to form polymers called polycarbonates.
  - Used in engineering because they are strong materials, but easily molded.
  - Polycarbonates are found in DVDs, compact discs, and Blu-ray discs.

21.10 Spectroscopy of Carboxylic Acid Derivatives

- IR of acid chlorides shows a strong carbonyl stretch around 1800 cm^{-1}.
- IR of anhydrides show two strong carbonyl stretch around 1750 and 1820 cm^{-1}.
- IR of esters shows a strong carbonyl stretch around 1740 cm^{-1} and a strong CO-O stretch around 1150 to 1250 cm^{-1}.
- IR of amides shows a strong carbonyl stretch around 1700 cm^{-1}, primary and secondary amides have two bands and tertiary amides have one band and a strong N-H stretch around 3170 to 3500 cm^{-1} in primary and secondary amides.
- ^{1}H NMR of acid halides do not have any distinctive peaks.
- ^{1}H NMR of anhydrides do not have any distinctive peaks, but symmetrical anhydrides will produce equivalent protons on either side.
- ^{1}H NMR of esters and thioesters have an alkyl group attached to the heteroatom. For esters, the alkoxide protons will show up in the 3.5-4.5 ppm region, while those attached to the sulfur in thioesters will show up in the 2.0-3.0 ppm region.
- ^{1}H NMR of amides have the possibility of alkyl groups or hydrogens attached. Resonances for protons attached to the carbon bonded to the nitrogen of the amide resonate between 2.0-3.0 ppm region. The NH protons of primary and secondary amides resonate in the 7.5-8.5 ppm regions, which will be broad.
- ^{13}C NMR of carboxylic acid derivatives show the carbonyl carbon at 160-180 ppm.
- ^{13}C NMR of esters also have the carbon attached to the alkoxide of the ester, which appears at 50-90 ppm.
- ^{13}C NMR of amides also have the carbon attached to the nitrogen of the amide, which appears at 20-65 ppm.
- ^{13}C NMR of thioesters also have the carbon attached to the sulfur, which appears at 20-45 ppm.
- Mass spectra of carboxylic acid derivatives show a base peak due to the acylium ion.

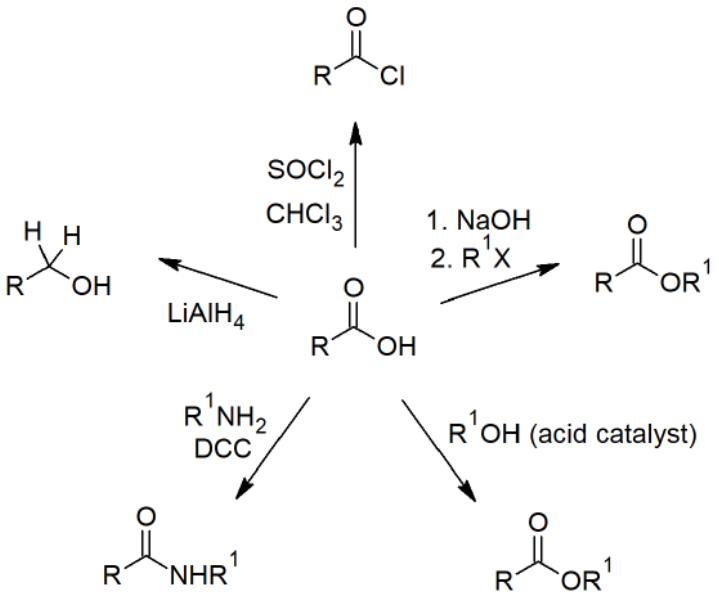
Skills to Master

- Skill 21.1 Name carboxyilic acid derivatives using IUPAC rules.
- Skill 21.2 Draw the structure of carboxylic acid derivatives from the IUPAC name.
- Skill 21.3 Compare the stability of different carboxylic acid derivatives to determine reactivity.
- Skill 21.4 Determine the products for nucleophilic acyl substitution reactions.
- Skill 21.5 Provide step-by-step mechanism for the Fischer esterification.
- Skill 21.6 Show how to synthesize an ester from a carboxylic acid and alcohol.

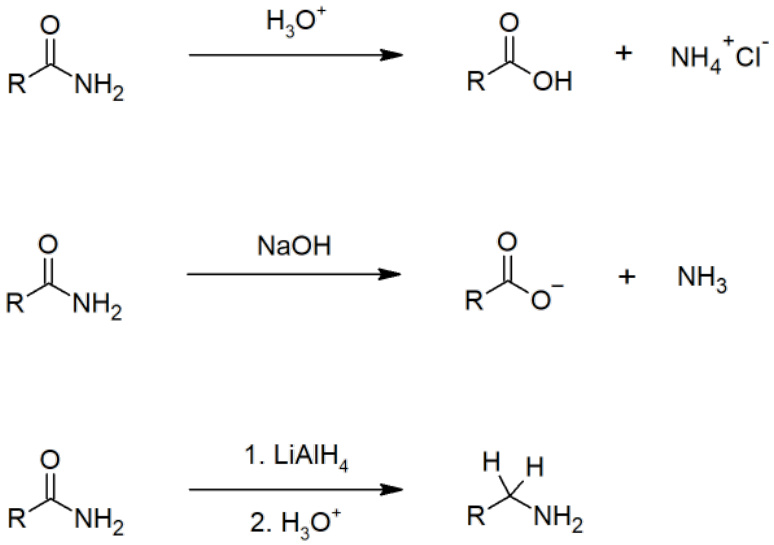
- Skill 21.7 Show mechanisms for the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.8 Show how to synthesize the different carboxylic acid derivatives starting from an acid chloride.
- Skill 21.9 Provide step-by-step mechanisms for the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.10 Show how to synthesize the different carboxylic acid derivatives starting from an anhydride.
- Skill 21.11 Understand why the hydrolysis of an ester is not reversible under basic conditions and why the reverse does not produce an ester.
- Skill 21.12 Be able to synthesize tertiary alcohols from esters.
- Skill 21.13 Provide a step-by-step mechanism for the hydrolysis of an amide under acidic and basic conditions.
- Skill 21.14 Provide the structure of different polymers using the bracketed notation and the monomers from the polymer.
- Skill 21.15 Use IR, NMR, and MS to identify different carboxylic acid derivatives.

SUMMARY OF REACTIONS

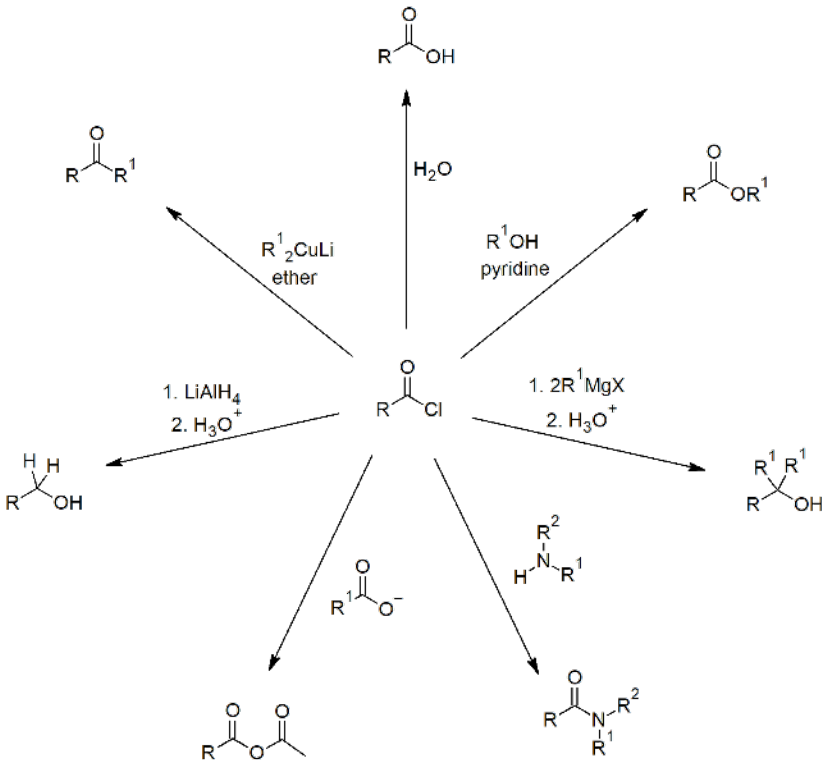
Carboxylic Acid Reactions



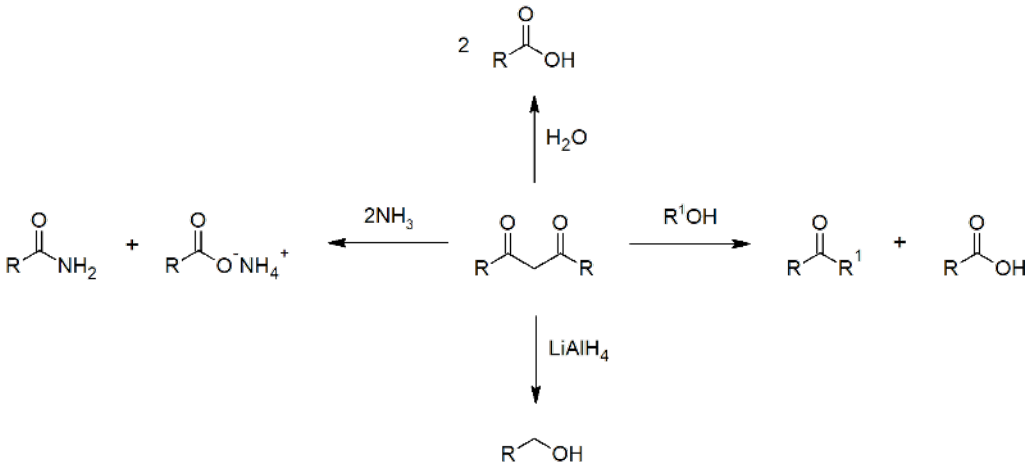
Amide Reactions



Acid Chloride Reactions

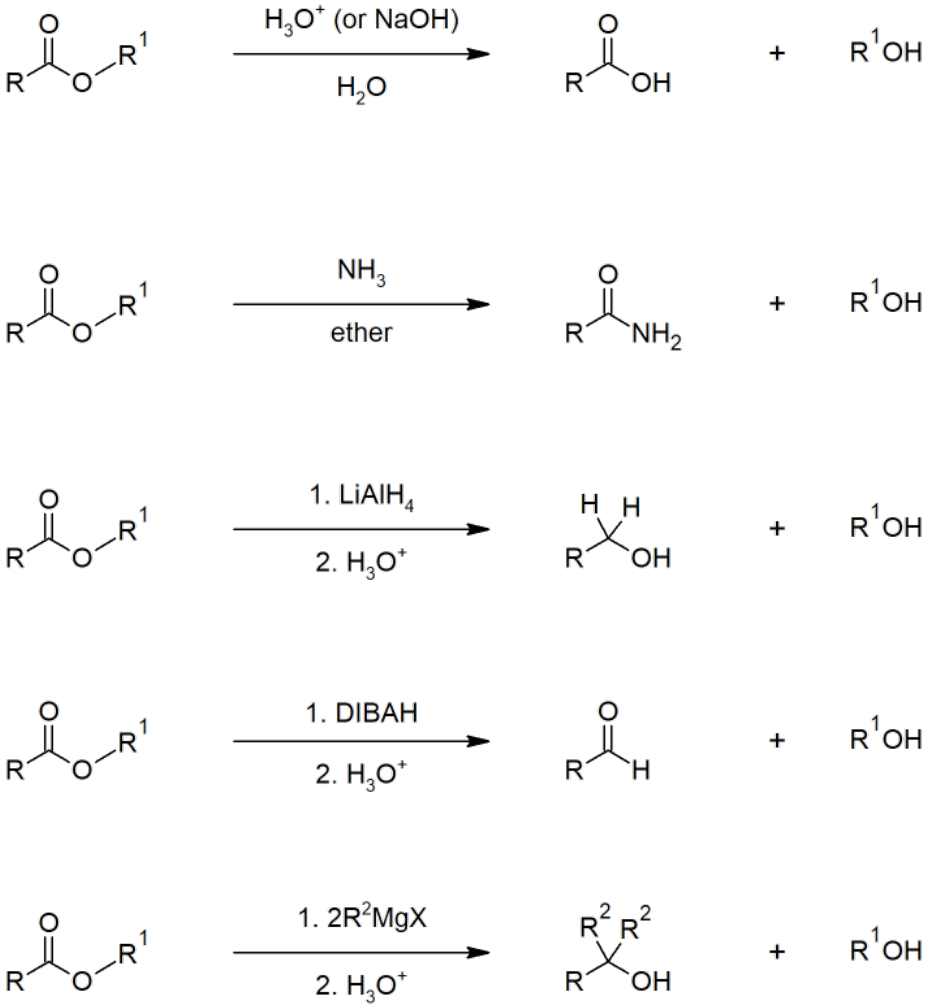


Acid Anhydride Reactions



Ester Reactions

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CHAPTER OVERVIEW

22: CARBONYL ALPHA-SUBSTITUTION REACTIONS

LEARNING OBJECTIVES

When you have completed Chapter 22, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
3. solve road-map problems that require a knowledge of carbonyl alpha-substitution reactions.
4. define, and use in context, the key terms introduced.

Alpha-substitution reactions are the third major type of reaction that you will study in your investigation of the chemistry of carbonyl compounds. As you will see, these reactions proceed through the formation of the enol form of the carbonyl compound.

After a brief review of keto-enol tautomerism, we begin our discussion of alpha-substitution reactions by looking at the methods in which the enol form of the carbonyl compound is directly involved. After discussing the factors that influence the formation and stability of enolate anions, we will examine some halogenation reactions in which an enolate ion is formed as an intermediate.

The chapter concludes with a study of the alkylation of enolate anions. These reactions are of tremendous use in organic syntheses, as they provide a method of forming new carbon-carbon bonds, and hence facilitate the laboratory preparation of increasingly complex compounds.

22.0: Chapter Objectives and Introduction to Carbonyl Alpha-Substitution Reactions
22.1: Keto-Enol Tautomerism
22.2: Reactivity of Enols- The Mechanism of Alpha-Substitution Reactions
22.3: Alpha Halogenation of Aldehydes and Ketones
22.4: Alpha Bromination of Carboxylic Acids
22.5: Acidity of Alpha Hydrogen Atoms- Enolate Ion Formation
22.6: Reactivity of Enolate Ions
22.7: Alkylation of Enolate Ions
22.S: Carbonyl Alpha-Substitution Reactions (Summary)

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22.0: CHAPTER OBJECTIVES AND INTRODUCTION TO CARBONYL ALPHA-SUBSTITUTION REACTIONS

OBJECTIVES

After completing this section, you should be able to write a general mechanism for an alpha-substitution reaction of a carbonyl compound.

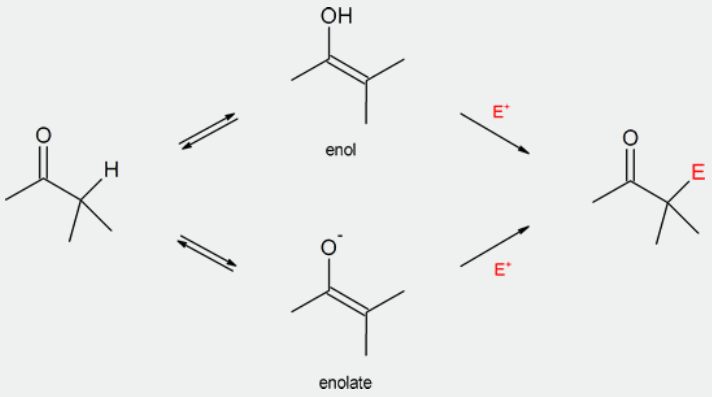
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- alpha (α) position
- alpha-substitution reaction

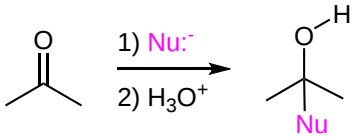
STUDY NOTES

An "alpha-substitution reaction" of a carbonyl compound is a reaction in which one of the hydrogen atoms on the carbon adjacent to the carbonyl group is substituted by some other atom or group. Attack by the electrophile (E^+) can occur on the enol or enolate intermediate.



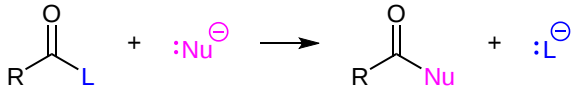
There are four common types of reactions involving compounds containing a carbonyl bond. The first two, nucleophilic addition and nucleophilic acyl substitution, have been discussed in previous chapters.

Nucleophilic addition occurs due to the electrophilic nature of the carbonyl carbon. After addition of a nucleophile, the carbonyl becomes a tetrahedral alkoxide intermediate which is usually protonated to become an -OH group.



Nucleophilic Addition to a Carbonyl

Nucleophilic acyl substitution is similar in that a tetrahedral alkoxide intermediate is formed after nucleophilic addition to the carbonyl. However, subsequent removal of the leaving group allows for the C=O (carbonyl) bond to reform. Overall, there is a substitution of the leaving group with the incoming nucleophile.



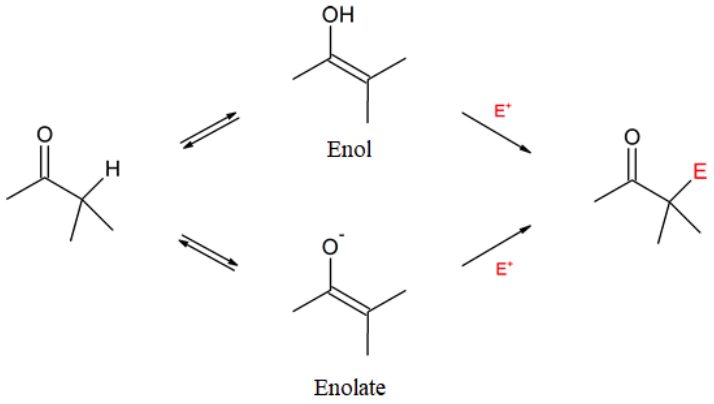
L = Leaving Group

Nucleophilic Acyl Substitution Involving a Carbonyl

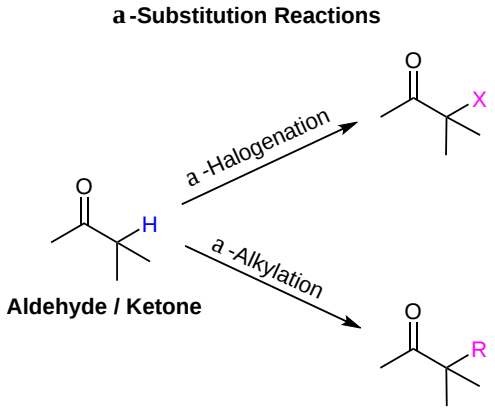
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REACTIONS AT THE ALPHA CARBON

The remaining common carbonyl reaction types are α-substitutions and carbonyl condensations. Both utilize the special properties of carbons directly adjacent to carbonyls which are called **α-carbons**. These reactions, which can be regarded as the backbone of much synthetic organic chemistry, usually result in the replacement of a hydrogen attached to an α-carbon with some type of electrophile. These reactions involve two new nucleophilic species called the enol and the enolate.



This chapter will focus on α-substitutions reactions. Although there are many carbonyl containing functional groups, the initial investigation in this chapter will focus on α-substitutions reactions using aldehydes and ketones. Important examples considered in this chapter include α-halogenation and α-alkylation.



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22.1: KETO-ENOL TAUTOMERISM

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate keto-enol tautomerism.
2. write a detailed mechanism for acid-catalyzed keto-enol tautomerism.
3. write a detailed mechanism for base-catalyzed keto-enol tautomerism.
4. draw the structure of the enol form of a given carbonyl compound.

KEY TERMS

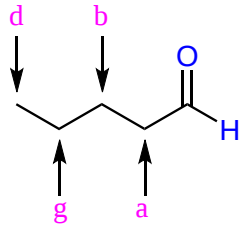
Make certain that you can define, and use in context, the key terms below.

- enol
- keto
- tautomerism
- tautomers
- enolate ion

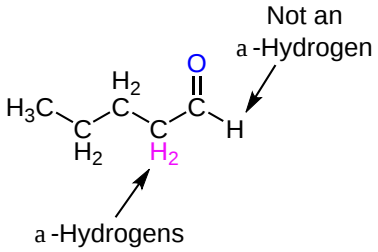
STUDY NOTES

Keto-enol tautomerism was first introduced in Section 9.4, in the discussion of the hydration of alkynes. The subject was raised again in the chapter entitled A Preview of Carbonyl Compounds, during the brief overview of the alpha-substitution reactions of carbonyl compounds. You may wish to review these sections before proceeding.

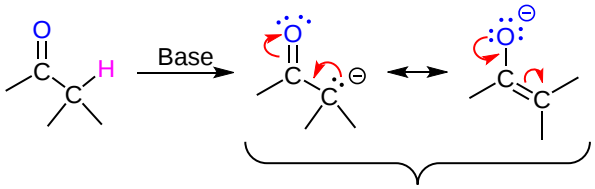
Often, the position of a carbon atom near a carbonyl group is designated using Greek letters. The atom adjacent to the carbonyl is alpha, the next removed is beta and so on. The carbon in the carbonyl group is used as reference point and is not assigned a Greek letter. Likewise, hydrogens bare the same Greek letter as the carbon atoms to which they are attached. α-Hydrogens are bonded to α-carbons and β-hydrogens are bonded to β-carbons etc.



The presence of α-hydrogens in a molecule provides the possibility of certain chemical reactions, which will be discussed in this chapter and in **Chapter 23**. Because of this, the ability to identify α-hydrogens is an important skill. As shown below, pentanal has two α-hydrogens. Note that aldehyde hydrogens are not given a Greek letter, they are simply referred to as an aldehyde hydrogen.

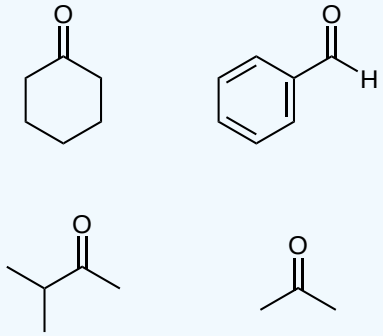


α-hydrogens, which are attached to a carbon directly adjacent to a carbonyl group, display unusual acidity. This is almost exclusively due to the resonance stabilization of the carbanion conjugate base, called an enolate, as illustrated in the diagram below. The effect of the the stabilizing C=O is seen when comparing the pK_a for the α-hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to that of a typical alkyl C-H bond (~40-50).

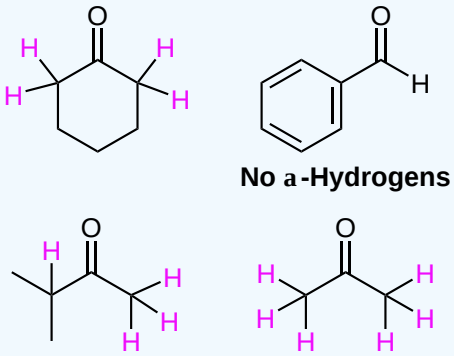


EXAMPLE 22.1.1

Indicate any α-hydrogens contained in the following molecules:



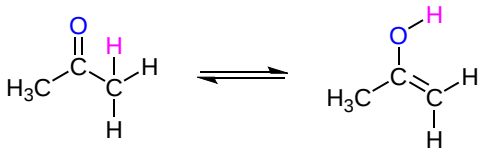
Solution



KETO-ENOL TAUTOMERIZATION

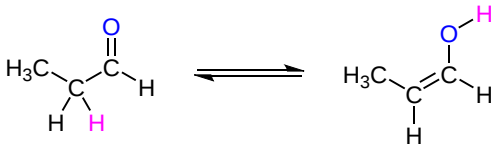
Because of the acidity of α-hydrogens, many carbonyl containing compounds undergo a proton-transfer equilibrium called tautomerism. Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group. Because tautomers involve the rearrangement of atoms, they are distinctly different than resonance forms, which only differ in the position of bonds and lone pair electrons. This discussion focuses on carbonyl groups with α-hydrogens, which undergo keto-enol tautomerism. Keto implies that the tautomer contains a carbonyl bond while enol implies the presence of a double bond and a hydroxyl group.

The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer. For simple carbonyl compounds under normal conditions, the equilibrium usually strongly favors the keto tautomer (acetone, for example, is >99.999% keto tautomer). The keto tautomer is preferred because it is usually more stable than the enol tautomer by about 45–60 kJ/mol, which is mainly due to the C=O double bond (-749 kJ/mol) being stronger than the C=C double bond (-611 kJ/mol). Because ketones have two alky groups donating electron density into the carbonyl carbon, they tend to be more stable and therefore less apt to form the enol tautomer than aldehydes. For example, propanal is 1000 times more likely to be in its enol tautomer than acetone. With carboxylic acid derivatives, the leaving group tends to stabilize the carbonyl through electron donation which makes the formation of the enol tautomer much less likely. In general, ketones are over 100,000,000 times more likely to be in an enol tautomer form than esters.



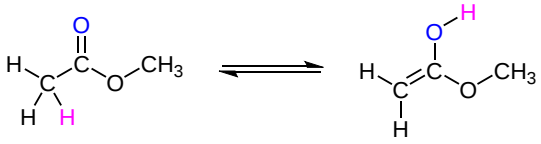
Acetone
Keto Tautomer
(>99.999%)

Propen-2-ol
Enol Tautomer
(~1.7 x 10^{-7}%)



Propanal

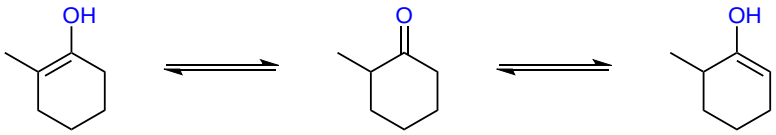
Propen-1-ol
(~1 x 10^{-4}%)



Ethyl Ethanoate

1-Methoxyethen-1-ol
(<1 x 10^{-15}%)

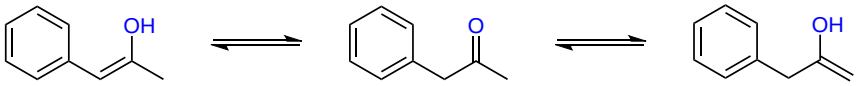
Aldehydes and symmetrical ketones typically only have one possible enol tautomer while asymmetrical ketones can have two or more. The preferred enol tautomer formed can be often be predicted by considering effects which can stabilize alkenes, such as conjugation and alkyl group substitution. The asymmetrical ketone, 2-methylcyclohexanone has two possible enol tautomers. Of the two tautomers, 2-methyl-1-cyclohexen-1-ol, is the more stable and therefore preferred due to the presence of an additional alkyl substituent. Likewise, 1-phenyl-1-propen-2-ol is the more stable enol tautomer of 1-phenyl-2-propanone due to conjugation with the phenyl ring.



Double Bond has more alkyl substituents
(More Stable Enol Tautomer)

2-Methylcyclohexanone

Double Bond has fewer alkyl substituents



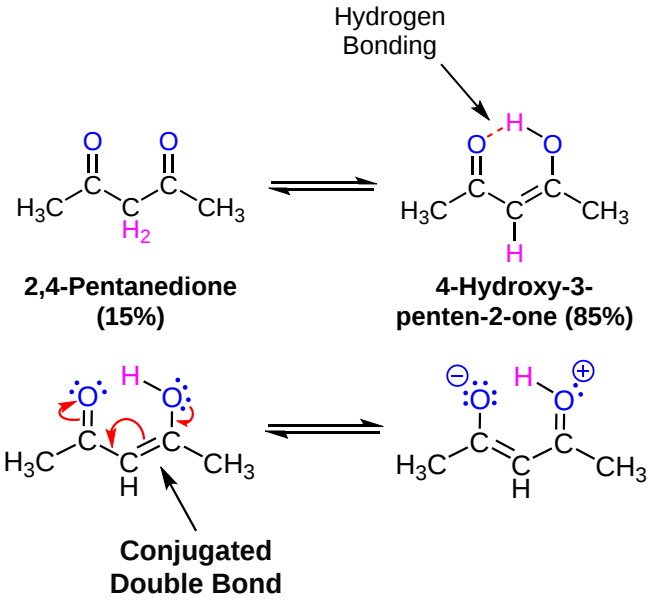
Double Bond is conjugated with the phenyl ring
(More Stable Enol Tautomer)

1-Phenyl-2-propanone

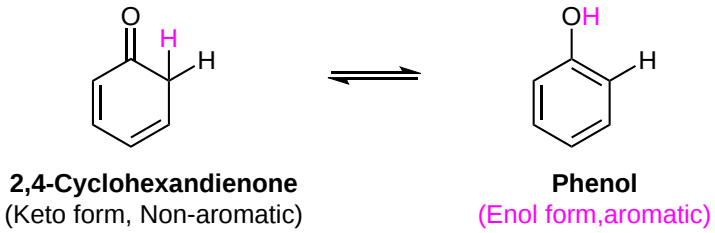
Double Bond is not conjugated with the phenyl ring

1,3-DICARBONYLS

In certain cases additional stabilizing effects allow the enol tautomer to be preferred in the tautomerization equilibrium. In particular, the 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium. The diketone, 2,4-pentanedione, is in its enol form 85% of the time under normal conditions. The positioning of the carbonyl groups allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. The alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization. Both of these stabilizing effects are not possible in the keto tautomer.



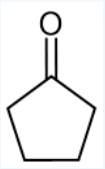
Another effect which can stabile an enol tautomer is aromaticity. When considering the molecule 2,4-cyclohexadienone, the enol tautomer is the aromatic molecule phenol. The stabilization gained by forming an aromatic ring is sufficient to make phenol the exclusive tautomer present in the equilibrium.



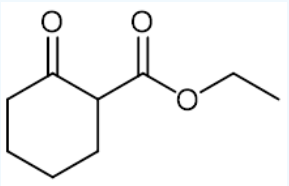
EXAMPLE 22.1.1

Please all of the possible enol tautomers for the following compounds. If more than one is possible then indicate which is the most stable and why.

a)

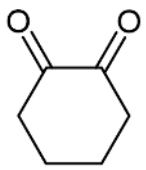


b)



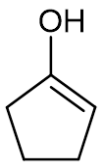
c)

https://chem.libretexts.org/@go/page/36412

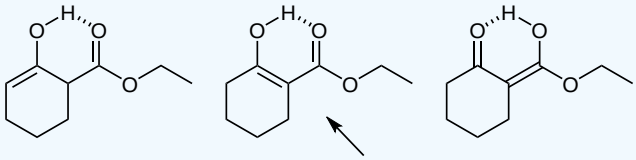


Solution

a)

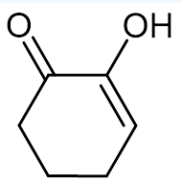


b)



This enol tautomer is the most stable due to hydrogen bonding, conjugation, and the ketone being in the enol form rather than the ester.

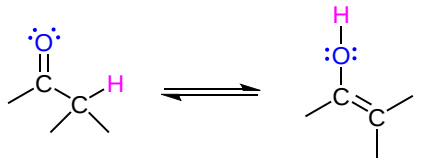
c)



MECHANISM FOR CATALYZED KETO-ENOL TAUTOMERIZATION

The enol tautomer has valuable nucleophilic characteristics. In neutral media, tautomerization is slow but it can be speed up by catalysis with acids or bases. Both pathways involve two separate proton transfer steps. Because enols are a key reactive intermediate, these mechanistic steps will be used repeatedly in later reactions. The following mechanistic steps represent the continuous interconversion between the keto and enol tautomers.

Overall Process



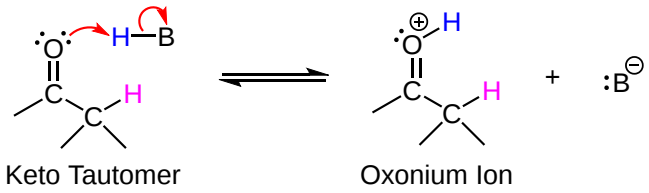
Keto Tautomer **Enol Tautomer**

ACIDIC CONDITIONS

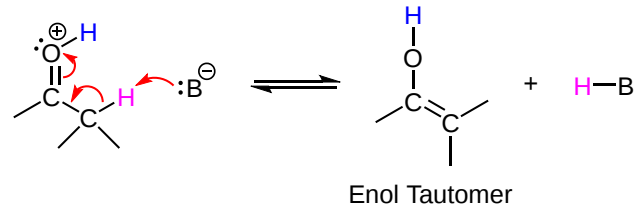
Keto Tautomer → Enol Tautomer

In the first step, the carbonyl oxygen is protonated by an acid to form an intermediate oxonium ion. A base removes an α-hydrogen during the second step forming a double bond by an E2 type reaction. This causes the pi electrons of the protonated carbonyl to move to the oxygen to form the hydroxyl group of the enol product and regenerating the acid catalyst.

1) Protonation of the carbonyl to form an oxonium ion



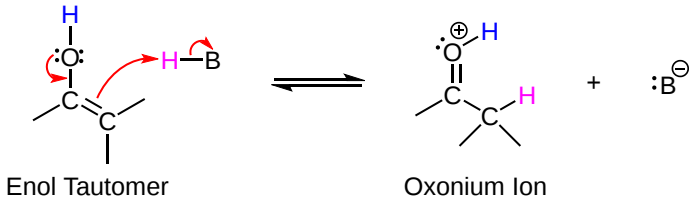
2) Deprotonation of an *α*-hydrogen to form an enol



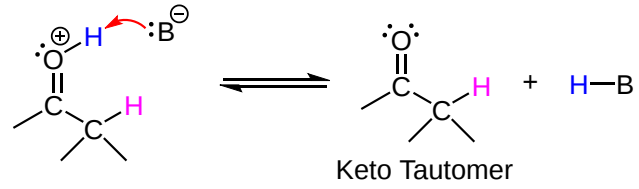
Enol Tautomer → Keto Tautomer

First, one of the lone pairs of electrons on the enol oxygen moves to form a pi bond with the adjacent carbon to create a oxonium ion. This also causes the pi bond electrons from the enol double bond to attack the electrophilic H^+ provided by acid catalyst forming a C-H bond in the α-position. This produced oxonium ion intermediate is subsequently deprotonated to form the neutral ketone and regenerate the acid catalyst.

1) Protonation at the α-carbon



2) Deprotonation

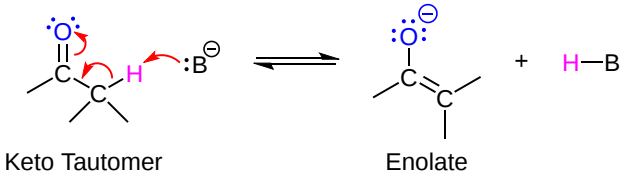


UNDER BASIC CONDITIONS

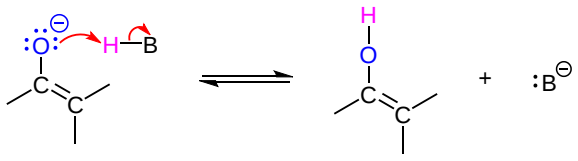
Keto Tautomer → Enol Tautomer

In the first step, a base removes an α-hydrogen from a carbonyl containing compound to form an alkene by an E2 like process. The causes the pi electrons of the carbonyl bond to move onto the carbonyl oxygen to form an enolate anion. The oxygen of the enolate anion is protonated in the second step to create a neutral enol and regenerate the base catalyst.

1) Deprotonation of a *α*-hydrogen to form an enolate ion



2) Protonation the enolate ion to form an enol

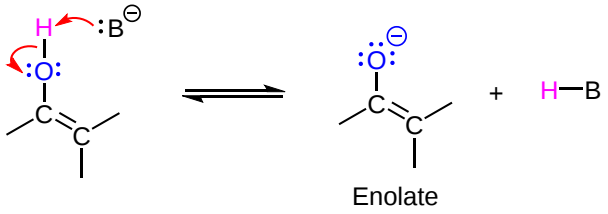


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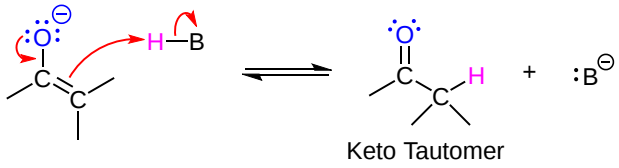
Enol Tautomer → Keto Tautomer

The mechanistic return to the keto tautomer begins with deprotonation of the hydroxyl hydrogen to produce an enolate ion. Then lone pair electrons from the enolate anion attack an electrophilic H^+ through conjugation with the double bond. This simultaneously forms the carbonyl double bond, adds an alpha hydrogen, and regenerates the base catalyst.

1) Deprotonation of the enol hydrogen

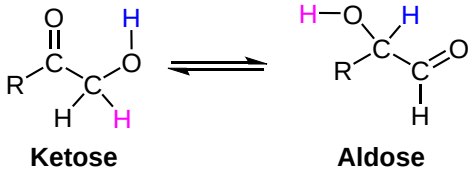


2) Protonation of the α-carbon



BIOLOGICAL ENOL FORMING REACTIONS

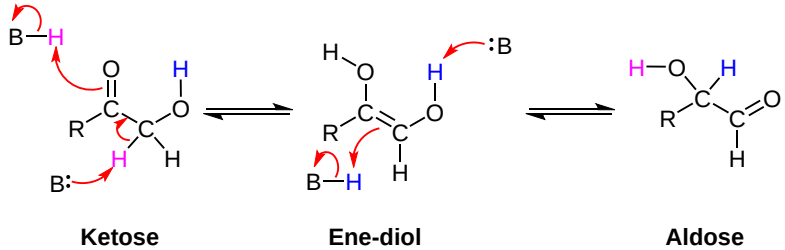
One very important family of isomerase enzymes catalyzes the shifting of a carbonyl group in sugar molecules using a process called an carbonyl isomerization. Carbonyl isomerization often involves converting between a ketose and an aldose. (recall that the terms ketose and aldose refer to sugar molecules containing ketone and aldehyde groups, respectively).



Carbonyl Isomerization

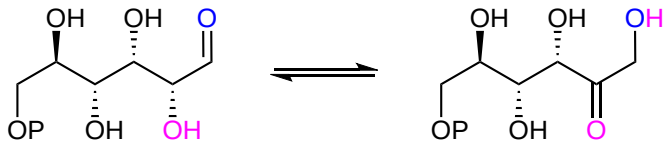
Mechanism

Carbonyl isomerization can only occur if there is an OH group adjacent to the carbonyl. Isomerization forms an ene-diol intermediate which has both OH hydrogens available to be removed to form a carbonyl. If the hydrogen from the original OH group is removed a new carbonyl bond is formed.



Carbonyl isomerization is involved in the metabolism of carbohydrates (starches and sugars) to their eventual conversion to CO_2 and H_2O. First, starches are broken down into glucose in the digestive tract. In the cells, the first step of the glycolysis pathway involves an enzyme converting glucose to glucose-6-phosphate. This is followed by the enzyme-catalyzed tautomerization of glucose-6-phosphate (an aldose) to

fructose-6-phosphate (a ketose) through an enediol intermediate. Notice how the carbonyl has moved from the 1-carbon (terminal) to the 2-carbon.



Glucose-6-phosphate Fructose-6-phosphate

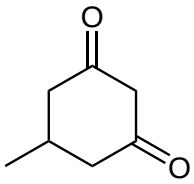
EXERCISES

1) Draw the enol forms of the following molecules

a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. 1-phenyl-2-butanone

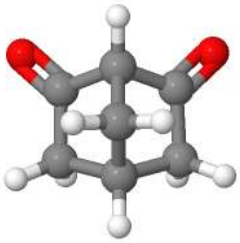
2) How many α-hydrogens do each of the molecules from the previous question have? Label them.

3) Draw all of the mono-enol forms for the following molecule. Which ones are most stable? Why?

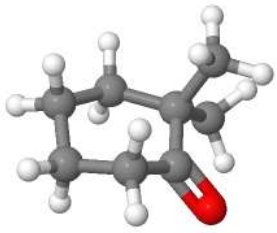


4) Under normal conditions cyclohexanone exists in the enol tautomer in a much higher percentage than acetone. Explain.

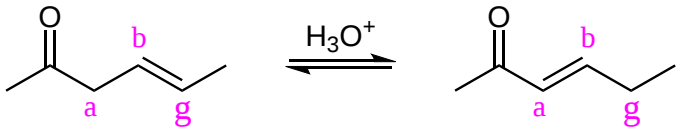
5) The 1,3-dicarbonyl shown below is only as acidic as acetone and does not form a detectable amount of the enol tautomer. Please explain.



6) For the following compound please identify the most acidic hydrogen atom. Remember that for an enolate conjugate base to be stabilized through conjugation, the lone pair electrons need to be contained in a p orbital which is parallel to the p orbitals which form the C=O pi bond.



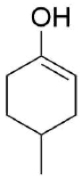
7) Nonconjugated ß, gamma-unsaturated ketones, such as 2-hexen-4-one, can be converted to their *α*, ß-unsaturated isomers by treatment with an acid catalyst. Please propose a mechanism for this isomerization.



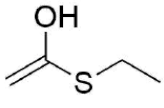
SOLUTIONS

1)

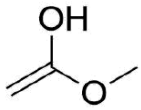
(a)



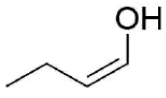
(b)



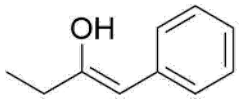
(c)



(d)

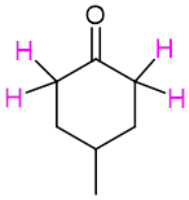


(e)

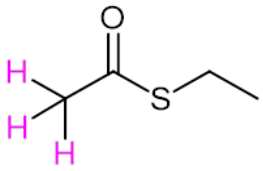


2)

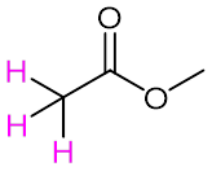
(a)



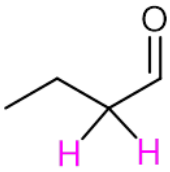
(b)



(c)

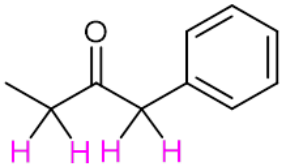


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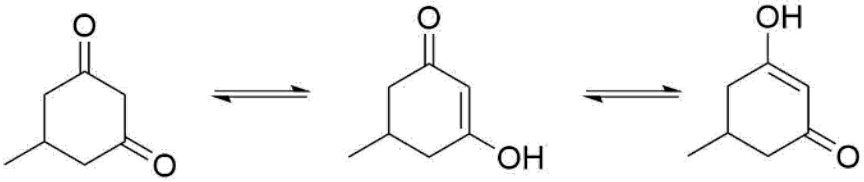


(d)

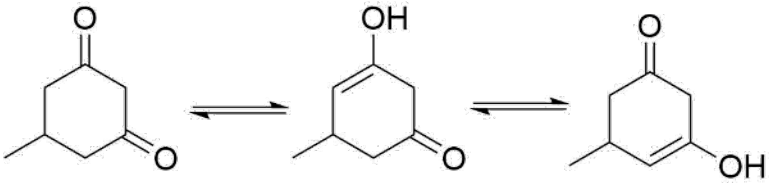
(e)



3)



Additional resonance forms stabilizes this enol.



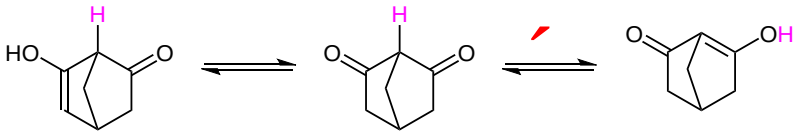
This enol has fewer resonance forms and is therefore less stable.

4) The enol tautomer of cyclohexanone has more alky substituents than the enol tautomer of acetone. This makes the double bond of the enol double bond of cyclohexanone more stable and easier to form.



Enol of Cyclohexane **Enol of Acetone**

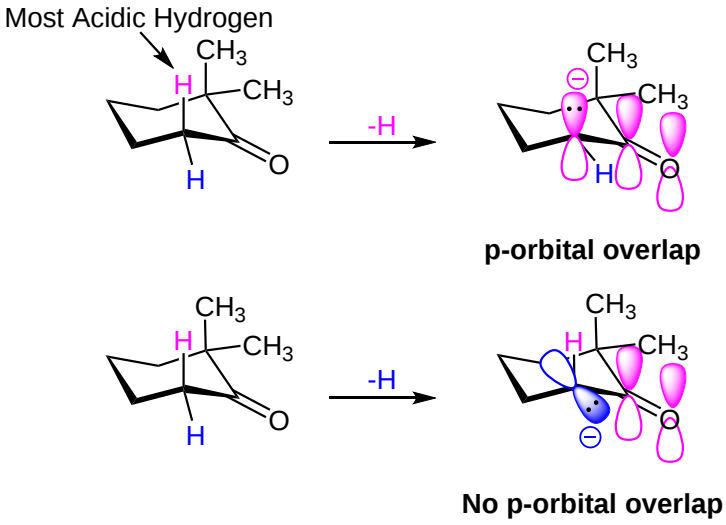
5) In many situations, the enol tautomer fo the a 1,3-dicarbonyl is preferred in the tautomerization equilibrium due to stabilizing effects created by the second carbonyl. However, in this case the alpha hydrogen used to create the enol tautomer is attached to a brigehead carbon of a bicyclic ring system. The positioning of the enol and the carbonyl prevents the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen. Also, the inherent steric restrictions of a bicyclic ring system prevents the formation of a double bond using a bridgehead carbon. Instead, an enol tautomer of the molecule would be expected to form outside the 1,3-dicarbonyl. This enol lacks the stabilizing effects typical of a 1,3-dicarbonyl, so it is not preferred in the tautomerization equilibrium.



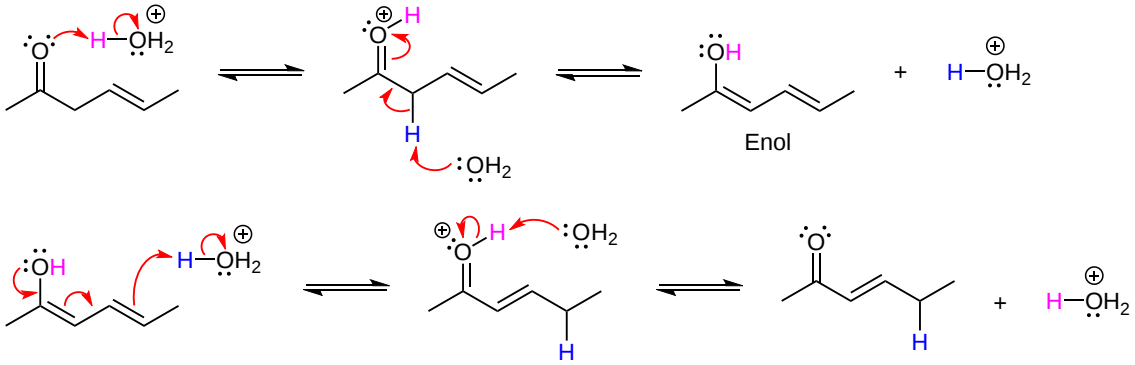
Not Formed

6) The presence of two methyl groups on one of the α-carbons of the carbonyl means that the two hydrogens on the other α-carbon may be deprotonated to form an enolate. When the indicated axial hydrogen is deprotonated the p-orbital formed is parallel with the carbonyl p-

orbitals and can participate in overlap. If the equatorial hydrogen were to be deprotonated, the p-orbital formed would be perpendicular with the carbonyl p-orbitals and prevented from participating in overlap.



7)



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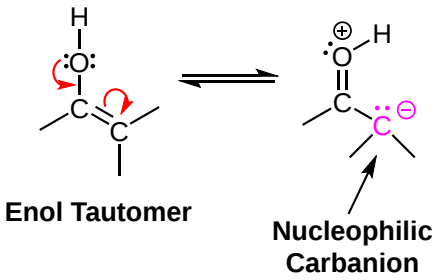
22.2: REACTIVITY OF ENOLS- THE MECHANISM OF ALPHA-SUBSTITUTION REACTIONS

OBJECTIVES

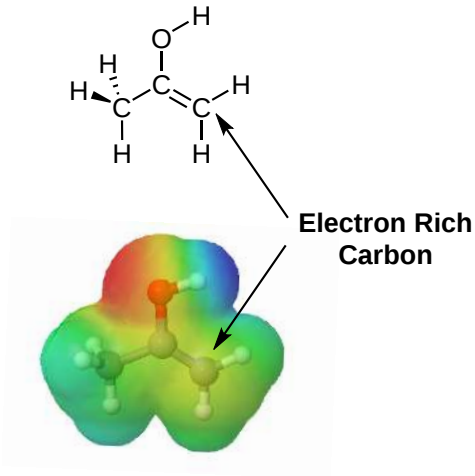
After completing this section, you should be able to write a detailed mechanism for an acid-catalyzed, alpha-substitution reaction of a carbonyl compound.

HOW ENOLS REACT

The oxygen of an enol can donate electron density into its double bond making it electron-rich and more reactive than typical alkenes.



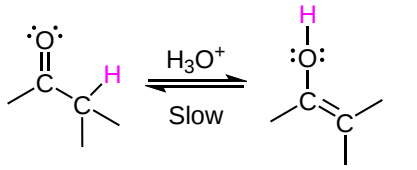
As seen in the electrostatic potential map for propen-2-ol ($CH_3COH=CH_2$), the enol tautomer of acetone, shows an increased electron density on the α-carbon (yellow) especially when compared to the $-CH_3$ carbon (blue/green). One of the resonance forms of an enol places a lone pair of electrons and a negative charge on the α-carbon forming a carbanion nucleophile. Enols react with electrophiles in a similar fashion as other carbanion nucleophiles, such as Grignard reagents.



MECHANISM OF ALPHA SUBSTITUTION REACTIONS USING AN ENOL

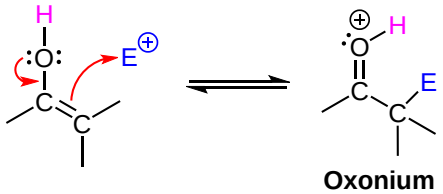
The mechanism begins with the acid-catalyzed tautomerization to form an enol via the mechanism discussed in **Section 22.1**. Lone pair electrons on the enol oxygen move to become a C=O pi bond thus creating a positively charged oxonium ion. This also causes electrons from the C=C enol pi bond to attack an electrophile forming a C-E sigma bond. These two electron movements in concert represent the enol acting as a nucleophile. In the last step, an H^+ is removed from the carbonyl oxygen, regenerating the acid catalyst, and forming an *α*-substituted carbonyl .

1) Acid catalyzed tautomerization to form an enol



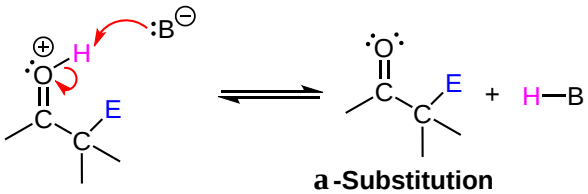
Keto Tautomer **Enol Tautomer**

2) The nucleophilic enol attacks the electrophile



Oxonium Ion

3) Deprotonation of the carbonyl to produce an α-substituted product

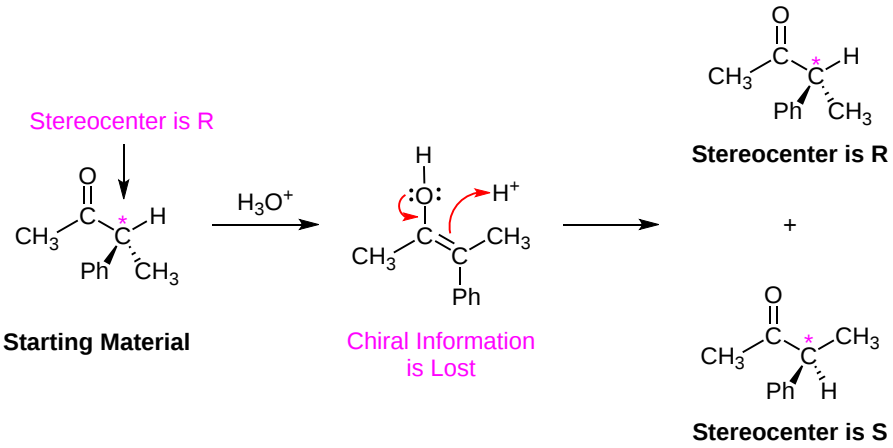


a-Substitution

STEREOCHEMICAL IMPLICATION OF ENOL FORMATION

During an acid-catalyzed enol formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original alpha carbon. Because the enol alkene is planar the incoming electrophile can attack from either the top or the bottom of the molecule. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter if formed during the reaction, the product will typically be a racemic mixture of enantiomers at the site of substitution.

One of the easiest ways of displaying this process is through acid-catalyzed racemization. If a carbonyl compound has an α-carbon with a defined stereochemisty and an α-hydrogen, a racemic mixture can be formed simply through tautomerization. The addition of acid promotes the formation of the enol tautomer which removes the chiral information of the α-carbon. The enol then attacks an H^+ electrophile to reform the keto tautomer which then contains a racemic mixture of enantiomers.

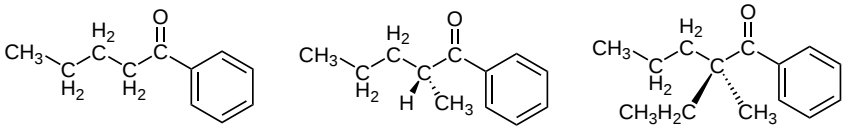


Starting Material Chiral Information is Lost **Stereocenter is R** **Stereocenter is S**

Example of Acid-Catalyzed Racemization

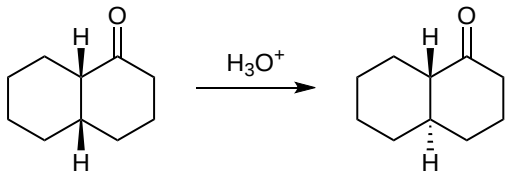
EXERCISES

1) Which of the following optically active ketones would undergo acid-catalyzed racemization? Explain.



A B C

2) When *cis*-Decalone is treated with an acid it becomes *trans*-Decalone almost exclusively becomes *trans*-Decalone. Explain.



***Cis*-Decalone** ***Trans*-Decalone**

SOLUTIONS

1) Molecule A would not because the alpha carbon is not a stereocenter. Molecule B would because the alpha carbon is a stereocenter and contains a hydrogen. Molecule C would not because it does not contain an alpha hydrogen.

2) This change involves a process call epimerization. Epimers as diastereomers which differ at only one chiral carbon. Epimerization is a process where only one of multiple chiral carbons is changed. In this example, the stereocenter in questions is a chiral carbon. The addition of an acid promotes this carbon becoming part of an enol thereby losing its chiral information. When the enol tautomer converts back the ketone tautomer the a mixture of both *cis* and *trans* epimers should form. However, as discussed in a previous section, we know that the *trans* isomer of the decalin ring system is more stable than the *cis*. Because there is a defined difference in stability, the trans isomer of decalone is preferred.

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22.3: ALPHA HALOGENATION OF ALDEHYDES AND KETONES

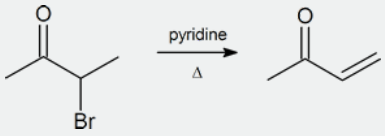
OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the alpha halogenation of aldehydes and ketones.
2. identify the product formed from the alpha halogenation of a given aldehyde or ketone.
3. identify the carbonyl compound, the reagents, or both, needed to prepare a given α-halogenated aldehyde or ketone.
4. illustrate the importance of the alpha halogenation of carbonyl compounds as an intermediate step in the synthesis of α,β-unsaturated aldehydes and ketones.
5. write a detailed mechanism for the acid-catalyzed halogenation of a ketone.
6. describe the evidence provided by kinetic experiments supporting the suggestion that the acid-catalyzed, alpha halogenation of ketones proceeds via the rate-determining formation of an enol.

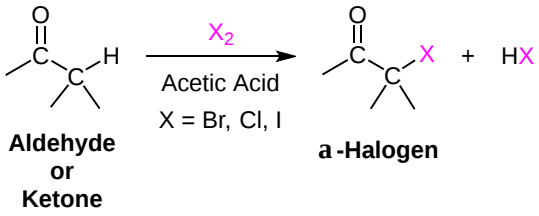
STUDY NOTES

Note: α-bromo ketones are a good starting material to generate α,β-unsaturated ketones by dehydrobromination.

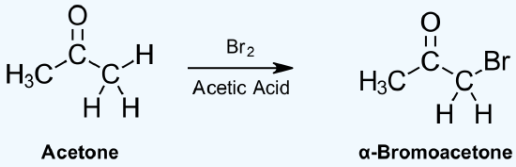


Aldehydes and ketones can substitute an α-hydrogen for a halogen atom in the presence of an acid. This reaction takes place using acid catalyzed tautomerization to form a nucleophilic enol, which then reacts with an electrophilic halogen (Cl_2, Br_2 or I_2). Because an enol intermediate is used, a racemic mixture of products can be produced. A particularly useful variation of this reaction uses bromine in an acetic acid solvent. The α-bromo substituted product can then be readily transformed into an α, β-unsaturated carbonyl through reaction with pyridine and heat.

GENERAL REACTION (*A* SUBSTITUTION)



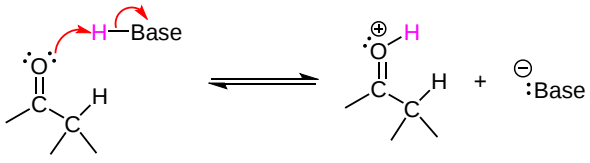
EXAMPLE 22.3.1



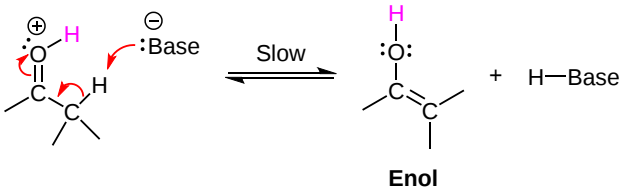
ACID CATALYZED MECHANISM

The mechanism begins with protonation of the carbonyl oxygen followed by removal of an α-hydrogen to form the enol. Lone pair electrons from the enol oxygen move to form a carbonyl while the pi electrons from the double bond attack the halogen forming an oxonium ion intermediate with a C-X sigma bond in the α-position. Deprotonation of the oxonium ion intermediate provides the α-halogen substituted product and regenerates the acid catalyst.

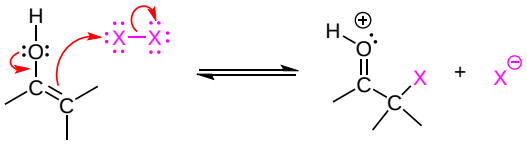
1) Protonation by the acid catalyst



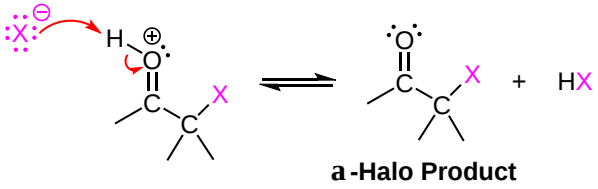
2) Removal of an α-hydrogen to form the enol. This step is slow and represent the rate determine step.



3) Nucleophilic attack on the halogen



4) Deprotonation



EXPERIMENTAL EVIDENCE OF THE ENOL INTERMEDIATE

This reaction was the focus of one of the first mechanistic investigations in organic chemistry. In the early 1900's chemist Arthur Lapworth showed that the rates of chlorination, bromination, and iodination of acetone were all the same. Also, it was shown that the rates for all three halogenation reactions were first-order with respect to acetone and the acid catalyst but independent of the halogen concentration (overall second-order for the mechanism). The rate law expression for the α-halogenation of a ketone can be given by:

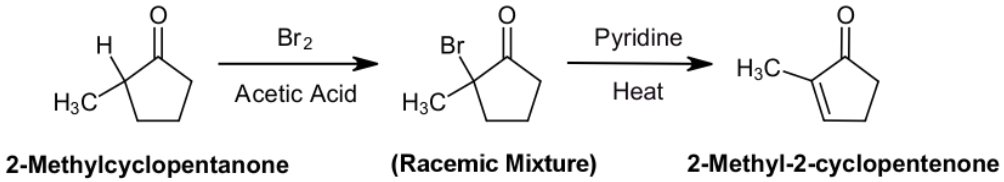
$$\text{rate} = k\,[\text{ketone}]\,[H^+]$$

This implies that the halogen participates in the mechanism through a fast step which occurs after the rate-determining step. These observations led Lapworth to theorize that the rate-determining step of the mechanism involves converting acetone to a more reactive form. The fact that the substitution occurs on the α-carbon led Lapworth to propose that the more reactive form was an enol tautomer of acetone.

Synthetic Uses for α-Halogenated Carbonyls

The product of an α-bromination can be converted to an α, β-unsaturated carbonyl by reaction with pyridine and heat which causes the elimination of H and Br. This reaction takes place by an E2 elimination mechanism and creates a C=C double bond which is conjugated with the carbonyl. In order to promote an E2 reaction, a sterically hindered base, pyridine, is often used.

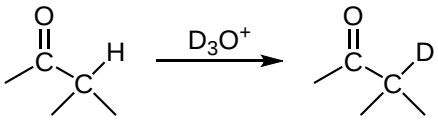
An example of this reaction involves the α-bromination of 2-methylcyclopentanone to form 2-bromo-2-methylcyclopentanone. Because enol tautomers prefer to form on the more substituted α-carbon, α-bromination also occurs on the more substituted α-carbon. Although the enol intermediate causes a racemic mixture of the α-brominated compound to form, it is irrelevant because the chiral carbon is subsequently converted to an achiral alkene. Subsequent reaction with pyridine and heat forms the α,β-unsaturated ketone, 2-methyl-2-cyclopentenone.



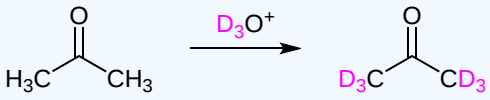
DEUTERIUM EXCHANGE

More evidence for the formation of an enol intermediate was provided using a reaction called deuterium exchange. Deuterium is an isotope of hydrogen which contains one proton and one neutron. Due to the acidic nature of α-hydrogens, they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O (deuterium oxide-heavy water). The process is accelerated by addition of the deuterium equivalent of a strong acid, such as deuterium chloride (DCl), which quickly reacts with D_2O to form D_3O^+, the deuterium equivalent of hydronium (H_3O^+). If an excess of D_2O is used, the exchange process continues to the end result of all α-hydrogens present in a given compound being replaced with deuterium. Deuterium exchange is an effective method for introducing an isotopic label into a molecule. Also, deuterium does not appear in ^1H NMR, so deuterium exchange can help determine peak assignments.

GENERAL REACTION (DEUTERIUM EXCHANGE)



EXAMPLE 22.3.2



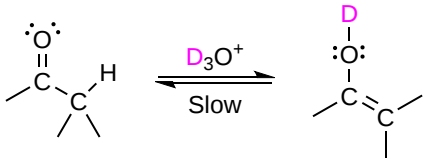
Acetone

Hexadeuteroacetone
Acetone-d6
Deuterated Acetone

MECHANISM IN ACIDIC CONDITIONS

The mechanism for deuterium exchange is virtually the same as keto-enol tautomerism under acidic conditions, as shown in **Section 22.2**. The only difference is that when the keto tautomer is reformed a deuterium is placed in the *α*-position.

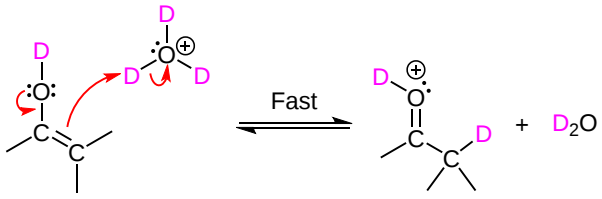
1) Formation of an enol



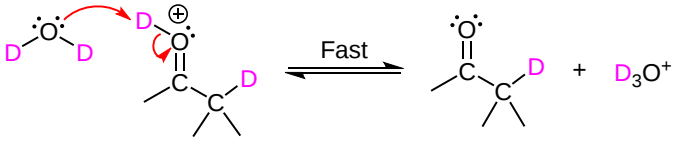
Aldehyde or Ketone

Enol

2) *α*-Deuteration



3) De-deuteration to form the keto tautomer



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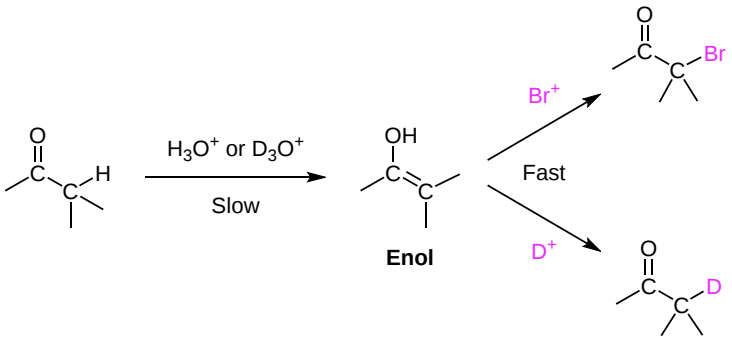
EXAMPLE 22.3.1

A simple method for determining the number of α-hydrogen in a compound is through reaction of D_3O^+. The reaction product is then isolated and its molecular weight is determined by mass spectrometry. For example, if cyclopentanone is reacted with D_3O^+, the isolated product has a molecular weight of 88 g/mol. Please explain how this method works and how many α-hydrogens cyclopentanone is predicted to have.

Solution

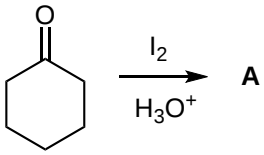
During acid catalyzed deuterium exchange each α-hydrogen in the compound is replaced with a deuterium. For each proton (AW = 1) replaced with a deuterium (AW = 2) the molecular weight of the compound is increased by one. Since cyclopentanone has a molecular weight of 84 g/mol and the isolated product has a molecular weight of 88 g/mol it can be predicted that cyclopentanone has four α-hydrogens.

Kinetic investigations into the mechanism of this reaction provided further evidence for the formation of a reactive enol intermediate. It was shown that the rate of deuterium exchange was the same as the rate of halogenation for ketones. This implies that both reactions have a common intermediate involved in the rate determining step of their mechanism, an enol.

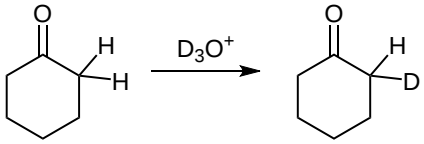


EXERCISES

1) Please draw the products of the following reactions

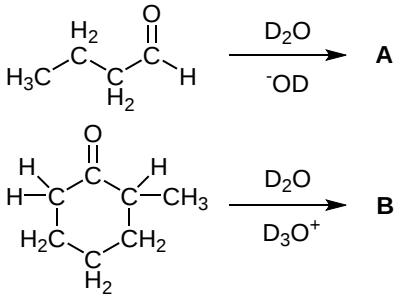


2)Draw out the mechanism for the following reaction.

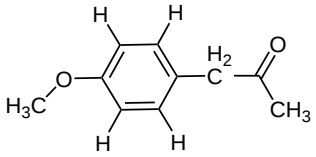


3) How might you form 2-hepten-4-one from 4-heptanone?

4) Show the products of the following reactions:

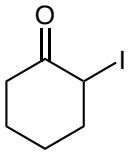


5) The following compound was reacted with D_3O^+. The only signals that could be found in the 1H NMR spectrum of the product were at 3.9 ppm (3H) and 6.6-6.9 ppm (4H). Please explain the results of the NMR.



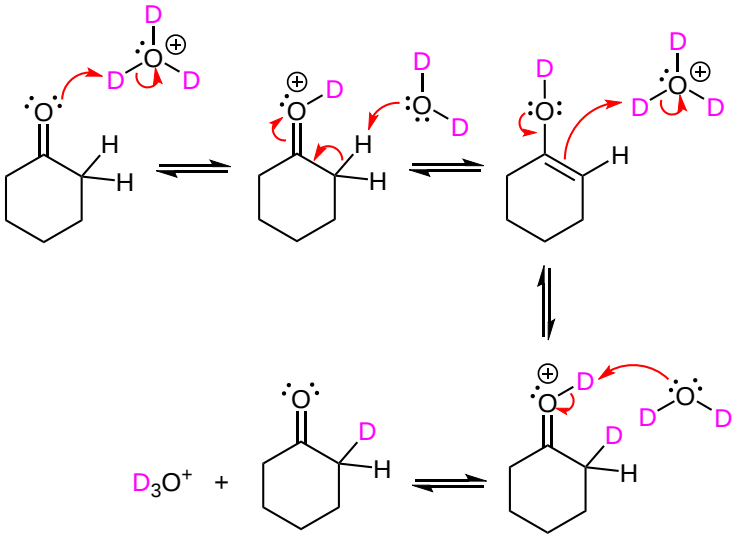
SOLUTIONS

1)



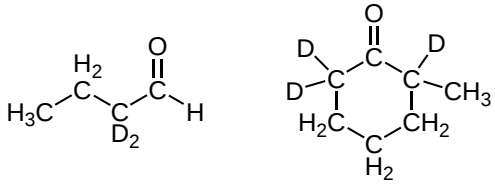
A

2)



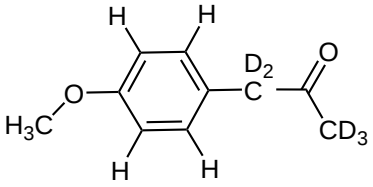
3) [1) Br_2, H_3O^+; 2) Pyridine, Heat]

4)



A **B**

5) A deuterium exchange reaction occurred. All of the alpha-hydrogens in the molecule have been exchanged with deuterium. Because detueriums do not appear in a typical ^1H NMR, only the remaining hydrogens appear.



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22.4: ALPHA BROMINATION OF CARBOXYLIC ACIDS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
2. identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
3. identify the carboxylic acid, the reagents, or both, needed to synthesize a given α-bromo carboxylic acid.
4. outline the stereochemical implications of the fact that the Hell-Volhard-Zelinskii reaction proceeds through the formation of an acid bromide enol.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Hell-Volhard-Zelinskii reaction

STUDY NOTES

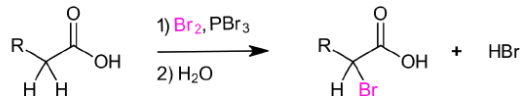
The reagents for the Hell-Volhard-Zelinskii reaction are given as bromine and phosphorus tribromide. In some questions, you may observe that only bromine and phosphorus are listed as reagents. Really there is no difference, as phosphorus tribromide would be formed *in situ* by the combination of bromine and red phosphorus:

$$3\,BR_2 + 2\,P \longrightarrow 2\,PBr_3$$

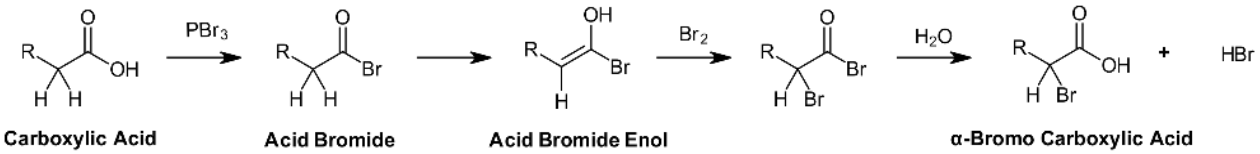
Excess bromine is required to ensure that enough reagent is available for the reaction with the enol.

HELL-VOLHARD-ZELINSKII REACTION

Although the α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with carboxylic acids, esters, and amides. Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen. However, carboxylic acids, can be brominated in the α-position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.

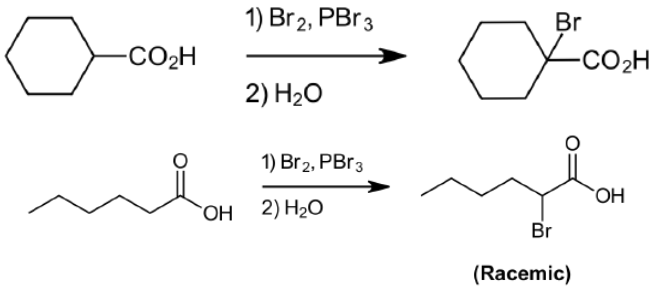


MECHANISM



This reaction is the combination of three separate reaction mechanisms all of which have been previously discussed. The mechanism starts with the reaction of the carboxylic acid with PBr_3 to form an acid bromide and HBr. Formation of an acid bromide is vital to this reaction because they lack the acidic carboxylic acid proton and can enolize much more readily making α-bromination possible. Next, HBr catalyzes the tautomerization of the acid bromide into its enol tautomer, acid bromide enol, which subsequently reacts with Br_2 to give α-bromination. Lastly, the product undergoes nucleophilic acyl substitution which cause the hydrolysis of the acid bromide to reform the carboxylic acid and the HBr catalyst. Because an enol intermediate is formed, this reaction will form a racemic mixture at the α-carbon.

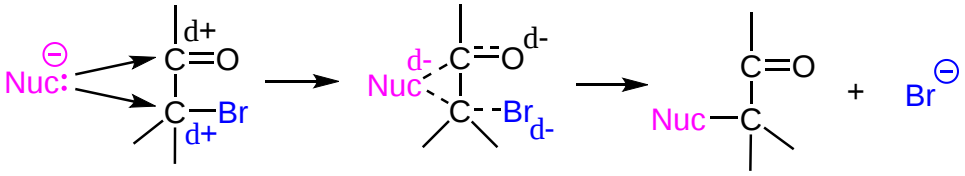
EXAMPLES



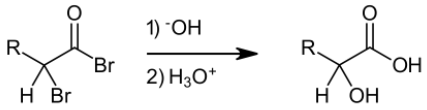
(Racemic)

FURTHER REACTIONS OF *A*-BROMO CARBOXYLIC ACIDS

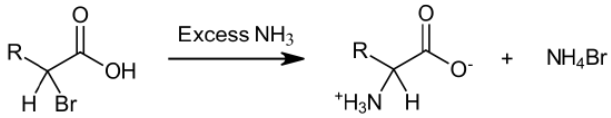
α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reactions. Having the electrophilic carbon of the carbonyl adjacent to the electrophilic *α*-carbon attached to the bromine allows an incoming nucleophile to share its charge between the two. This stabilizes the transition state of the S_N2 reaction, lowering the energy of activation, and increasing reaction rates. Primary *α*-Halogenated carbonyls have S_N2 reaction rates which are much greater than the corresponding primary aliphatic halogens.



Because bromides are capable of reacting with a wide variety of nucleophiles, *α*-bromo carboxylic acids serve as important intermediates. Reaction of *α*-bromo carboxylic acids with an aqueous basic solution followed by an acidic work-up produces *α*-hydroxy carboxylic acids. Reaction of *α*-bromo carboxylic acids with an excess of ammonia provides *α*-amination, which provides a possible route to amino acids.

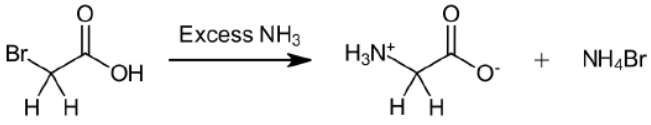


α-Bromo Carboxylic Acid **α-Hydroxy Carboxylic Acid**



α-Amino Carboxylic Acid

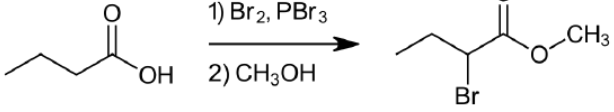
EXAMPLE



Bromoacetic acid **Glycine**

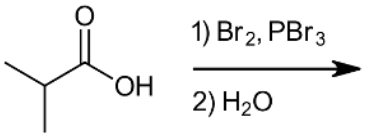
EXERCISES

1) Explain why the following reaction occurs.

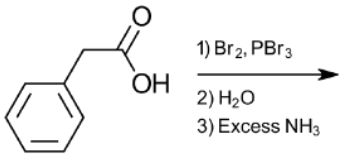


2) Draw the products of the following reactions:

a)

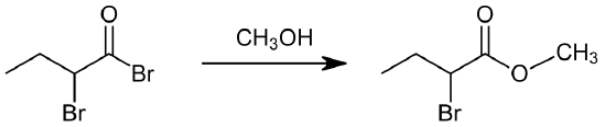


b)



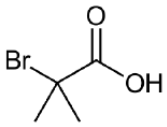
SOLUTIONS

1) The first step represents the beginning of the Hell-Volhard-Zelinskii reaction which provides a-bromination and creates and acid bromide intermediate. The second step adds methanol which reacts with the acid bromide to produce an ester.



2)

a)



b)

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22.5: ACIDITY OF ALPHA HYDROGEN ATOMS- ENOLATE ION FORMATION

OBJECTIVES

After completing this section, you should be able to

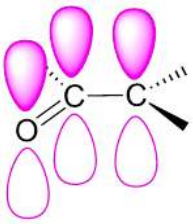
1. explain why the alpha hydrogens of carbonyl compounds are more acidic than the hydrogens in a typical hydrocarbon.
2. list the properties that make lithium diisopropylamide a suitable reagent for converting a wide range of carbonyl compounds into their enolate anions.
3. arrange a given list of carbonyl compounds in order of increasing or decreasing acidity.
4. determine whether a given carbonyl-containing compound is more or less acidic than selected other compounds, such as water, ammonia, alcohols, alkanes, alkenes, alkynes and amines.
5. explain why dicarbonyl compounds, such as *β*-diketones, are more acidic than compounds that contain only a single carbonyl group.

KEY TERMS

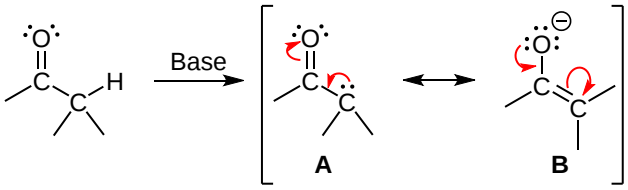
Make certain that you can define, and use in context, the key terms below.

- *β*-diketone
- *β*-keto ester

α-hydrogens are weakly acidic because their conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl. Removal of an α-hydrogen creates an sp^2 hybridized carbon anion. The negative charge and lone pair electrons of the carbon anion are contained in an unhybridized p orbital. Orbital overlap with p orbitals from the adjacent carbonyl pi bond allows for the lone pair electrons and negative charge to be shared with the electronegative Carbonyl oxygen, stabilizing the negative charge of the enolate ion.

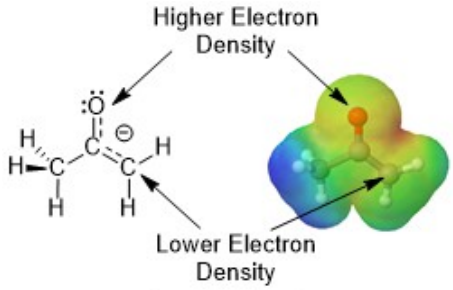


Enolate conjugation can be represent by two major resonance forms represented by structures A and B which share the negative charge (Shown Below). In resonance form A, the negative charge is on a carbon while in resonance form B the negative change is on an oxygen.



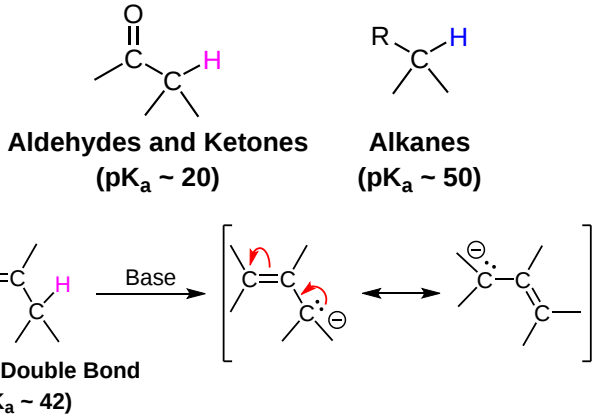
Enolate Ion

Resonance form B is preferred because oxygen is highly electronegative and better able to stabilize the negative charge. Both resonance form contribute to an overall resonance hybrid but not equally. Due to its stability, resonance form A makes a greater contribution to the resonance hybrid structure. Form A's increased contribution to the hybrid is seen when considering the electrostatic potential map of an acetone enolate. The red/yellow color shows there is a high electron density around the oxygen. The yellow/green color around the enolate carbon shows that there is a lower but still significant electron density present. Notice that the electron density on the enolate carbon is much larger than the non-enolate carbon (blue color).



Acetone Enolate Resonance Hybrid

The effect of an adjacent carbonyl on the acidity of α-hydrogens is seen when comparing the pK_a of aldehydes (~16-18) and ketones (~19-21) to the pK_a of an alkane (~50). The ability of the electronegative oxygen to stabilize a negative charge can be seen by considering the pK_a of an allyl C-H bond (~42). Having a C-H bond adjacent to a C=C double bond allows the conjugate base created by deprotonating an allyl C-H bond to be stabilized by conjugation. However, the stability gained only provides a 10^8 increase in acidity when compared to an alkane. In comparison, the presence of an electronegative oxygen allows the acidity of an α-hydrogen to be 10^{20} times greater than that of an alkane.

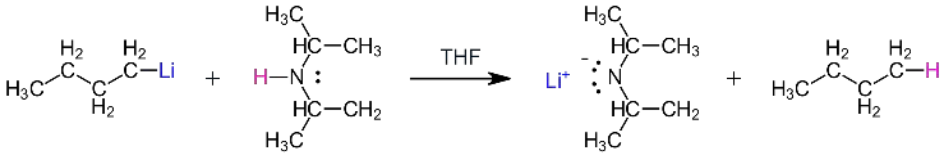


Aldehydes and Ketones (pK_a ~ 20)

Alkanes (pK_a ~ 50)

Adjacent Double Bond (pK_a ~ 42)

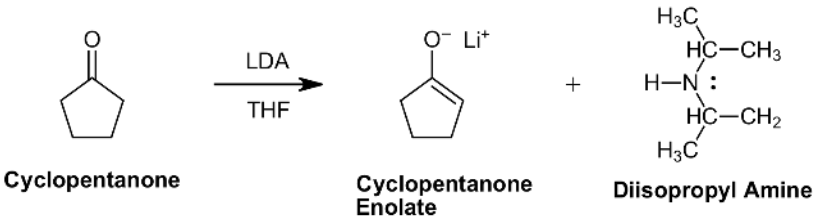
Although α-hydrogens are weakly acidic, typical strong bases such as a hydroxide or alkoxides are only capable of forming the enolate ion in very low concentrations. This can leave a significant concentration of the electrophilic carbonyl carbon remaining, which can react with the bases or the enolate. To achieve the complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used. Complete deprotonation removes the carbonyl groups of the starting material from the reaction mixture and prevents their ability to form unwanted products. Also, the large alkyl substituents sterically hinder the ability of LDA and its corresponding amine (diisopropyl amine) to undergo nucleophilic addition to the carbonyl. In addition to aldehydes and ketones, LDA readily deprotonates a wide variety of carbonyl containing functional groups including esters, amides and nitriles. Ether solvents like tetrahydrofuran (THF) are commonly used for enolate formation reactions using LDA. Certain other strong bases, such as alkyl lithium and Grignard reagents, cannot be used to make enolate anions because they rapidly and irreversibly add to the carbonyl groups. Nevertheless, these very strong bases are useful in the preparation of LDA. By reacting *n*-butyllithium with diisopropylamine (pK_a 36), LDA can be easily formed.



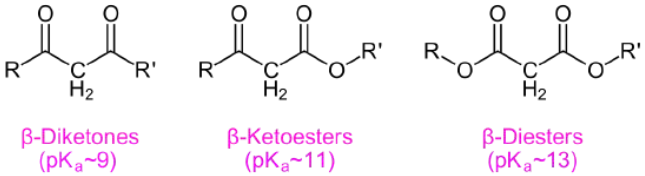
n-Butyllithium **Diisopropyl Amine** **Lithium Diisopropyl Amide (LDA)** **Butane**

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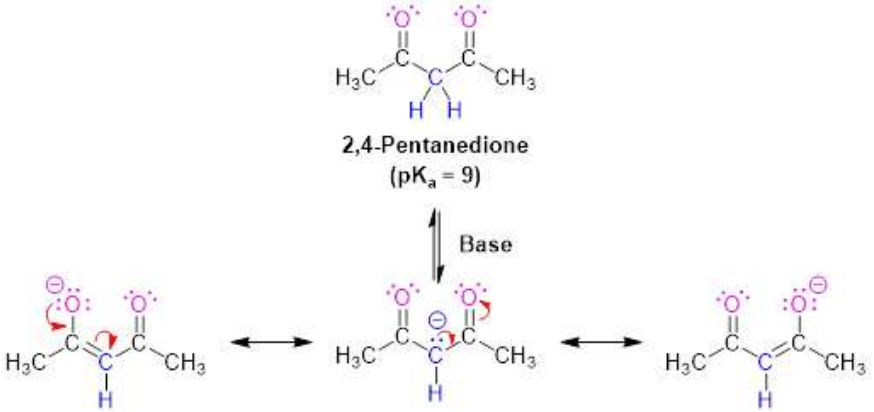
EXAMPLE



Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α-hydrogens.



The enolate ions of compound such as *β*-diketones, *β*-keto-esters, and *β*-diesters are stabilized through additional resonance forms which share the negative charge with multiple carbonyl oxygens. The acidity of these compounds is increased to the point where weaker bases, such as sodium ethoxide ($NaOCH_2CH_3$) can be used to form the enolate.



The pK_a and acidic hydrogens of multiple functional groups are shown in the table below.

* = a functional group with two ketones.

Functional Group	Structure	pK_a
carboxylic acid	HO–(C=O)R	5
nitro	$RCH_2–NO_2$	9
β-diketone *	R(O=C)–CH_2–(C=O)R	9
β-ketoester *	R(O=C)–CH_2–(C=O)OR	11
β-diester *	RO(O=C)–CH_2–(C=O)OR	13
amide	RNH–(C=O)R	15
alcohol	RCH_2–OH	16
aldehyde	RCH_2–(C=O)H	17
ketone	RCH_2–(C=O)R	20
thioester	RCH_2–(C=O)SR	21
ester	RCH_2–(C=O)OR	25
nitrile	RCH_2–C≡N	25
sulfone	$RCH_2–SO_2R$	25
amide	RCH_2–(C=O)$N(CH_3)_2$	30
alkane	CH_3–R	50

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22.6: REACTIVITY OF ENOLATE IONS

OBJECTIVES

After completing this section, you should be able to

1. identify the two possible ways in which a given enolate anion could conceivably react with an electrophile.
2. write an equation to illustrate the haloform reaction.
3. identify the products formed from the reaction of a given methyl ketone with a halogen and excess base.
4. identify the methyl ketone, the reagents, or both, needed to obtain a specified carboxylic acid through a haloform reaction.

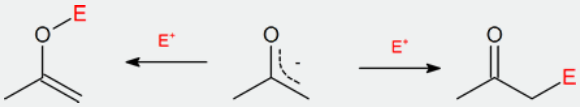
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- haloform
- haloform reaction

STUDY NOTES

Because the negative charge on an enolate ion is delocalized, there are two reactive sites and therefore two potential products. The α-substituted product is much more common.



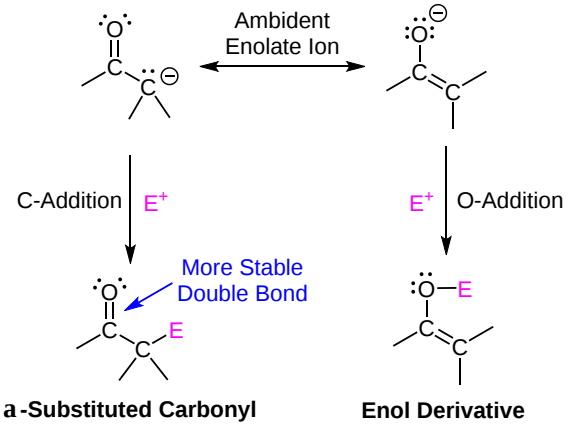
A "haloform" is any compound of the type CHX_3, where X = Cl, Br or I. Of these three compounds, chloroform is the most common.

The haloform reaction describedin the reading is usually carried out with iodine. This reaction is called the "iodoform test," and is one of the reactions carried out in the laboratory as a simple qualitative test for methyl ketones.

HOW ENOLATES REACT

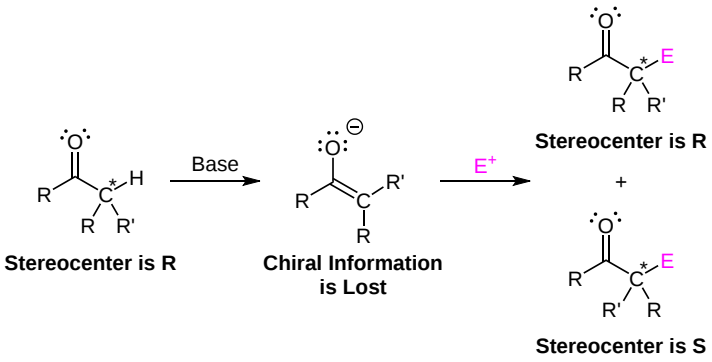
Due to their negative charges, enolates are better and more versatile nucleophiles than enols. The increased reactivity of enolates makes them capable of a wider range of reactions than enols. Also, α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base. Whereas enols can only be created in small amounts through manipulating their equilibrium.

Since the negative charge of an enolate anion is delocalized between the α-carbon and an oxygen, electrophiles may bond to either atom. Reactants having two or more reactive sites are called ambident, so this term applies to enolate anions. Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions. Reactions with the oxygen would create a new O-E bond and produce an enol derivative. Reactions with the α-carbon creates a new C-E bond and creates an α-substituted carbonyl compound. Although reactions with the nucleophilic oxygen are possible, reactions involving the nucleophilic α-carbon are much more common, partially due to the thermodynamic stability of the C=O bonds in the final products. Also, the enolate counter ion, such as Li^+ or Na^+, is more tightly associated with the negatively charged enolate oxygen which can then block incoming electrophiles, reducing their chance of reaction at the oxygen.



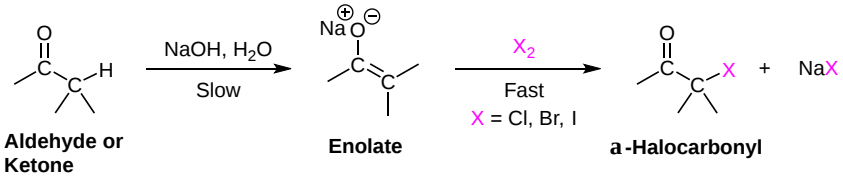
STEREOCHEMICAL IMPLICATION OF ENOLATE FORMATION

During enolate formation, an α-hydrogen is removed to form a sp^2-hybridized, trigonal planar C=C bond which removes any chiral information from the original α-carbon. Because the enol alkene is planar, the incoming electrophile can attack from either the top or the bottom. If the α-carbon of the starting material has a defined stereochemistry or if a new stereocenter is formed during the reaction, the product will be a racemic mixture of enantiomers.



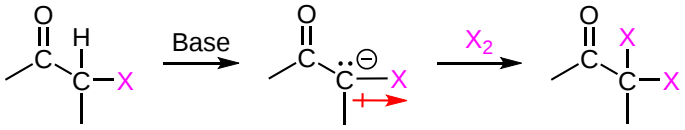
BASE PROMOTED A-HALOGENATION

An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products. This reaction has the tendency to overreact and create polyhalogenated products. If a monohalogenated product is sought, the acid catalyzed halogenation reaction discussed in section 22.3 is preferred. Because complete formation to the enolate is not necessary, weak bases, such as the hydroxide anion, are sufficient to produce this reaction. Once a small amount of enolate is formed, it quickly reacts with the halogen. This removes the enolate and shifts the equilibrium toward forming more enolate by Le Chatelier's principle.



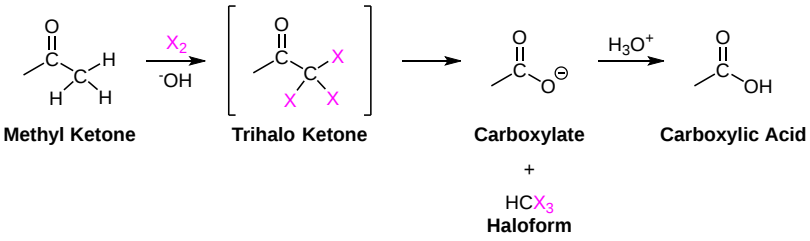
OVERREACTION DURING BASE PROMOTED A-HALOGENATION

The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds. The inductive electron withdrawing effect of the electronegative halogen stabilizes the negative charge of the enolate ion. This promotes further enolate formation and also further halogenation of the α-carbon. Monohalogenated carbonyls form an enolate over 100 times faster than their non-halogenated counterparts making multiple halogenations of the α-carbon frequent. This effect is exploited to cause the haloform reaction.

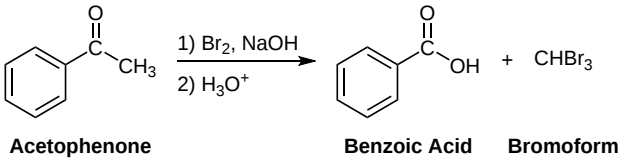


THE HALOFORM REACTION

Overall, the haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids. Due to the increased reactivity of α-halogenated products, methyl ketones typically undergo base promoted halogenation three times to give a trihalo-ketone. A halomethyl ion leaving group is then substituted with a hydroxide ion during nucleophilic acyl substitution. The resulting carboxylate can then be protonated to form a carboxylic acid.



EXAMPLE

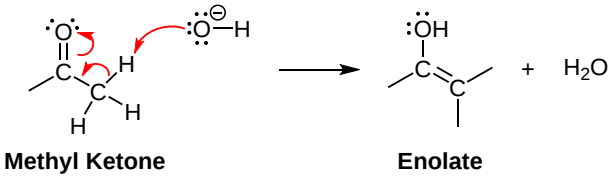


MECHANISM

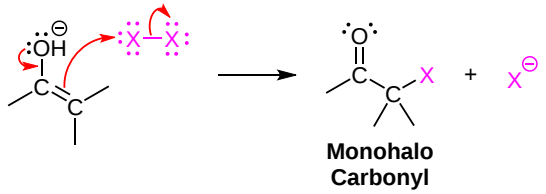
Note! This reaction is considered to be base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation. Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen. The increasing acidity of α-halogenated ketone causes this reaction to occur two more times. Once formed, the $-CX_3$ group attached to the carbonyl can act as a leaving group. Nucleophilic acyl substitution with a hydroxide anion causes C-C bond cleavage and eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion. The carboxylate ion is easily protonated with acid to form a carboxylic acid functional group. Often, this reaction is performed using iodine (I_2) because the subsequent iodoform (CHI_3) side-product is a bright yellow solid which is easily filtered off.

This reaction represents one of the few examples of a carbanion leaving group. The trihalomethyl ion ($^-:CX_3$) is particularly stabilized due to the inductive electron-withdrawing effects of the three halogens. The stability of the carbanion can be seen when considering the pK_a corresponding conjugate acid. In particular, bromoform ($CHBr_3$) has a pK_a of 13.7 which is more than 10^{20} times more acidic than a typical alkane C-H bond.

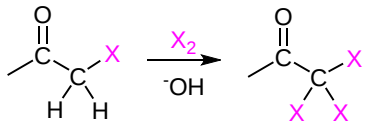
1) Enolate formation



2) Nucleophilic attack on the halogen

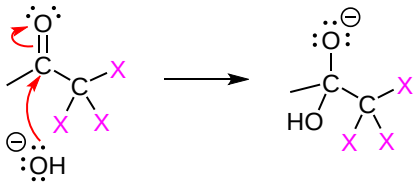


3) Repeat the halogenation two more times

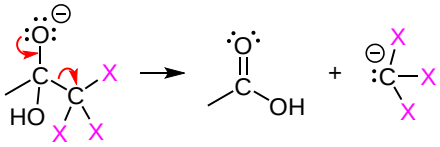


Trihalo Ketone

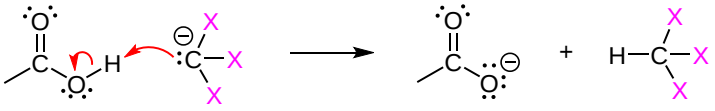
4) Nucleophilic attack on the electrophilic carbonyl carbon



5) Nucleophilic acyl substitution

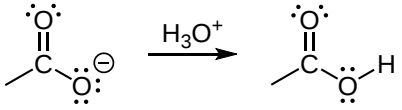


6) Deprotonation



Carboxylate **Haloform**

7) Protonation of the carboxylate

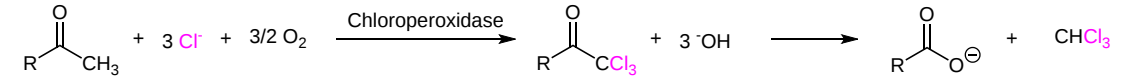


Carboxylic Acid

BIOLOGICAL HALOFORM REACTION

Interest in the haloform reaction has increased since the discovery that certain plants and marine algae can biosynthize chloroform, bromoform, and other small halocarbons through an analogous process. Previously it was assumed that these toxic compounds were present in the environment as a man-made pollutants.

The likely starting material of the biosynthesis are biogenic methyl ketones, a halogen anion, and oxygen. The enzyme, chloroperoxidase, catalyzes the polyhalogenation of the methyl groups. As in the haloform reaction, the final biosynthesis step involves a nucleophilic acyl substitution with a hydroxide anion to create a haloform and a carboxylate anion.



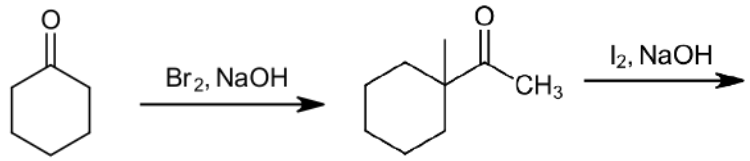
Methyl Ketone **Trichloromethyl Ketone** **Carboxylate anion** **Chloroform**

EXERCISES

1) Please predict the expected products of the following reactions:

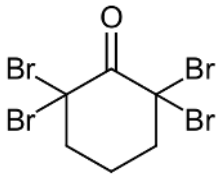
a)

b)

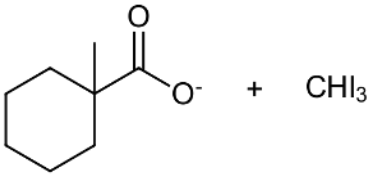


SOLUTIONS

a)



b)



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22.7: ALKYLATION OF ENOLATE IONS

OBJECTIVES

After completing this section, you should be able to

1. write a general mechanism for the attack of an enolate anion on an alkyl halide.
2. write a reaction sequence to illustrate the preparation of carboxylic acids via the malonic ester synthesis.
3. identify the product formed, and all the intermediates, in a given malonic ester synthesis.
4. identify all of the compounds needed to prepare a given carboxylic acid by a malonic ester synthesis.
5. write a detailed mechanism for each of the steps involved in a malonic ester synthesis.
6. write a reaction sequence to illustrate the preparation of ketones through the acetoacetic ester synthesis.
7. identify the product formed, and all the intermediates, in a given acetoacetic ester synthesis.
8. identify all of the compounds needed to prepare a given ketone by an acetoacetic ester synthesis.
9. write a detailed mechanism for each of the steps involved in an acetoacetic ester synthesis.
10. identify the product or products formed when a given lactone, ester, nitrile or ketone is treated with lithium diisopropylamide followed by an alkyl halide.
11. identify the compounds needed to prepare a given α-substituted ketone, ester, lactone or nitrile by a method involving the alkylation of an enolate anion.

KEY TERMS

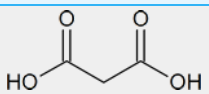
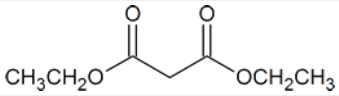
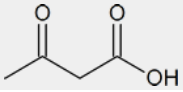
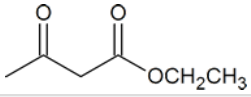
Make certain that you can define, and use in context, the key terms below.

- alkylation
- malonic ester synthesis

STUDY NOTES

The two syntheses discussed in this section provide routes to a wide variety of carboxylic acids and methyl ketones. You may wish to review the factors influencing S_N2 reactions (Section 11.3) in conjunction with this section.

You should try to memorize the structures of malonic ester and ethyl acetoacetate. The IUPAC names of these compounds are shown in the table below.

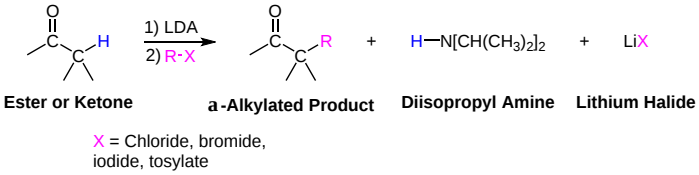
Structure	Common name	IUPAC name
	malonic acid	propanedioic acid
	malonic ester or diethyl malonate	diethyl propanedioate
	acetoacetic acid	3-oxobutanoic acid
	ethyl acetoacetate or acetoacetic ester	ethyl 3-oxobutanoate

ALKYLATION OF ENOLATES

Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides. During this reaction an α-hydrogen is replaced with an alkyl group and a new C-C bond is formed. The limitations of S_N2 reactions still apply. This includes preferring a good primary or secondary leaving group, X = chloride, bromide, iodide, tosylate. Tertiary leaving groups cannot be used in this reaction and typically give undesired E2 elimination products. A very strong base, such as LDA, is often used because of its ability to form the enolate completely. Removal of the carbonyl starting material from the reaction mixture makes it unavailable for nucleophilic addition by the enolate. Aldehydes are usually not directly alkylated because their enolates prefer to undergo the carbonyl condensation reactions discussed later in

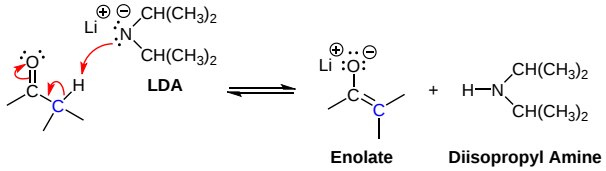
Section 23.1. In addition, the acidic hydrogen on carboxylic acids inhibits the formation of an enolate, and makes their direct alkylation difficult. Esters, including lactones, and symmetrical ketones readily undergo direct alkylation. However, direct alkylations, like all enolate-based reactions, can form a racemic mixture if the alkylated α-carbon produced is chiral.

GENERAL REACTION

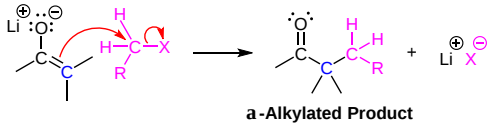


MECHANISM

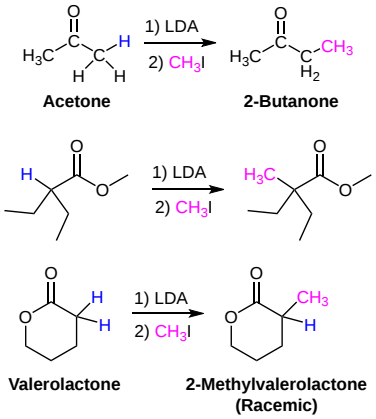
1) Enolate formation



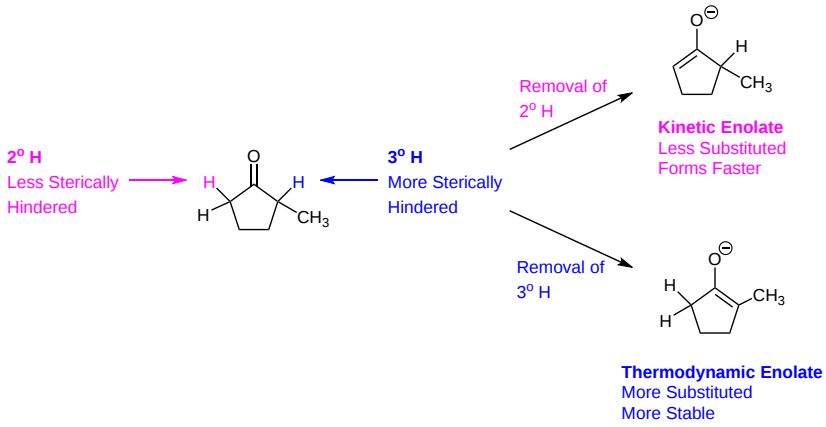
2) S_N2 attack



EXAMPLES



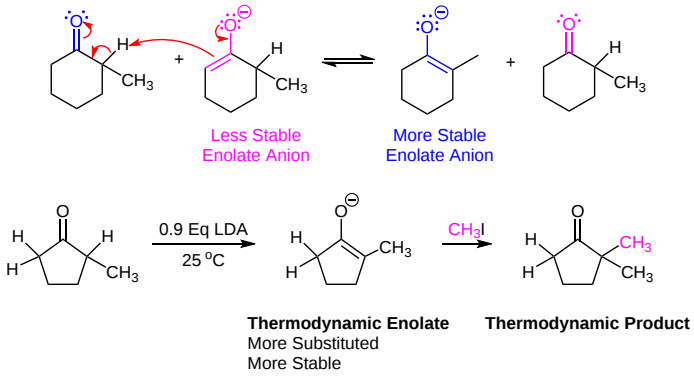
When an unsymmetrical ketone with two sets of non-equivalent α-hydrogens is treated with a base, two possible enolates can form. Regioselective enolate formation is possible under the proper conditions. The main determinant is whether the reaction is under kinetic control (rate) or thermodynamic control (equilibrium). Although a predominant product can be produced, a mixture of products is usually formed causing a reduction in product yield.



THERMODYNAMIC ENOLATES

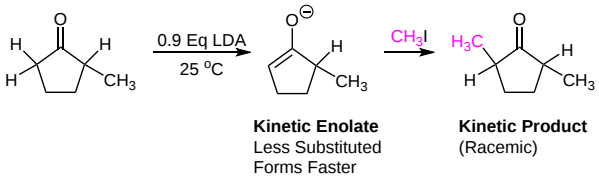
The thermodynamic enolate is formed when the more substituted α-hydrogen is removed. This leads to the more alkyl substituted, therefore the more stable, enolate to be formed. The presence of additional alkyl groups causes the formation of the thermodynamic enolate to be sterically hindered and kinetically slow, especially when a bulky base like LDA is used. Thermodynamic enolates are favored by conditions which allow for equilibration between the possible enolates. When the ketone starting material is not completely deprotonated, equilibrium between the possible enolates and the α-hydrogens of the ketone can occur. During equilibrium, interconversion between the enolates allows the lower energy of the thermodynamic enolate to dominate. Other conditions can also promote the formation of the thermodynamic enolate, such as higher reaction temperatures, or the use of a smaller less sterically hindered base such as sodium hydride (NaH). Weaker bases, such as sodium ethoxide, do not completely deprotonate the ketone starting material which also allows for enolate equilibrium to occur.

Example of enolate equilibration



KINETIC ENOLATES

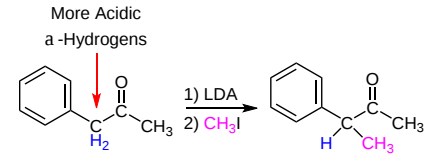
Kinetic enolates are favored under conditions which do not allow for equilibration between the enolates, such as the use of a strong bulky base, like LDA, in a molar equivalent to the ketone starting material. Kinetic enolates are formed when the less substituted α-hydrogen is deprotonated. Being less sterically hindered allows this α-hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate. Using a molar equivalent of LDA completely converts the ketone starting material to an enolate, removing it from the reaction mixture and preventing equilibration between the possible enolates. Low reaction temperatures (-78 °C) prevent enolate equilibration and promote the formation of the kinetic enolate.



When and enolate of an asymmetric ketone is stabilized through additional resonance forms there is no competition between possible enolates despite kinetic or thermodynamics conditions. The resonance stabilized enolate will be preferentially alkylated to the point that

formation of the alkylated products of other possible enolates will be minimal.

EXAMPLE

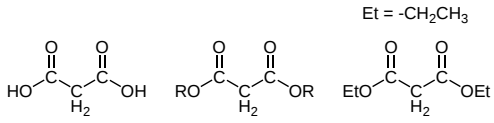


1-Phenyl-2-propanone **1-Methyl-1-phenyl-2-propanone (Racemic)**

MALONIC ESTER SYNTHESIS

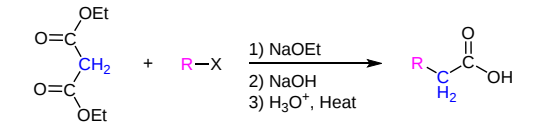
The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons. One important use of this synthesis pathway is that it allows for the creation of α-alkylated carboxylic acids which cannot be created by direct alkylation.

The starting material of this reaction is a malonic ester: a diester derivative of malonic acid. Diethyl propanedioate, also known as diethyl malonate, is the malonic ester most commonly used in pathway. Since it is a 1,3-dicarbonyl compound, diethyl malonate has relatively acidic α-hydrogens (pK_a = 12.6) and can be transformed to its enolate using sodium ethoxide as a base. Other alkoxide bases are not typically used given the possibility of a transesterification reaction.



Malonic Acid **Malonic Ester** **Diethyl Malonate**

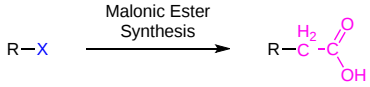
GENERAL REACTION



Diethyl malonate **Alkyl Halide** **a -Alkyl Carboxylic Acid**

PREDICTING THE PRODUCT OF A MALONIC ESTER SYNTHESIS

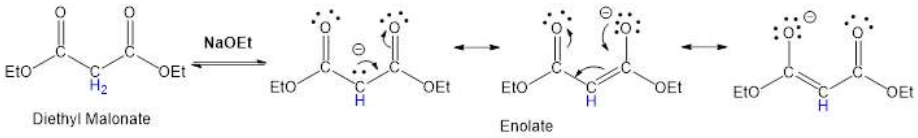
The product of a Malonic Ester Synthesis can be created by simply replacing the halogen on the alkyl halide with a $-CH_2CO_2H$ group.



MALONIC ESTER SYNTHESIS TAKES PLACE IN FOUR STEPS:

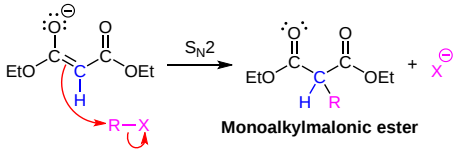
1) Enolate Formation

Reacting diethyl malonate with sodium ethoxide (NaOEt) forms a resonance-stabilized enolate.



2) Alkylation

The enolate is alkylated via an S_N2 reaction to form an monoalkylmalonic ester.

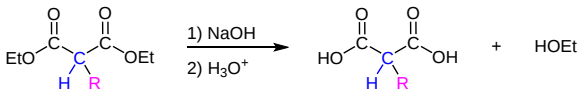


Monoalkylmalonic ester

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3) Ester hydrolysis and protonation

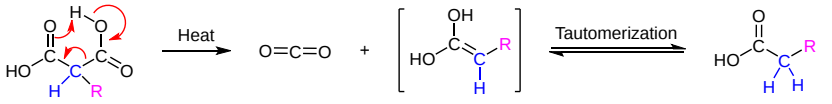
After alkylation, the diester undergoes hydrolysis with sodium hydroxide to form a dicarboxylate. Subsequent protonation with acid forms a monoalkyl malonic acid.



Monoalkyl Malonic Acid

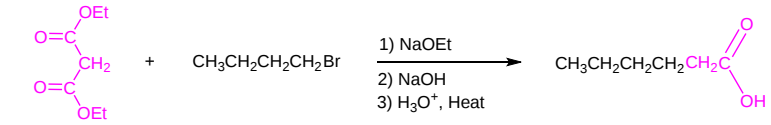
4) Decarboxylation & Tautomerization

Monoalkyl malonic acids decarboxylate when heated, forming an α-alkyl carboxylic acid and carbon dioxide (CO_2). Decarboxylation can only occur in compounds with a second carbonyl group two atoms away from carboxylic acid such as in malonic acids and β-keto acids. The mechanism occurs via a concerted mechanism involving a proton transfer between the carboxyl acid hydrogen and the nearby carbonyl group to form the enol of a carboxylic acid and CO_2. The enol undergoes tautomerization to form the carboxylic acid.



Carbon Dioxide **Carboxylic Acid Enol** **a -Alkylated Carboxylic acid**

EXAMPLE

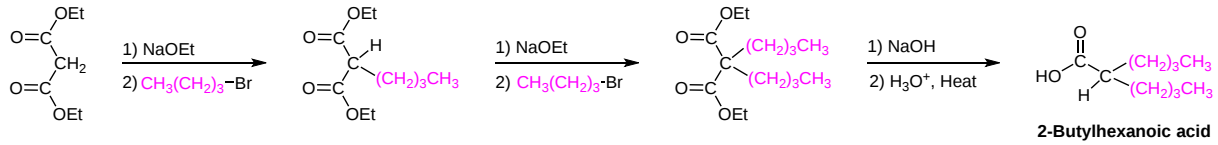


Diethyl malonate **1-Bromobutane** **Hexanoic Acid**

DIALKYLATION

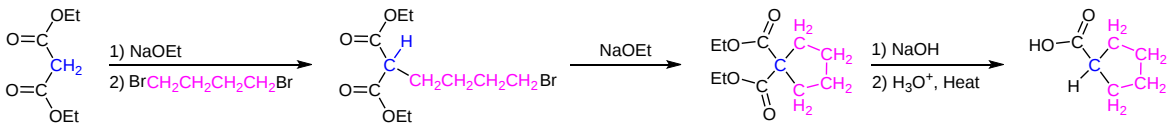
The presence of two α-hydrogens in malonic esters allows for a second alkylation to be performed prior to decarboxylation. This leads to dialkylated carboxylic acids. Due to the lack of stereochemical control inherent in enolate based reactions, if the two added alkyl groups are different, a racemic mixture of products will result.

EXAMPLES



2-Butylhexanoic acid

In a variation of the dialkylation reaction - if one molar equivalent of malonic ester is reacted with one molar equivalent of a dihaloalkane and two molar equivalents of sodium ethoxide, a cyclization reaction occurs. By changing the dihaloalkane, three, four, five, and six-membered rings can be created.

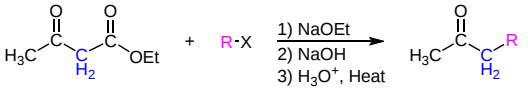


Cyclopentanecarboxylic acid

THE ACETOACETIC ESTER SYNTHESIS

The acetoacetic ester synthesis is a series of reactions which converts alkyl halides into a methyl ketone with three additional carbons. This reaction creates an α-substituted methyl ketone without side-products. The starting reagent for this pathway is ethyl 3-oxobutanoate, also called ethyl acetoacetate, or acetoacetic ester. Like other 1,3-dicarbonyl compounds, ethyl acetoacetate is more acidic than ordinary esters being almost completely converted to an enolate by sodium ethoxide.

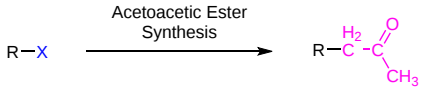
GENERAL REACTION



Acetoacetic ester **Alkyl Halide** **a-Alkyl Methyl Ketone**

PREDICTING THE PRODUCT OF AN ACETOACETIC ESTER SYNTHESIS

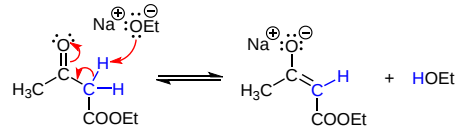
The product of a acetoacetic ester synthesis can be created by replacing halogen on the alkyl halide with a $-CH_2COCH_3$ group.



REACTION STEPS

1) Formation of the enolate

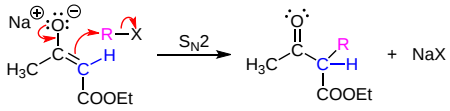
As previously described, the α-hydrogens of acetoacetic ester are rather acidic (pK_a = 10.7) allowing the enolate to be easily formed when sodium ethoxide is used as a base.



Acetoacetic ester **Sodioacetoacetic ester**

2) Alkylation via an S_N2 Reaction

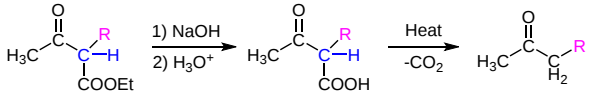
Subsequent reaction with an alkyl halide produces a monoalkylacetoacetic ester.



Monoalkylacetoacetic ester

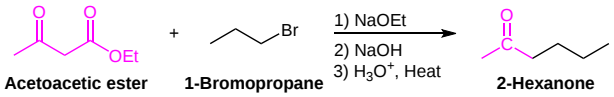
3) Ester hydrolysis and decarboxylation

Hydrolysis with NaOH followed by protonation produces an alkylated beta-ketoacid. β-ketoacids are easily decoboxylated to form an α-alkyl substituted methyl ketone and carbon dioxide (CO_2) using a similar mechanism as the malonic ester synthesis.



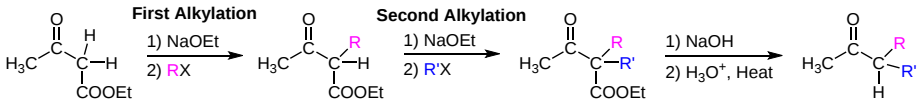
Monoalkyl b-ketoacid **Monoalkyl-methyl ketone**

EXAMPLES



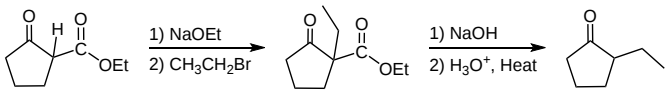
Acetoacetic ester **1-Bromopropane** **2-Hexanone**

Much like the malonic ester synthesis, a second alkyl group can added before the decarboxylation step.



The reaction steps of the acetoacetic ester synthesis can also be applied to other β-keto esters with acidic α-hydrogens. Because the α-hydrogens between the two carbonyls are the most acidic, they are preferentially deprotonated allowing for a single enolate to be formed. Even cyclic beta-keto esters can be alkylated and subsequently decarboxylated to give an α-alkylated cyclic ketone.

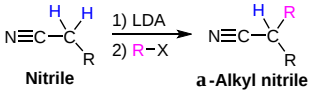
EXAMPLES



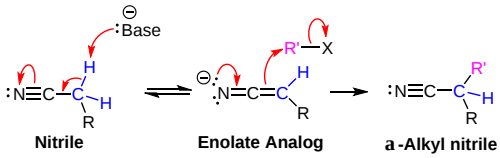
DIRECT ALKYLATION OF NITRILES

The presence of acidic α-hydrogens in nitriles gives them the ability to form an enolate equivalent which can be also be directly alkylated.

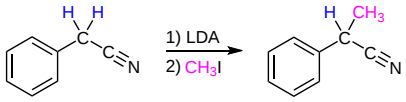
GENERAL REACTION



MECHANISM



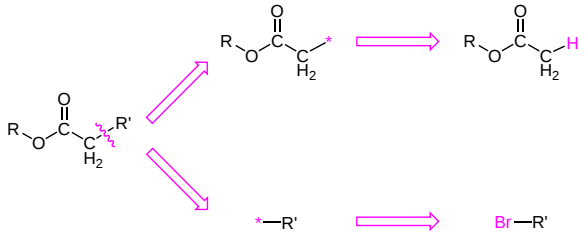
EXAMPLE



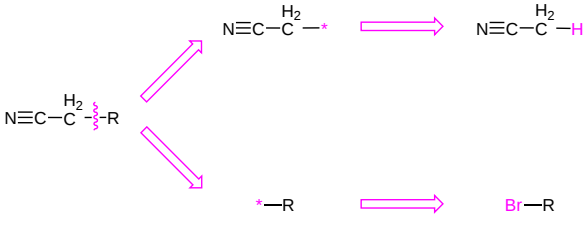
PLANNING A SYNTHESIS USING ENOLATE ALKYLATIONS

When planning a synthesis that could involve enolates, the key is to recognize the functionality which can form an enolate. During retrosynthetic analysis a C-C bond is broken between the α-carbon and the β-carbon away from this functionality. It is also important to be able to identify specific groups of atoms which indicate if a malonic ester or an acetoacetic ester synthesis can be used. Having multiple C-C bonds which can be broken allows for multiple synthetic pathways.

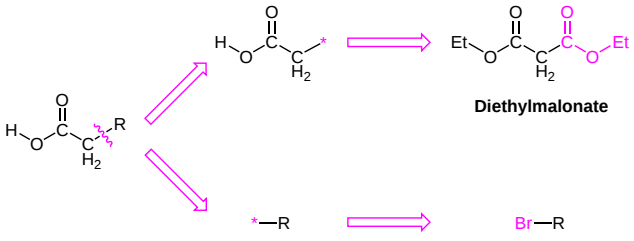
After retrosynthetically breaking the C-C bond, the fragment with the functionality will gain a hydrogen and the other fragment will gain a halogen. Sometimes the fragment with the functionality will become diethyl malonate or acetoacetic ester.



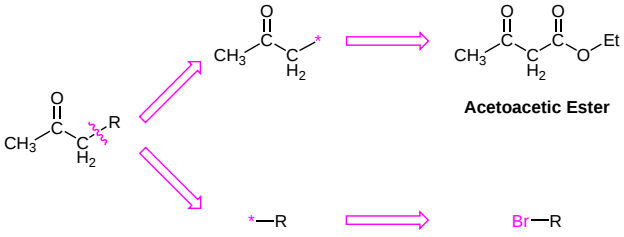
Direct Alkylation of an Ester



Direct Alkylation of a Nitrile



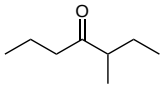
Malonic Ester Synthesis



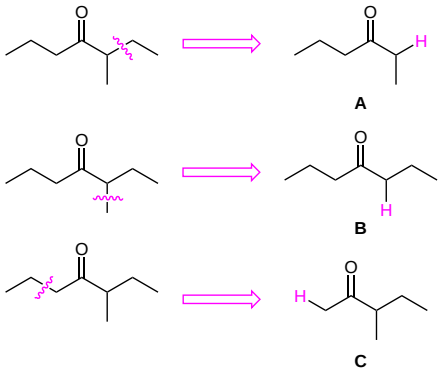
Acetoacetic Ester Synthesis

WORKED OUT EXAMPLE:

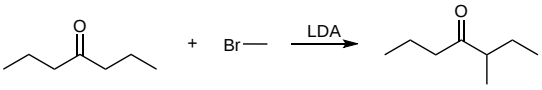
Plan a synthesis of the following molecule using an alkylation of an enolate. Consider multiple pathways and explain which is preferable.



The target molecule does not contain the appropriate fragments to utilize either the malonic ester or acetoacetic acid synthesis so direct alkylation of a ketone will likely be used. When analyzing this molecule, there are three α-β C-C bonds which could be cleaved to create a possible starting material. When looking at the possible starting materials, A and C are asymmetrical ketones and therefore can create multiple products during alkylation. B is a symmetrical ketone and should be the most likely to create the target molecule in high yield.



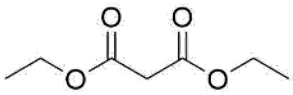
Possible Synthesis



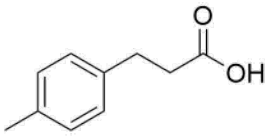
EXERCISES

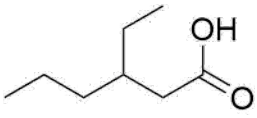
QUESTIONS

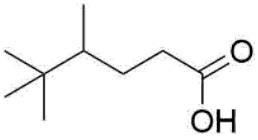
1) Propose a synthesis for each of the following molecules from this malonic ester.



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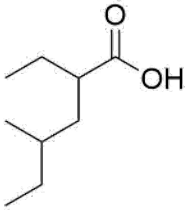
(a) 

(b) 

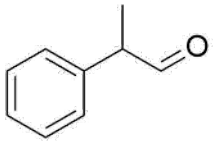
(c) 

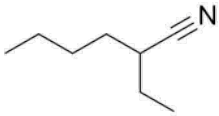
2) Why can't you prepare tri substituted acetic acids from a malonic ester?

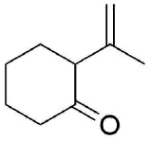
3) Propose a synthesis for the following molecule via a malonic ester.

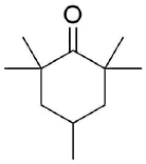


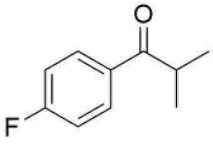
4) How might you prepare the following compounds from an alkylation reaction?

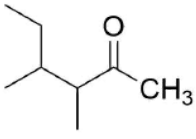
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

SOLUTIONS

1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

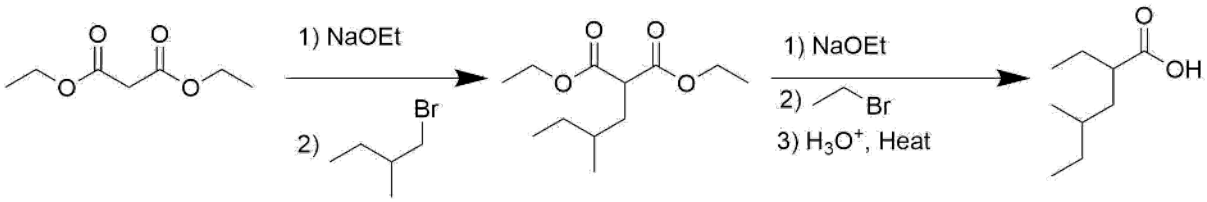
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

2

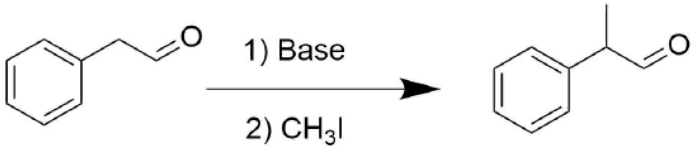
Malonic esters only contain two acid protons.

3

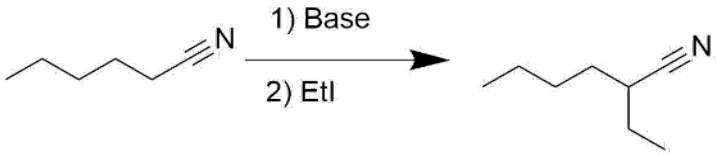


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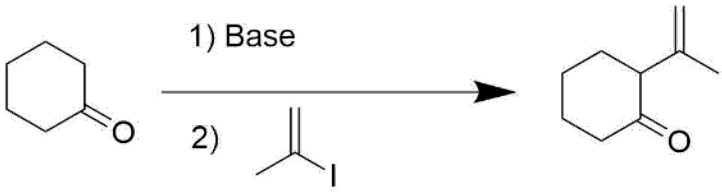
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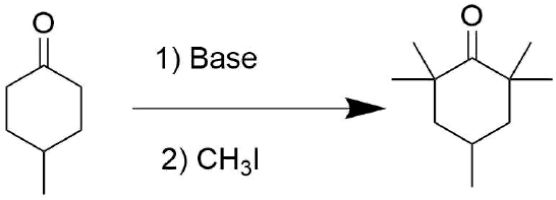
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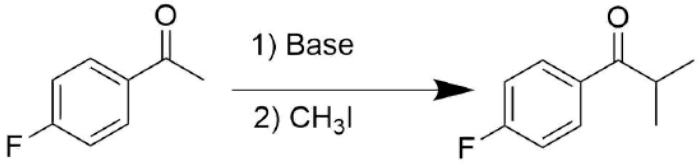
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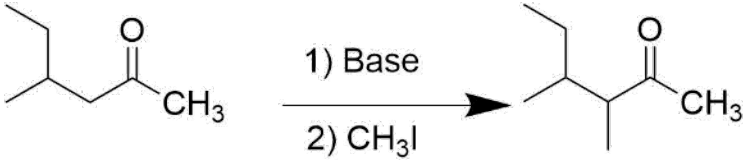
(d)



(e)



(f)



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22.S: CARBONYL ALPHA-SUBSTITUTION REACTIONS (SUMMARY)

CONCEPTS & VOCABULARY

- Four common types of reactions involving carbonyl reactions: 1) nucleophilic addition; 2) nucleophilic acyl substitution; 3) alpha substitution; 4) carbonyl condensations. The first two were previously discussed and the second two involve the properties of the carbon directly adjacent to the carbonyls, **α carbons**.
- Alpha-substitution reactions results in the replacement of an H attached to the alpha carbon with an electrophile.
- The nucleophile in these reactions are new and called enols and enolates.
- In this chapter, the focus is on α substitutions reactions with aldehydes and ketones.

22.1 Keto-Enol Tautomerization

- Greek letters are used to denote the carbon atoms near carbonyls.
- The carbon in the carbonyl is the reference point and the alpha carbon is adjacent to the carbonyl carbon.
- Hydrogen atoms attached the these carbons denoted with Greek letters will have the same designation, so an alpha hydrogen is attached to an alpha carbon.
- Aldehyde hydrogens not given Greek leters.
- α hydrogens display unusual acidity, due to the resonance stabilization of the carbanion conjugate base, called an enolate.
- Tautomers are readily interconverted constitutional isomers, usually distinguished by a different location for an atom or a group, which is different than resonance.
- The tautomerization in this chapter focuses on the carbonyl group with alpha hydrogen, which undergo keto-enol tautomerism.
- Keto refers to the tautomer containing the carbonyl while enol implies a double bond and a hydroxyl group present in the tautomer.
- The keto-enol tautomerization equilibrium is dependent on stabilization factors of both the keto tautomer and the enol tautomer, though the keto form is typically favored for simple carbonyl compounds.
- The 1,3 arrangement of two carbonyl groups can work synergistically to stabilize the enol tautomer, increasing the amount present at equilibrium.
- The positioning of the carbonyl groups in the 1,3 arrangement allows for the formation of a stabilizing intramolecular hydrogen bond between the hydroxyl group of the enol and the carbonyl oxygen as well as the alkene group of the enol tautomer is also conjugated with the carbonyl double bond which provides additional stabilization.
- Aromaticity can also stabilize the enol tautomer over the keto tautomer.
- Under neutral conditions, the tautomerization is slow, but both acid and base catalysts can be utilized to speed the reaction up.
- Biological enol forming reactions use isomerase enzymes to catalyze the shifting of a carbonyl group in sugar molecules, often converting between a ketose and an aldose in a process called carbonyl isomerization.

22.2 Reactivity of Enols: The Mechanism of Alpha-Substitution Reactions

- The oxygen of the enol donates electron density to the double bond making it more electron rich and thus more reactive than a typical alkene.
- The mechanism starts with an acid-catalyzed tautomerization to form an enol.
- The double bond is then able to act as a nucleophile and attack an electrophile.
- The final product is an alpha-substituted carbonyl after the deprotonation of the carbonyl to also regenerate the acid-catalyst.
- The enol formed has planar geometry, which means the electrophile can attach on the top or bottom of the alpha-carbon.
- A racemic mixture can result if a sterocenter is created at the site of substitution.

22.3 Alpha Halogenation of Aldehydes and Ketones

- Aldehydes and ketons can undergo a substitution of an alpha hydrogen to a halogen.
- An acid-catalyzed tautomerization starts the mechanism followed by the enol attacking molecular halogens.
- The nucleophile in this reaction is the enol and the electrophile is the halogen.
- Mechanistic studies showed that the reaction was a first-order in the ketone.
- The halogen is part of a fast step after the rate-determing step.
- The formation of an enol intermediate was provided using a reaction called deuterium exchange.
- Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with the isotopic form of water, D_2O.
- The mechanism for deuterium exchange is virtually the same as that of keto-enol tautomerism under acidic conditions, the difference being a deuterium is placed in the *α*-position.

- Both alpha halogenation and deuterium exhange reactions were found to have a common intermediate involved in the rate determining step of their mechanism, an enol.

22.4 Alpha Bromination of Carboxylic Acids

- The α-bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, but the reaction will generally not occur with more stable carboxylic acid derivatives.
- Carboxylic acids do not enolize to a sufficient extent since the carboxylic acid proton is preferably removed before an α-hydrogen.
- Carboxylic acids, can be brominated in the α position with a mixture of Br_2 and phosphorus tribromide (PBr_3) in what is called the Hell-Volhard-Zelinskii reaction.
- α-Bromo carboxylic acids are extremely useful synthetic intermediates because the halogen is highly reactive towards S_N2 reaction.
- Reaction of a α-bromo carboxylic acids with an excess of ammonia provides α-amination, which is a possible route to amino acids.

22.5 Acidity of Alpha Hydrogen Atoms: Enolate Ion Formation

- α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the adjacent carbonyl.
- The enolate has two resonance structures to contribute to the resonance hybrid.
- While α-hydrogens are weakly acidic, typical strong bases such as hydroxide or alkoxide are only capable of forming the enolate ion in very low concentrations.
- To achieve complete deprotonation of aldehyde or ketone reactants to their enolate conjugate bases, a very strong base such as LDA (lithium diisopropylamide) must be used.
- Hydrogen atoms with two or more adjacent carbonyl groups are more acidic than typical α hydrogens, such as β-diketones, β-keto-esters, and β-diesters, which create enolates that are stabilized through additional resonance forms which share the negative charge with multiple carbonyl carbons.
- The acidity of these compounds is increased to the point where typical strong bases such as hydroxide and alkoxide can be used to form the enolate.

22.6 Reactivity of Enolate Ions

- Enolates are better nucleophlies than enols.
- α-hydrogen containing compounds can be completely converted to an enolate by reaction with a strong base whereas enols can only be created in small amounts through manipulating their equilibrium.
- Either the C of the O reactive site in an enolate may act as a nucleophile depending on the reaction conditions, but reactions involving the nucleophilic α-carbon are more common, partially due to the thermodynamic stability of the C=O bonds in the final products.
- An enolate reacts rapidly with a halogen to produce α-halogenated carbonyl products.
- The α-hydrogens of halogenated carbonyl products are usually more acidic than the corresponding non-halogenated compounds, which promotes polyhalogenated products.
- The Haloform reaction represents a method for the conversion of methyl ketones to carboxylic acids.
- This reaction is considered a base promoted and not base catalyzed because an entire equivalent of base is required for each α-halogenation.
- Deprotonation of an α-hydrogen with hydroxide produces the nucleophilic enolate ion which subsequently reacts with the halogen.
- The increasing acidity of α-halogenated ketone causes this reaction to occur two more times.
- Once formed, the CX_3 group attached to the carbonyl can act as a leaving group, eventually produces a haloform ($CHCl_3$, $CHBr_3$, CHI_3) and a carboxylate anion.

22.7 Alkylation of Enolate Ions

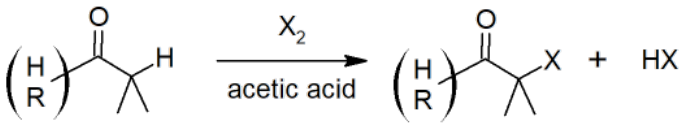
- Enolates can be alkylated in the alpha position through an S_N2 reaction with alkyl halides.
- An α hydrogen is replaced with an alkyl group and a new C-C bond is formed.
- Very strong bases like LDA are often used to fully deprotonate the carbonyl and completely form the enolate.
- Direct alkylations, like all enolate-based reactions, will form a racemic mixture if the alkylated alpha carbon is chiral.
- When an unsymmetrical ketone with two sets of nonequivalent alpha hydrogens is treated with a base, two possible enolates can form.
- The main determinant for which enolate is formed is whether the reaction is under kinetic control (rate) or thermodynamic (equilibrium) control.
- The thermodynamic enolate is formed when the more substituted alpha hydrogen is removed, yielding the more alkyl substituted, therefore the most stable, enolate.
- Formation of the thermodynamic enolate is sterically hindered and is kinetically slow, especially with a bulky base like LDA.

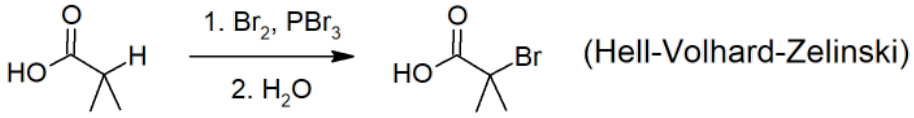
- Kinetic enolates are formed when the less substituted alpha hydrogen is deprotonated, being less sterically hindered allows this alpha hydrogen to be deprotonated faster even though it forms a less thermodynamically stable enolate.
- The malonic ester synthesis is a series of reactions which converts an alkyl halide to a carboxylic acid with two additional carbons.
- The importance of this synthesis pathways is that it allows for the creation of alpha alkylated carboxylic acids which cannot be created by direct alkylation.
- The acetoacetic ester synthesis is a series of reaction which converts alkyl halides into a methyl ketone with three additional carbons.
- This reaction creates an alpha substituted methyl ketone without side-products.
- In retrosynthetic analysis, a C-C bond is broken between the alpha carbon and the beta carbon away from this functionality.

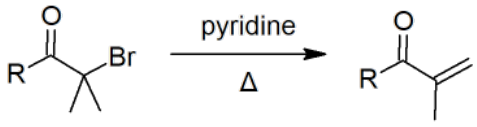
SKILLS TO MASTER

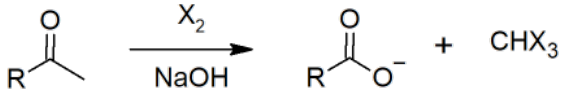
- Skill 22.1 Determine alpha carbons and alpha hydrogens.
- Skill 22.2 Draw the enols formed from carbonyl derivatives.
- Skill 22.3 Provide the mechanism for the keto-enol tautomerization under neutral, acidic and basic conditions.
- Skill 22.4 Provide the mechanism for the enol-keto tautomerization under neutral, acidic and basic conditions.
- Skill 22.5 Draw the products of halogenation reactions.
- Skill 22.6 Provide the mechanism for halogenation reactions.
- Skill 22.7 Write an equation to illustrate the Hell-Volhard-Zelinskii reaction.
- Skill 22.8 Identify the product formed from the reaction of a given carboxylic acid with bromine and phosphorus tribromide.
- Skill 22.9 Explain why the alpha hydrogen of carbonyl compounds are more acidic than a typical hydrogen.
- Skill 22.10 Explain why dicarbonyl protons are more acidic than compounds that contain a single carbonyl.
- Skill 22.11 Provide a mechanism for the haloform reaction.
- Skill 22.12 Provide a mechanism for an alkylation reaction with an enolate.
- Skill 22.13 Provide a mechanism for malonic ester synthesis.
- Skill 22.14 Propose synthesis for alkylated carboxylic acids.
- Skill 22.15 Provide a mechanism for acetoacetic acid synthesis.
- Skill 22.16 Propose a synthesis for alkylated methyl ketones.

SUMMARY OF REACTIONS

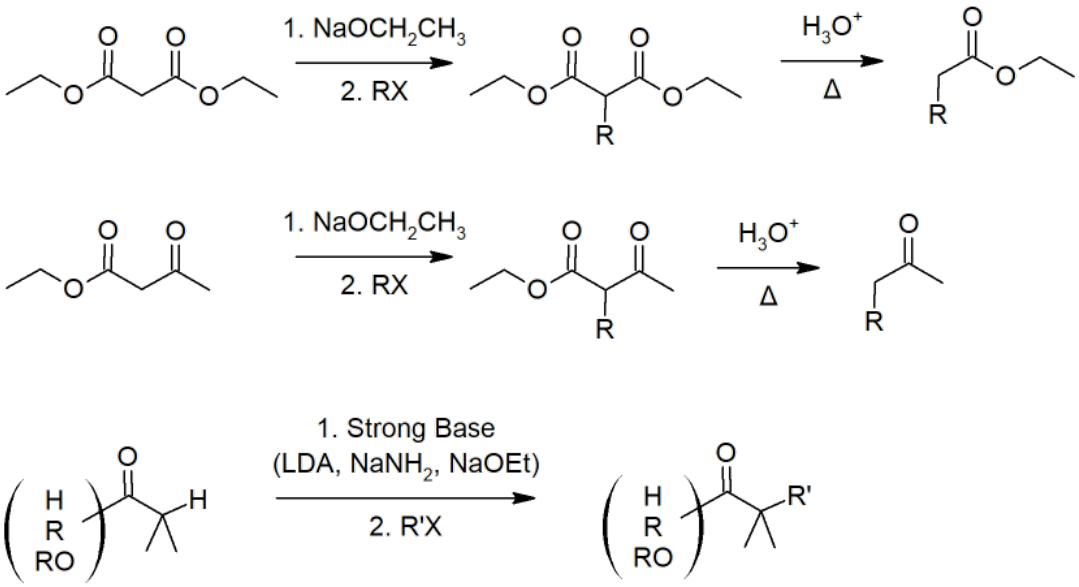








Alkylation



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CHAPTER OVERVIEW

23: CARBONYL CONDENSATION REACTIONS

LEARNING OBJECTIVES

When you have completed Chapter 23, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- solve road-map problems that require a knowledge of carbonyl condensation reactions.
- define, and use in context, any of the key terms introduced.

In this chapter, we consider the fourth and final general type of reaction that carbonyl compounds undergo—the carbonyl condensation reaction. Carbonyl condensation reactions take place between two carbonyl-containing reactants, one of which must possess an alpha-hydrogen atom. The first step of the reaction involves the removal of an alpha-hydrogen atom by a base. In the second step, the enolate anion that results from this removal attacks the carbonyl-carbon of the second reacting molecule. In the final step of the reaction, a proton is transferred to the tetrahedral intermediate formed in the second step, although in some cases the product that results may subsequently be dehydrated.

23.0: Chapter Objectives
23.1: Carbonyl Condensations - The Aldol Reaction
23.2: Carbonyl Condensations versus Alpha Substitutions
23.3: Dehydration of Aldol Products - Synthesis of Enones
23.4: Using Aldol Reactions in Synthesis
23.5: Mixed Aldol Reactions
23.6: Intramolecular Aldol Reactions
23.7: The Claisen Condensation Reaction
23.8: Mixed Claisen Condensations
23.9: Intramolecular Claisen Condensations - The Dieckmann Cyclization
23.10: Conjugate Carbonyl Additions - The Michael Reaction
23.11: Carbonyl Condensations with Enamines - The Stork Reaction
23.12: The Robinson Annulation Reaction
23.13: Some Biological Carbonyl Condensation Reactions
23.S: Carbonyl Condensation Reactions (Summary)

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23.0: CHAPTER OBJECTIVES

The importance of carbonyl condensation reactions to synthetic organic chemistry arises from the large number of combinations of carbonyl compounds that can be used in such reactions. Aldehydes or ketones can be used in a simple aldol condensation to produce β-hydroxy aldehydes, β-hydroxy ketones, or their dehydration products. Mixtures of aldehydes, ketones, or both, can be used in a mixed aldol condensation. Internal aldol condensations can occur in compounds containing two suitable carbonyl groups. Aldol-like condensations can be brought about between aldehydes and a variety of compounds containing acidic alpha-hydrogen atoms, including diethyl malonate, acetic anhydride, nitriles and nitro compounds. Esters can be used in Claisen condensations and 1,6- and 1,7-diesters can give rise to internal condensations, called Dieckmann cyclizations. Related reactions include the Michael reaction, in which an α,β-unsaturated carbonyl compound is reacted with an enolate anion; and the Stork enamine reaction, where an enamine adds to an α,β-unsaturated ketone.

The chapter concludes with a look at how condensation reactions can be used in the synthesis of complex ring-containing organic compounds, and at the role played by carbonyl condensation reactions in biological systems.

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23.1: CARBONYL CONDENSATIONS - THE ALDOL REACTION

OBJECTIVES

After completing this section, you should be able to

1. write a general mechanism for carbonyl condensation reactions.
2. write an equation to illustrate the aldol condensation reaction.
3. identify the product formed when an aldehyde or ketone having an alpha-hydrogen atom is treated with base in a protic medium.
4. identify the aldehyde or ketone, and other reagents required to produce a given *β*-hydroxy carbonyl compound by an aldol reaction.
5. determine whether a given aldehyde or ketone will undergo an aldol reaction.
6. write the detailed mechanism of the aldol reaction.

KEY TERMS

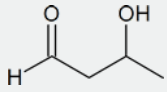
- aldol
- aldol reaction
- carbonyl condensation reaction (see Chapter 18 Affix)

STUDY NOTES

It is important that you understand the general mechanism of carbonyl condensation described in this section: once you grasp this mechanism, you will see that all the reactions that follow are very similar.

The aldol reaction is sometimes referred to as the aldol condensation. However, a condensation reaction is often regarded as a reaction in which two molecules join together with the elimination of a molecule of water (or some other compound of low molar mass). Thus, the aldol reaction described here is not a true condensation; the true aldol condensation is described later, in Section 23.3. It is perhaps unfortunate that the reactions discussed in this unit are all described as condensation reactions whether or not water is eliminated.

The term “aldol” (from "aldehyde alcohol") is used both to describe the specific compound 3-hydroxybutanal:

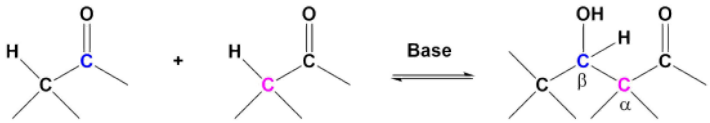


and to describe *β*-hydroxy aldehydes in general.

A useful carbon-carbon bond-forming reaction known as the Aldol Reaction is another example of electrophilic substitution at the alpha carbon in enolate anions. This reaction requires the formation of an enolate so at least one of the reactants must have an α-hydrogen. Due to the carbanion like nature of enolates, they can add to carbonyls through nucleophilic addition much like Grignard reagents.

The aldol reaction takes advantage of a carbonyl compound’s ability to undergo both alpha substitution and nucleophilic addition reactions. The fundamental transformation in the aldol reaction is a dimerization of an aldehyde (or ketone) to form a beta-hydroxy aldehyde (or ketone). A C-C bond is formed between the alpha carbon of one reactant molecule and the carbonyl carbon of a second reactant molecule. In the reaction’s product, the formed C-C bond links a carbon in the alpha position and a carbon in the beta position away from the carbonyl.

GENERAL ALDOL REACTION



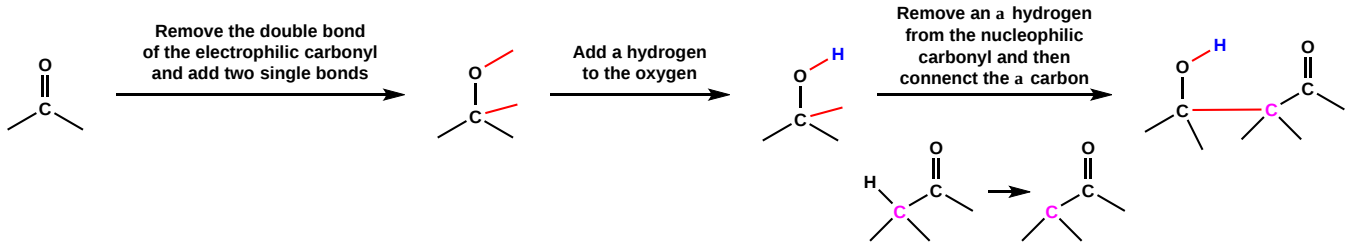
β–Hydroxycarbonyl

A typical example involves two molecules of acetaldehyde (ethanal) reacting to form beta-hydroxybuteraldehyde (3-hydroxybutanal). This product and other beta-hydroxy aldehydes are generically called “aldols” because they contain both an aldehyde and an alcohol functional group.

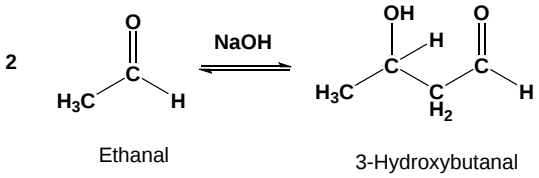
An aldol reaction, like many carbonyl addition reactions, is an equilibrium reaction and is reversible. The presence of an equilibrium means weaker bases, such a hydroxides or alkoxides, can be used to perform this reaction. The reaction equilibrium favors the products when

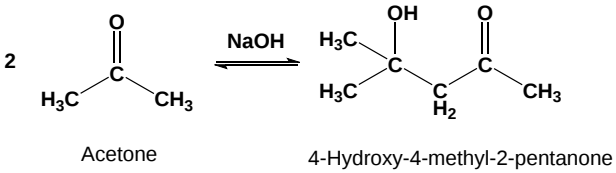
aldehydes with little steric hindrance around the carbonyl are used. However, the reaction equilibrium for ketones and sterically hindered aldehydes favors the reactants. To provide good reaction yields when using these reactants, the equilibrium must be pushed towards the products. Typically, this is done by utilizing a method to remove the product as it is formed during the reaction.

PREDICTING THE PRODUCT OF AN ALDOL REACTION



EXAMPLES

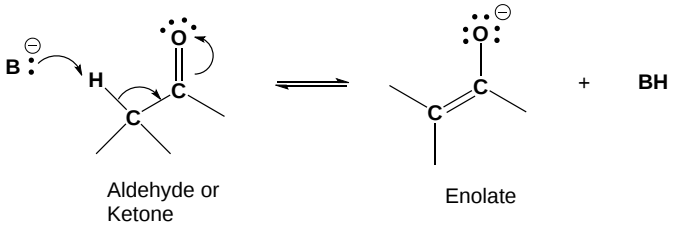




MECHANISM OF ALDOL REACTION

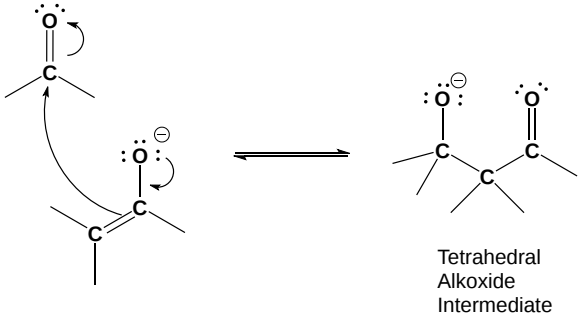
1) ENOLATE FORMATION

The reaction starts with a base removing an alpha hydrogen to form a nucleophilic enolate.



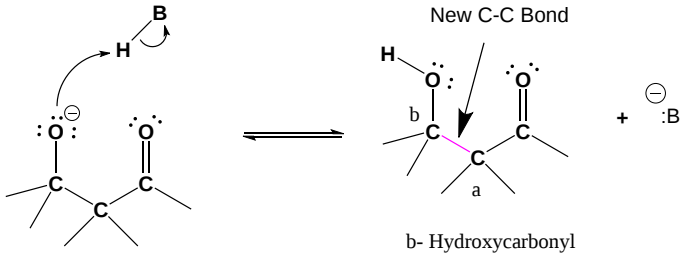
2) NUCLEOPHILIC ATTACK BY THE ENOLATE

Through nucleophilic addition, the enolate adds to the electrophilic carbonyl group on a second molecule. As with other nucleophilic addition reaction a tetrahedral alkoxide intermediate is formed.



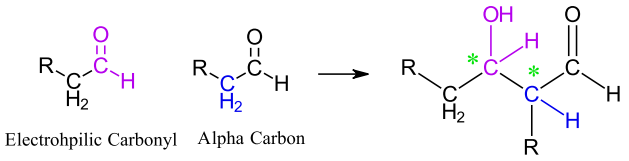
3) PROTONATION

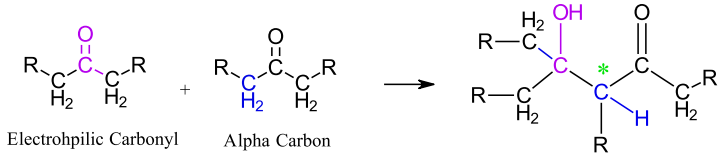
Protonation of the alkoxide forms the neutral aldol product and regenerates the base.



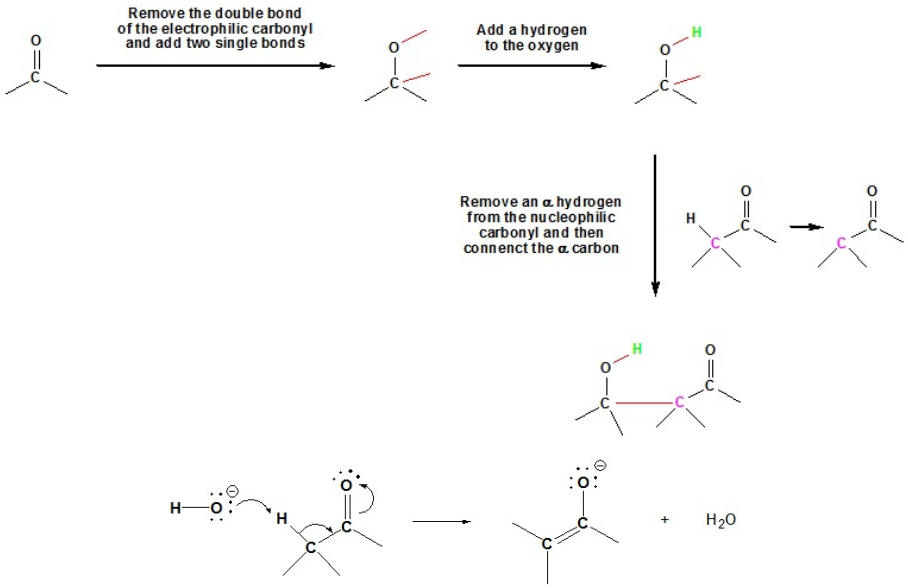
STEREOCHEMICAL RAMIFICATIONS OF THE ALDOL REACTION

As previously discussed, both nucleophilic addition and alpha-substitution reactions have the possibility of creating chiral carbons. The alpha carbon and the electrophilic carbon of the reactants should be identified in the aldol product to assess their possible chirality. Most aldehydes produce chirality in both of these carbons. Most symmetrical ketones create a chiral carbon from the alpha-carbon of the reactant.





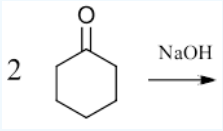
GOING FROM REACTANTS TO PRODUCTS SIMPLY



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WORKED EXAMPLE

What would be the expect product of the following aldol reaction?

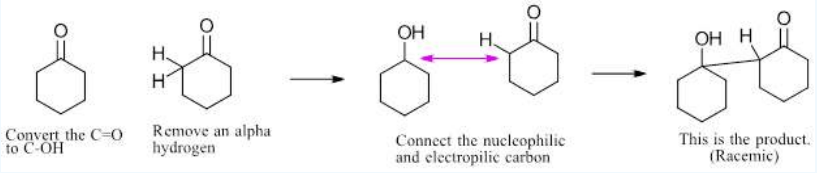


Answer

Analysis:

When considering the product of an aldol reaction it is vital to consider each reactant molecule separately. Also,

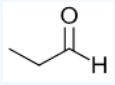
Identify electrophilic carbonyl carbon and any alpha hydrogens present.



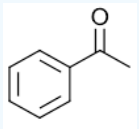
EXERCISES 23.1.1

1) Predict the product of an aldol reaction with the following molecules:

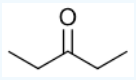
a)



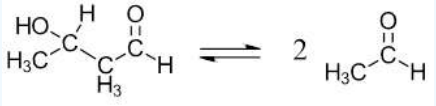
b)



c)



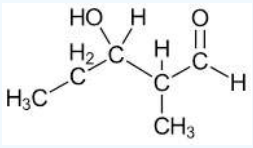
2) Because the aldol reaction is reversible it is possible for a beta-hydroxy carbonyl compound to undergo a retro-aldol reaction. Please draw the mechanism or the based catalyzed retro-aldol reaction shown below.



Answers

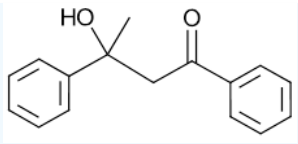
1)

a)

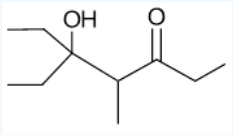


b)

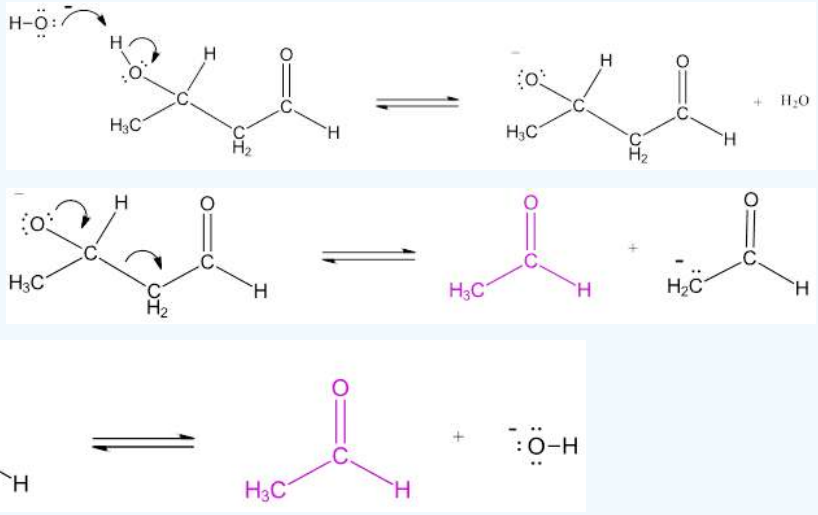
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c)



2)



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23.2: CARBONYL CONDENSATIONS VERSUS ALPHA SUBSTITUTIONS

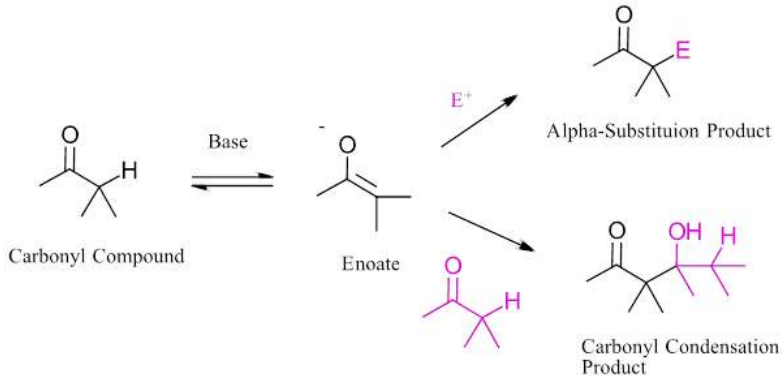
OBJECTIVES

After completing this section, you should be able to describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction, and determine which of these two types of reaction is most likely to occur, given the appropriate experimental data.

STUDY NOTES

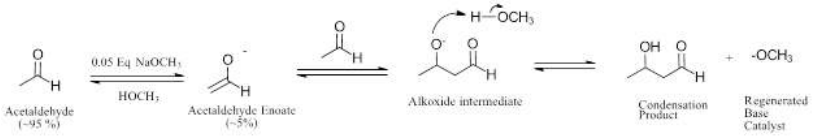
So far we have discussed three of the four general reactions of carbonyl compounds: nucleophilic additions of aldehydes and ketones (Chapter 19), nucleophilic acyl substitution reactions of carboxylic acid derivatives (Chapter 21) and alpha-substitution reactions (Chapter 22). The fourth general reaction, carbonyl condensation, is similar to the alpha-substitution reaction, so you need to appreciate how it differs from the other three and the conditions under which it occurs.

Carbonyl condensation and alpha-substitution reactions both involve the formation of a reactive enolate ion intermediate. How is it possible to generate an enolate ion for a alpha substitution reaction without a carbonyl condensation also occurring? What reaction conditions are required to cause one reaction and not the other?



In a carbonyl condensation a catalytic amount of base is used to generate only a small amount of the the enolate ion. Most of the carbonyl compound is unreacted and can react with the enolate. During the reaction the base catalyst is regenerated which can then produce more enolate ion and continue the cycle.

If acetaldehyde was reacted with 0.05 equivalents of sodium methoxide in a methanol solvent only a small amount (~5%) of the enolate would form. The majority of the acetaldehyde would be unchanged and capable of undergoing a condensation reaction with the enolate present. The alkoxide intermediate produced is protonated by methanol to the neutral condensation product and regenerates the methoxide base catalyst. Methoxide can then deprotonate a new acetaldehyde molecule to create another enolate allowing the reaction cycle to continue.

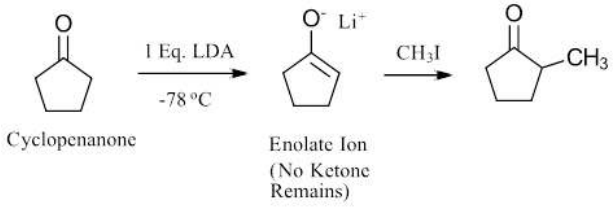


These steps are all reversible and it should be noted that reactants and products that are close in energy level can potentially undergo the reverse reaction if conditions change enough. While from a synthetic point of view in the laboratory this may mean increasing yields by driving the reaction to completion (e.g. adding heat, removing product), in biological systems it can have more drastic consequences. Indeed, depending on metabolic conditions, retro-aldol reactions (the reverse of aldol condensations, in which carbon-carbon bonds are broken) can occur.

In contrast, the alpha-substitution reaction is often more directional by design. To reduce unwanted competition from carbonyl condensation, the enolate ion intermediate is generated all at once with a full equivalent of strong base at low temperature. This effectively removes the carbonyl from the reactive mixture making it difficult for a carbonyl condensation to occur. The reactive enolate intermediate

then is quickly quenched by rapid addition of the electrophile to complete the substitution reaction. As discussed in Section 22.7, for direct alkylation, strong bases like $NaNH_2$ and LDA were used to generate the enolate intermediate followed by addition of an alkylhalide.

An example is shown with the alpha-alkylation reaction of cyclopentanone. During this reaction, one equivalent of lithium diisopropyamide (LDA) is added to the reactant at -78 ^oC which completely converts cyclopenanone to the corresponding enolate ion. This leaves none of the ketone carbonyl remaining to undergo a condensation reaction. Methyliodide is quickly added to react with enolate ion forming the alpha-alkylated product.



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23.3: DEHYDRATION OF ALDOL PRODUCTS - SYNTHESIS OF ENONES

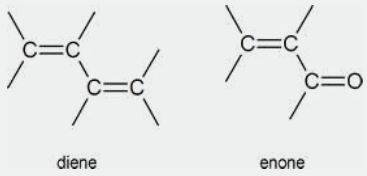
OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the formation of a conjugated enone from a *β*-hydroxy aldehyde or ketone.
2. write a detailed mechanism for the basic or acidic elimination of water from a *β*-hydroxy aldehyde or ketone.
3. explain why *β*-hydroxy aldehydes and ketones undergo elimination reactions much more readily than most other alcohols.
4. identify the enone products from the aldol condensation of a given aldehyde or ketone.

STUDY NOTES

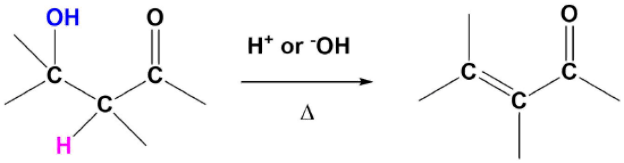
Conjugated enones, like conjugated dienes, have more inherent stability compared with their non-conjugated counterparts. You may wish to review Section 14.1 on dienes, which gives a molecular orbital description showing π electron distribution over four atomic centres.



Note that both of the elimination mechanisms described here (acidic and basic) involve either the enol form or the enolate anion of the *β*-hydroxy carbonyl compound.

ALDOL CONDENSATION

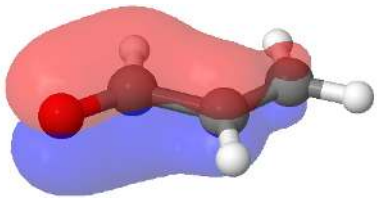
Reactions in which a larger molecule is formed from smaller components, with the elimination of a very small by-product such as water are termed Condensations. Hence the following examples are properly referred to as aldol condensations.

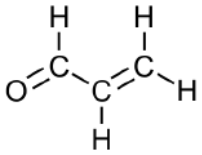


DEHYDRATION OF ALDOL PRODUCTS TO SYNTHESIZE A, B UNSATURATED CARBONYL (ENONES)

The products of aldol reactions, with heating, often undergo a subsequent elimination of water, made up from an alpha-hydrogen and the beta-hydroxyl group. The product of this acid or base-catalyzed E1cB elimination reaction (Section 11-10) reaction is an α,β-unsaturated aldehyde or ketone (Enones). Although there may be multiple position where the alkene may form, it will always prefer to be in conjugation with the carbonyl.

Conjugated enone products are more stable than non-conjugated due to extended P orbital overlap. Conjugation of the p electrons of the alkene and carbonyl bonds provide a molecular-orbital description showing the interaction of p electrons of all four atoms. The additional stability provided by the conjugated carbonyl system of the product makes many aldol reactions thermodynamically factorable.



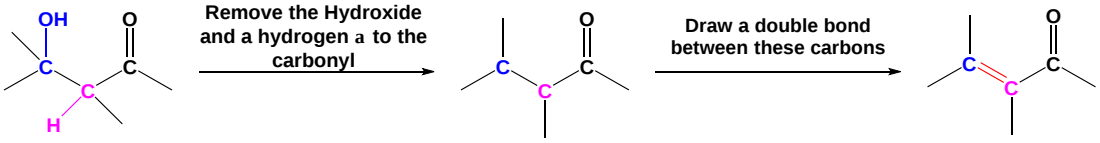


Propenal

A representation of pi bonding molecular orbitals of the conjugated enone, propenal, are delocalized through p-orbital overlap

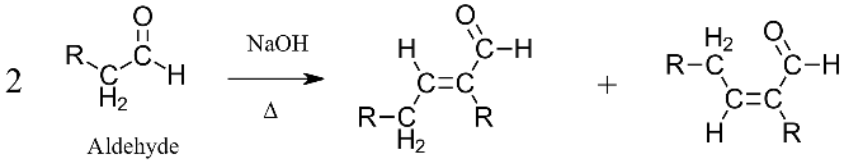
The elimination of water from the reaction mixture can be used to drive the equilibrium towards the products by Le Chatelier's principal. This coupled with the thermodynamic stability of the conjugated product allow for good reaction yields when the formation of the initial aldol intermediate is unfavorable (ketones & sterically hindered aldehydes).

PREDICTING THE PRODUCT OF AN ENONE FORMATION



STEREOCHEMICAL CONSIDERATIONS

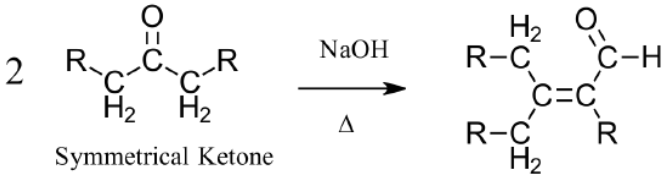
When aldehyde starting materials are used for an aldol condensation, there is the possibility of forming both E and Z alkene isomers. When symmetrical ketones are used, the alkene formed lacks the ability to form isomers so a single product is made.



Aldehyde

E Isomer

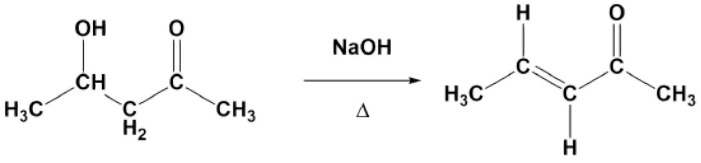
Z Isomer



Symmetrical Ketone

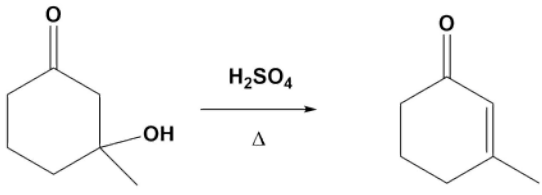
No Isomers Possible

Examples



4-Hydroxy-2-Pentanone

3-Penten-2-one



3-Hydroxy-3-methylcyclohexanone

3-Methyl-2-Cyclohexenone

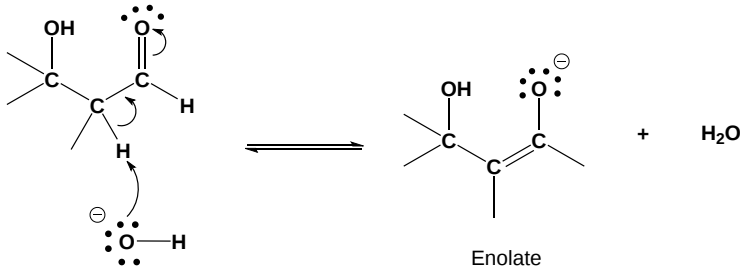
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MECHANISM

BASE CATALYZED MECHANISM

1) FORM AN ENOLATE

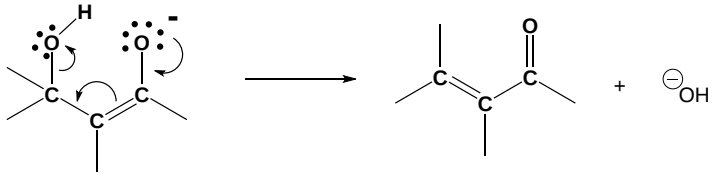
The mechanism starts with the base removing an alpha-hydrogen to form an enolate ion.



Enolate

2) FORM THE ENONE

The alkoxide reforming the carbonyl C=O bond promotes the elimination of alcohol OH as a leaving group which reforms the base catalyst. Although the base catalyzed elimination of alcohols is rare, it happens in this case in part due to the stability of the conjugated enone product.

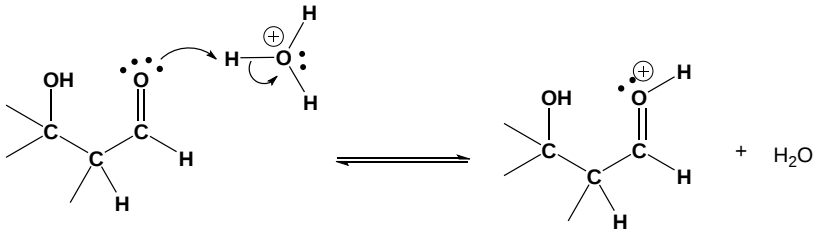


Enone

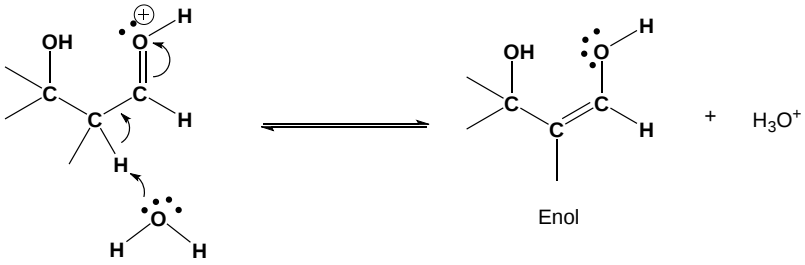
ACIDIC CONDITIONS MECHANISM

1) PROTONATION

The mechanism starts with the two step tautomerization process to form an enol.



2) FORM AN ENOL

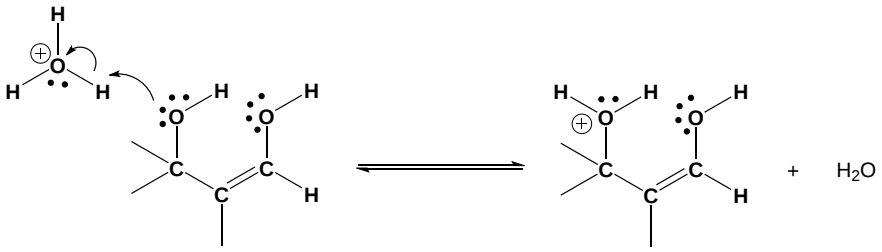


Enol

3) PROTONATION

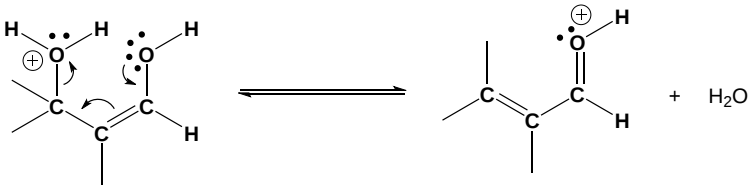
Protonation of the alcohol OH increases its ability to act as a leaving group.

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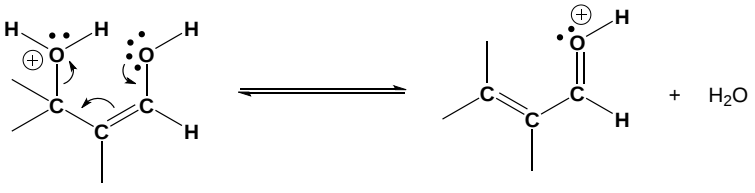


4) ELIMINATION

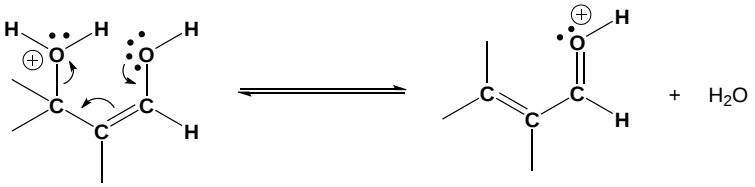
Lone pair electrons from the enol reform the carbonyl C=O bond and promoted the elimination of water as a leaving group.



Protonated Enone



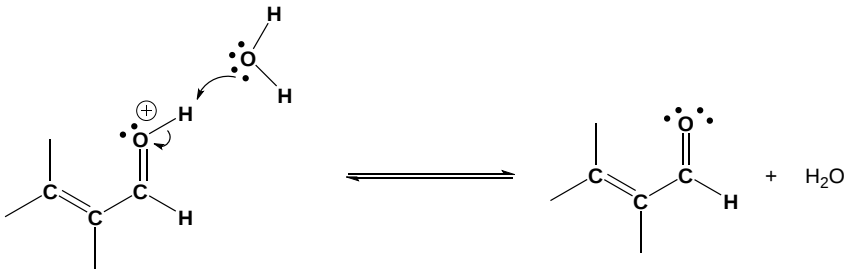
Protonated Enone



Protonated Enone

5) DEPROTONATION

Deprotonation by water in the final step create the neutral enone product and regenerates the acid catalyst.



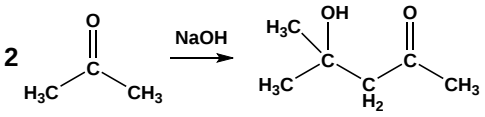
Enone

ALDOL CONDENSATION

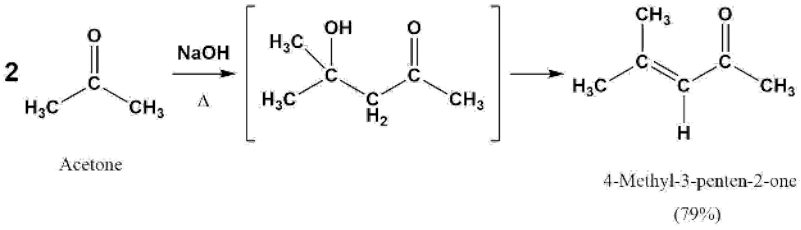
Whether an aldol reaction or an aldol condensation product is formed during a reaction largely depends on the reaction conditions. Typically, a reaction with a base at room temperature provides the aldol reaction product. However, if the reaction mixture is heated the aldol product is quickly converted into the aldol condensation product. If the condensation product is desired the aldol intermediate is usually not isolated.

Examples

Aldol Reaction

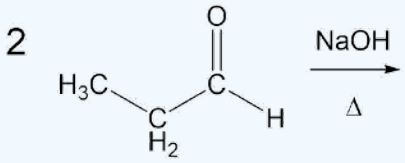


Aldol Condensation



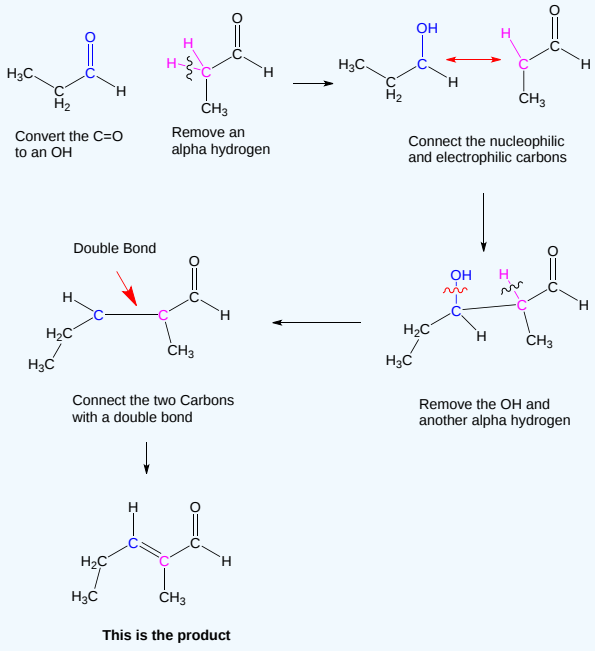
WORKED EXAMPLE

Draw the product of an aldol condensation with the following molecule:



Answer

The overall reaction is a combination of two major steps, an aldol reaction followed by a dehydration to form the enone. In this situation it is best to consider the aldol product first (as discussed in Section 23.3, then convert it to the enone. Note! The double bond always forms in conjugation with the carbonyl.



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23.4: USING ALDOL REACTIONS IN SYNTHESIS

OBJECTIVES

After completing this section, you should be able to identify the aldehyde or ketone and other necessary reagents that should be used to prepare a given enone by an aldol condensation.

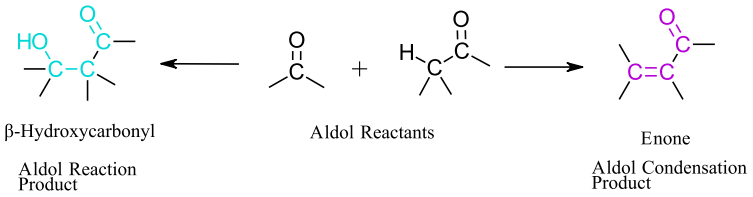
STUDY NOTES

This section stresses the importance of being able to think logically.

The experience that you have already gained through designing multi-step syntheses and solving road-map problems should help you to recognize when an aldol reaction may have been one of the steps in the synthesis of a given compound.

It is important that you recognize that the aldol condensation is an important part of a synthetic chemist's repertoire, both because it involves the formation of a new carbon-carbon bond, and also because it yields a product containing two functional groups.

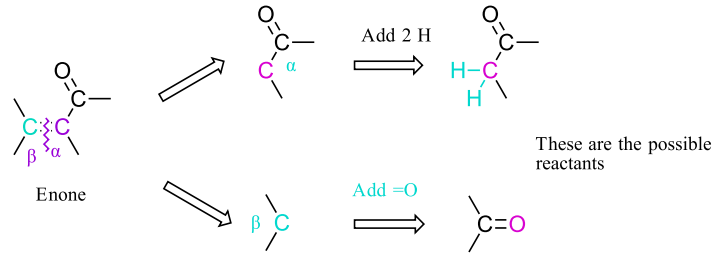
Aldol reactions are excellent methods for the synthesis of many enones or beta-hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This can be accomplished by identifying these combinations of atoms and bonds and then, working backwards, theoretically breaking the target molecule apart into possible reactants.



Fragments which are easily formed by an aldol reaction

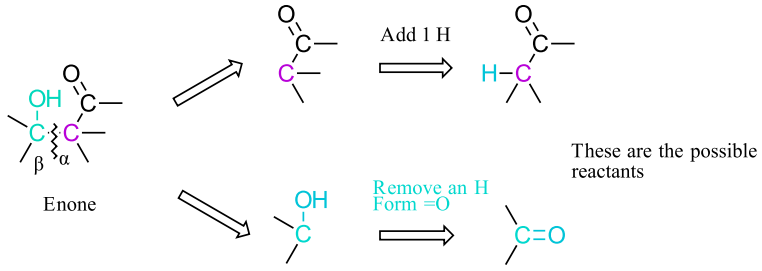
DETERMINING THE REACTANTS FOR AN ALDOL CONDENSATION

During an aldol condensation a C-C sigma and a C-C pi bond are formed. This makes the key bond cleavage in the target molecule the C=C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (on the fragment with the carbonyl) gains two hydrogens. The carbon that was in the beta gains a =O to form a carbonyl.



DETERMINING THE REACTANTS FOR AN ALDOL REACTION

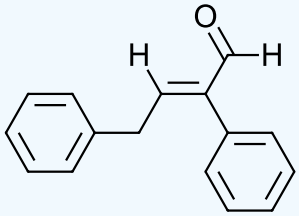
During an aldol condensation a C-C sigma bond is formed. This makes the key bond cleavage in the target molecule the C-C bond between the carbons alpha and beta away from the carbonyl. After the cleavage, the carbon that was in the alpha position (the fragment with the carbonyl) gains one hydrogen. The fragment loses a hydrogen from the OH and then forms a C=O carbonyl bond.



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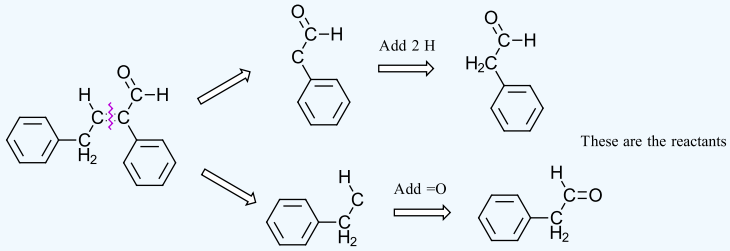
Worked Example

Show how the following molecule could be made using an aldol condensation?

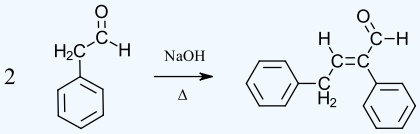


Answer

Analysis: The C=C bond in the target molecule is cleaved to form two fragments. The fragment with the carbonyl gains two alpha hydrogens. The other fragment gains a =O to form a carbonyl. Both fragments end up producing the same reactant which is typical for an aldol condensation.

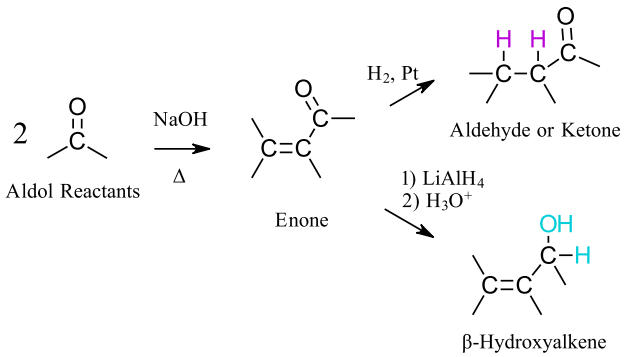


Solution



ADDITIONAL SYNTHETIC CONSIDERATIONS

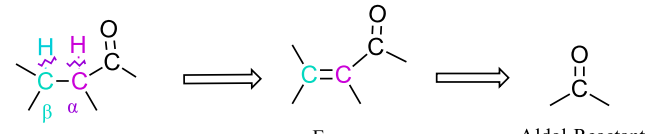
The enone product of an aldol condensation is versatile because it contains two functional groups (alkene & carbonyl) which can be subject to further reactions. Among many possible reactions, an enone can undergo hydrogenation to produce an aldehyde or ketone. Also, the carbonyl group can undergo hydride reduction to produce a beta-hydroxyalkene.



These additional reactions can be applied with the consideration of using an aldol reaction in the synthesis of a target molecule. A similar analysis can be extrapolated to the other reactions possible with the alkene and carbonyl present in an enone.

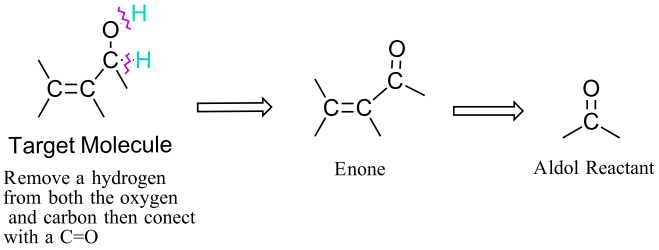
Analysis for Hydrogenation

To consider a hydrogenation, remove a hydrogen from a carbon in both the alpha and beta positions relative to the carbonyl. Then connect these two carbons with a C=C double bond. This create a possible enone which can be broken apart further using the analysis described above. Target molecules can have often have multiple alkyl chains which can be used to form a double bond.



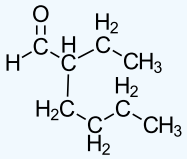
Analysis for Hydride Reduction

To consider a hydride reduction remove a hydrogen from the alcohol oxygen then a hydrogen from the adjacent carbon. Connect the oxygen and carbon with a double bond to form a C=O carbonyl. This provides an enone which can undergo further analysis.



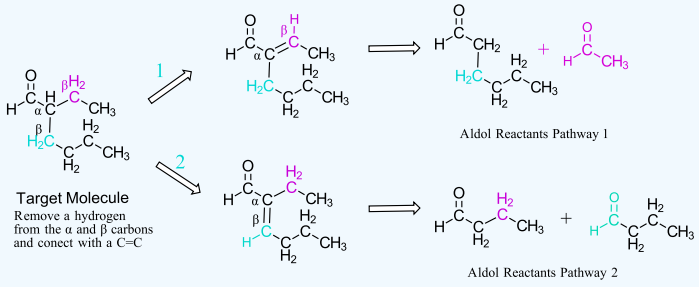
EXERCISE 23.4.1

Please devise a synthesis pathway for the following molecule using an aldol reaction:

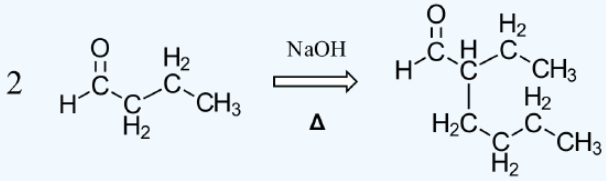


Answer

Analysis: Because the target molecule has two beta-carbons with hydrogens there are two possible synthesis pathways. Both should be considered for their effectiveness. Because a carbonyl is already present fragmentations will first be performed to create two possible enone intermediates. These enones will both be broken into their aldol reactants. When looking a possible aldol reactants produced by each pathway it is clear that pathway 2 is preferred. Because both fragments are the same they will react to form on major product.

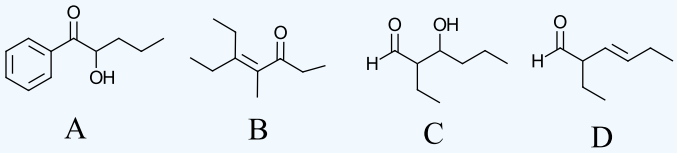


Solution



EXERCISES 23.4.1

1) Which of the following molecules could be made using an aldol reaction or condensation. Please show the starting material for the reactions that are possible.



2) Please show the reaction steps required to make 4-methyl-2-pentanol from an aldol condensation.

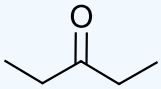
3) Please design a synthesis for the following molecule: Red = Oxygen, Grey = Carbon, White = Hydrogen



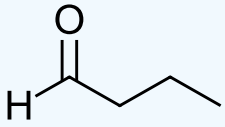
Answers

1) Molecules A and C are possible.

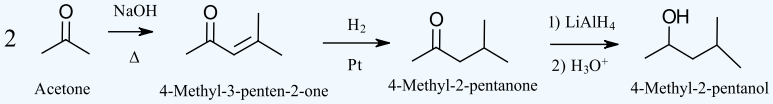
Solution for molecule A



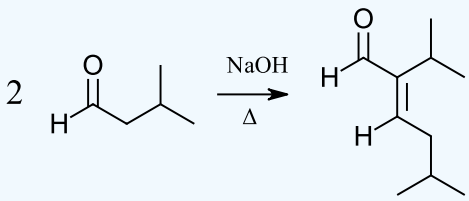
Solution for molecule C



2)



3)



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23.5: MIXED ALDOL REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a mixed aldol reaction.
2. identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
3. determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
4. identify the product or products formed in a given mixed aldol reaction.
5. identify the carbonyl compounds needed to produce a given enone or *β*-hydroxy aldehyde or ketone by a mixed aldol reaction.

STUDY NOTES

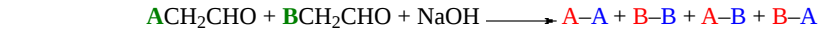
You should satisfy yourself that you understand how the four products shown in Example 23.5.2 arise from the condensation of 2-propanone and 2-phenylacetaldehyde.

MIXED ALDOL REACTION AND CONDENSATIONS

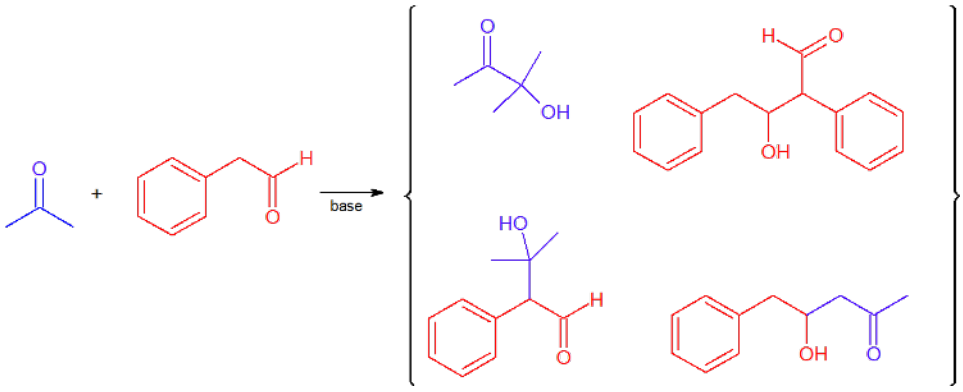
The previous examples of aldol reactions and condensations used a common reactant as both the enolate donor and the electrophilic acceptor. The product in such cases is always a dimer of the reactant carbonyl compound. Aldol condensations between different carbonyl reactants are called crossed or mixed reactions, and under certain conditions such crossed aldol condensations can be effective.

Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols. Because of this, most mixed aldol reactions are usually not performed unless one reactant has no a H's

The following abbreviated formulas illustrate the possible products in such a case, red letters representing the acceptor component and blue the donor. If all the reactions occurred at the same rate, equal quantities of the four products would be obtained. Separation and purification of the components of such a mixture would be difficult.



Products of a Uncontrolled Mixed Aldol Reaction

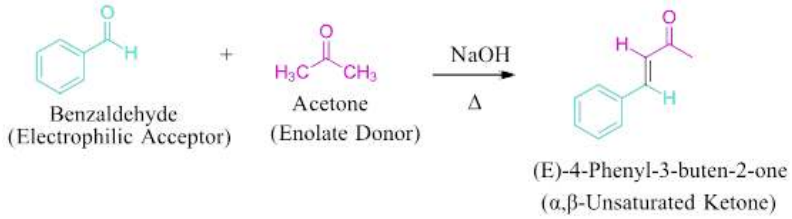


To avoid complex reaction mixtures the reactants should be chosen to favor one particular donor/acceptor reaction. Successful mixed aldol reactions usually use one of two combination of factors.

1) A reaction of an aldehyde with no alpha-hydrogens with a ketone that has alpha hydrogens: Aldehydes lacking alpha-hydrogens cannot form an enolate so they can only function as electrophilic acceptor reactants. This reduces the number of possible products by half. Although it would be possible for the ketone to react with itself it is unlikely. Aldehydes are more reactive acceptor electrophiles than ketones. This makes the preferred reaction one with the ketone as an enoloate donor and the aldehyde as an electrophilic acceptor.

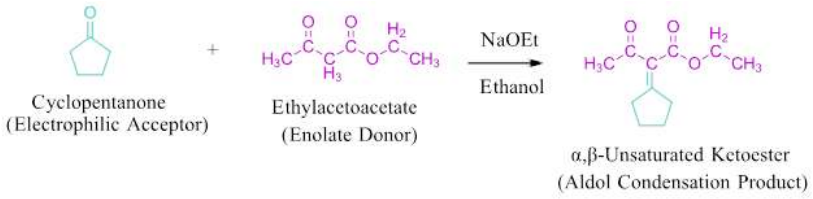
The aldol condensation between an aromatic aldehyde with no α-hydrogens and an aliphatic aldehyde or ketone with α-hydrogen is called a **Claisen–Schmidt condensation**. The reaction product is a highly conjugated α,β-unsaturated aldehyde or ketone which forms in the more stable (E)-alkene isomer.

Example: Claisen–Schmidt Condensation



2) One of the reactants has alpha-hydrogens which are highly acidic: The acidic compound will be preferably converted into an enolate donor which removes the possibility of its carbonyl acting as an electrophilic acceptor. An example is the aldol condensation of ethylacetoacetate and cyclopentanone. Ethylacetoacetate has α-hydrogens which are particularly acidic due to their conjugate base being stabilized by two carbonyl bonds (**Section 22.5**). Upon reaction with base, ethylacetoacetate is converted to the enolate donor leaving cyclopentanone to be the electrophilic acceptor. This provides one predominant aldol condensation product. In this reaction sodium ethoxide is used as a base to prevent hydrolysis side-reactions with the ester of ethylacetoacetate.

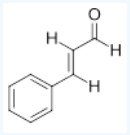
Example



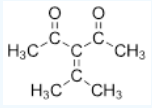
EXERCISES 23.5.1

1) Show the reactants required to make the following using a mixed aldol condensation. Indicate those which would be likely to produce a mixture of products.

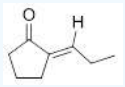
a)



b)

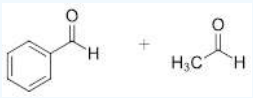


c)

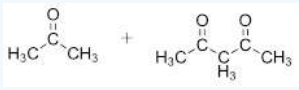


Answers

a)

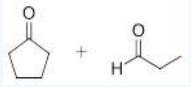


b)



c) Because both reactants have α-hydrogens and neither are particularly acidic, the reaction probably will produce a mixture of condensation products.

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23.6: INTRAMOLECULAR ALDOL REACTIONS

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate an intramolecular aldol reaction.
2. identify the product formed when a given dicarbonyl compound undergoes an intramolecular aldol condensation.
3. identify the dicarbonyl compound which, when treated with a suitable base, could be used to prepare a given cyclic enone by an intramolecular aldol condensation.

STUDY NOTES

"Intramolecular " means "within the same molecule." You have already seen some examples of intramolecular reactions in previous chapters. Another term for intramolecular aldol reaction is "internal aldol reaction."

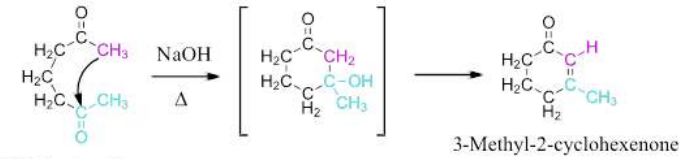
INTRAMOLECULAR ALDOL REACTION

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. The term "Intramolecular" means "within the same molecule." In this case, it means that the enolate donor and the electrophilic acceptor of an aldol reaction are contained in the same molecule such as dialdehydes, keto aldehydes, or diketones. In these cases, the small distance between the donor and acceptor leads to faster reaction rates for intramolecular condensations making intermolecular condensations (which require two molecules to collide in solution) less favorable.

In most cases multiple sets of α-hydrogens need to be considered when determining the donor/acceptor roles for the reaction, which might lead to a mixture of products. The intramolecular aldol reaction of a 1,5-diketone, 2,6-heptanedione, could possibly yield either the six-membered ring product, 3-methyl-2-cyclohexenone, or the four-membered ring product, (2-methylcyclobutenyl)ethanone. However, the cyclohexanone product is exclusively formed.

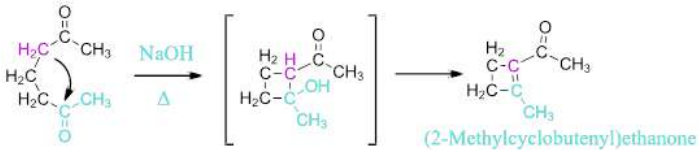
This product selectivity is possible due to all of the steps of the mechanism being reversibly, which tends to produce the most stable product. As with most ring forming reactions, five and six membered rings are preferred due to their relative lack of ring strain compared to other sized rings (See Sections 4.4 & 4.5). Once equilibrium is reached, the relatively strain free and therefore more thermodynamically stable, cyclohexanone product will be preferably formed.

Example



2,6-Heptanedione
(A 1,5-Diketone)

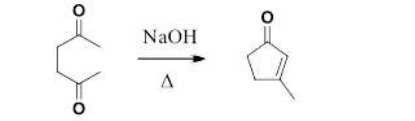
3-Methyl-2-cyclohexenone



(2-Methylcyclobutenyl)ethanone
Not Formed!

Similar analysis can be used to predict the products of other intramolecular aldol reactions. In a similar reaction, 1,4-diketones, such as 2,5-hexanedione, only form the five-membered ring product, ex. 3-methyl-2-cyclopentenone, without any of the possible cyclopropane product forming.

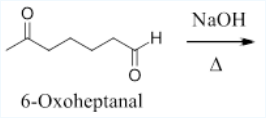
Example



2,5-Hexanedione 3-Methyl-2-cyclopentenone

? WORKED EXAMPLE

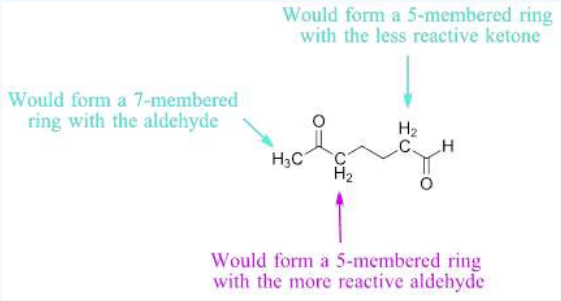
Please draw the expected product of an intramolecular aldol condensation with the following molecule:



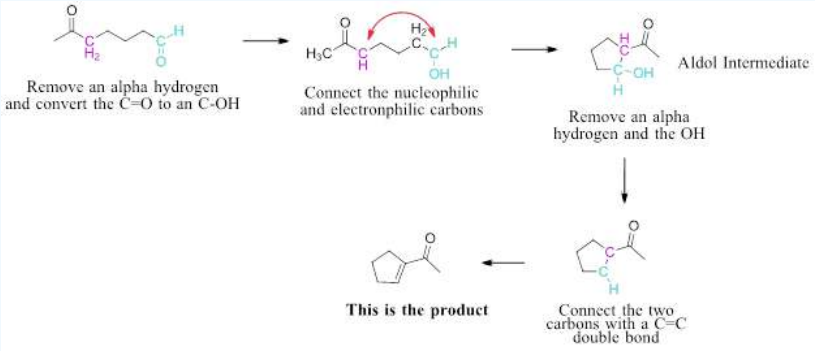
6-Oxoheptanal

Answer

Analysis: 6-Oxoheptanal has three unique sets of alpha-hydrogens which could be deprotonated to form an enolate. Selecting the correct set involves analyzing the carbonyl reactivity's along with the possible ring sizes of the products.



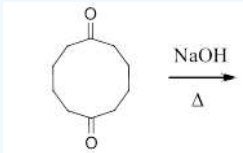
Solution: Once the preferred alpha-hydrogens are determined go through the steps discussed in the previous sections to determine the aldol condensation product. Remember to form the aldol intermediate first.



? EXERCISES 23.6.1

1) Briefly explain why the molecule, 2,4-pentanedione, when reacted with a base would mostly likely not produce an intramolecular aldol condensation product.

2) Draw the product of the following aldol condensation:



1,6-Cyclodecanedione

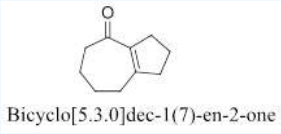
Answers

1) 2,4-Pentanedione like other 1,3-Diketones have particularly acidic alpha-hydrogens between the two carbonyl. When base is applied these will be the first to deprotonate and form an enolate. For an intramolecular aldol condensation to occur an alpha-hydrogen one of the methyl groups would have to be removed which would be difficult.



2,4-Pentanedione

2)



Bicyclo[5.3.0]dec-1(7)-en-2-one

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23.7: THE CLAISEN CONDENSATION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate a Claisen condensation reaction.
2. write a detailed mechanism for a Claisen condensation reaction or its reverse.
3. identify the product formed in a given Claisen condensation reaction.
4. identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.

KEY TERMS

- Claisen condensation reaction

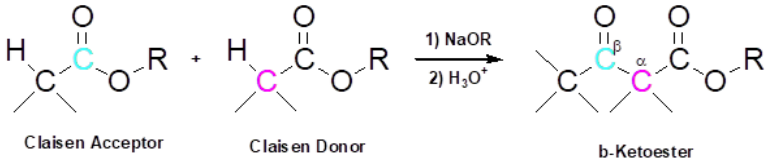
STUDY NOTES

You have already seen that ethyl acetoacetate-type compounds are very useful in organic syntheses. Any reaction which results in the formation of these compounds will also be of importance. In the next section, you will see how the range of β-keto esters that can be prepared by this method is extended through the use of two different esters as starting materials.

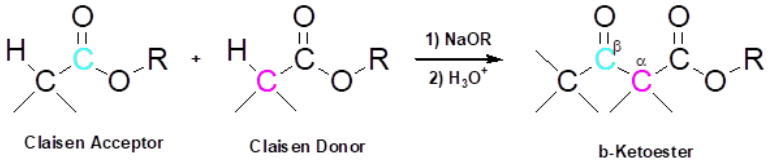
CLAISEN CONDENSATION

Because esters commonly contain both α-hydrogens and a carbonyl bond, they can undergo a reversible condensation similar to the aldol reaction called a Claisen Condensation. In a fashion similar to the aldol reaction, one ester acts as a Claisen enolate donor (nucleophile) while a second ester acts as the Claisen acceptor (electrophile). During the reaction a new carbon-carbon is formed to produce a β-keto ester product. This reaction is considered a condensation because it eliminates a small alcohol as an unwanted side-product.

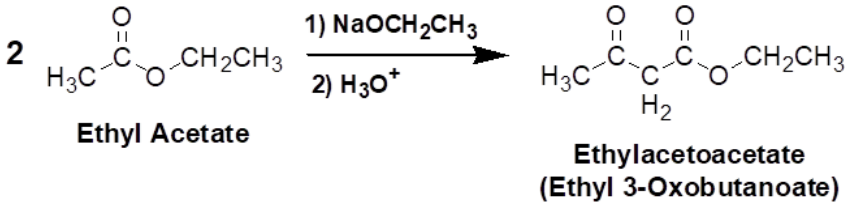
GENERAL REACTION



PREDICTING THE PRODUCT OF A CLAISEN CONDENSATION



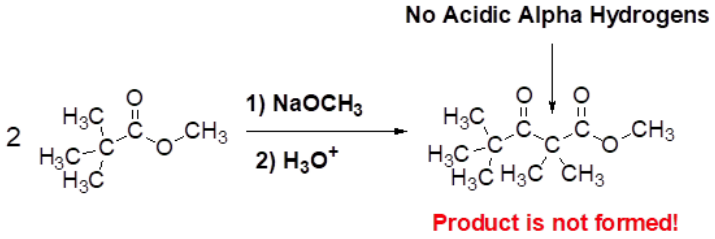
EXAMPLE



Although they may appear similar, there are a number of fundamental differences between an aldol and Claisen condensation. During the mechanism of the reaction, the formed tetrahedral alkoxide intermediate is not protonated to from an “aldol” type product. Rather, the alkoxide intermediate will reform the C=O carbonyl bond and eliminate a (-OR) leaving group to produce a nucleophilic acyl substitution product.

Claisen condensations cannot use a hydroxide for the reaction base due to the possibility of ester hydrolysis. Also, to prevent transesterification side products, the alkoxide base typically has the same alkyl group as alkoxy group present in the ester starting material.

Lastly, the β-keto ester products of Claisen condensation can be acidic enough to be deprotonated by the reaction's base during the final steps of the mechanism. This means the base is not catalytically regenerated during the reaction and a full equivalent of base is required. The β-keto ester condensation products are removed from the equilibrium by this deprotonation, which causes the reaction to be driven forward by Le Chatelier's principle. This concept is so important that a Claisen product will not form unless it contains an alpha hydrogen acidic enough to react completely with the reaction base. This requires that the ester starting materials have at least two alpha-hydrogens for a Claisen condensation product to form. One is removed to form an ester enolate and the second is removed to drive the reaction forward.

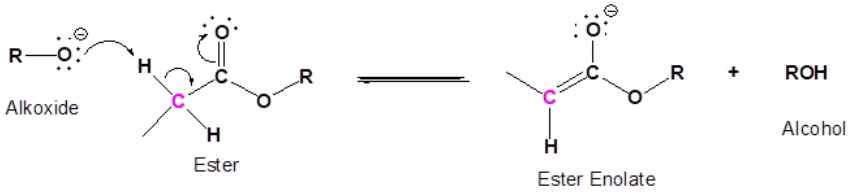


MECHANISM

The Claisen condensation mechanism is analogous to the ester saponification reaction seen in *Section 21.6*.

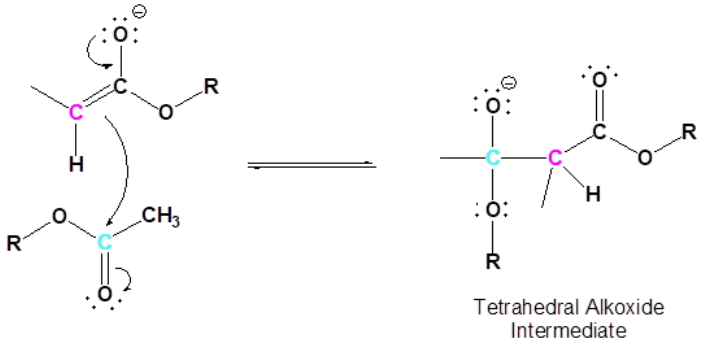
1) ENOLATE FORMATION

The mechanism starts with the alkoxide base removing an alpha-hydrogen from the ester to form a nucleophilic ester enolate ion.



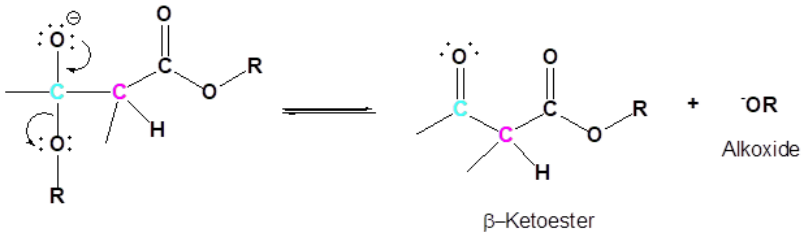
2) NUCLEOPHILIC ATTACK

The enolate nucleophile adds to carbonyl carbon of a different ester, forming a tetrahedral alkoxide intermediate.



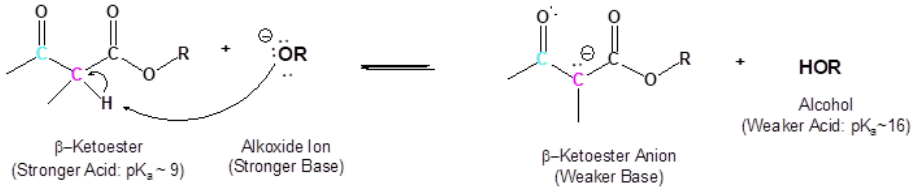
3) REMOVAL OF LEAVING GROUP

The alkoxide then reforms the carbonyl, eliminating the –OR leaving group to form a beta-ketoester.



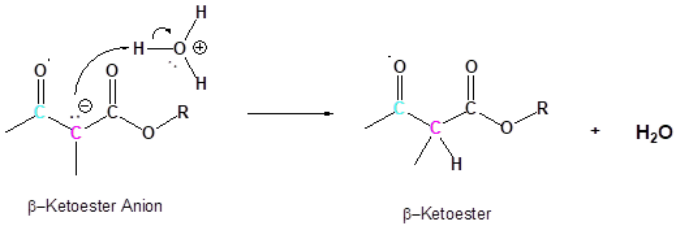
4) DEPROTONATION

The acidity of beta-ketoesters (pK_a ~9) is high enough to allow them to be completely deprotonated by alkoxide bases (pK_a of an alcohol ~16) to form a second enolate. This make the equilibrium of this step very favorable, which is enough to drive the whole reaction towards the product.



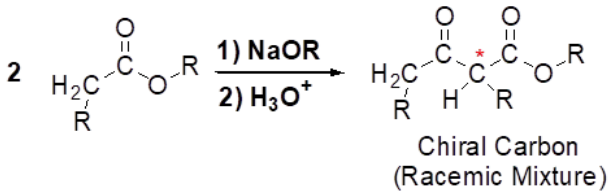
5) PROTONATION

The enolate is protonated in an acid work-up to form the neutral beta-ketoester product.



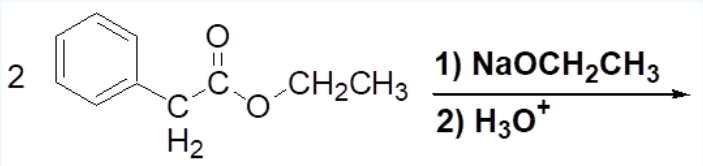
Stereochemical Considerations

The alpha-carbon gains a substituent during the reaction which means it will most likely form a chiral carbon. The fact that the alpha-carbon is temporarily converted to an enolate in the last step of the mechanism means that a racemic mixture of enantiomers will form.



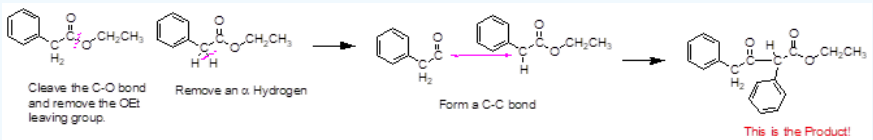
? WORKED EXAMPLE

Draw the products of the following reaction:



Answer

Analysis: Remember to consider each start ester separately.

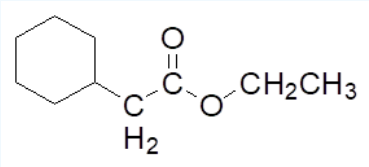


? EXERCISE 23.7.1

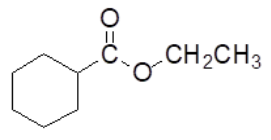
Please draw the products if the following molecules were to undergo a Claisen condensation.

a)

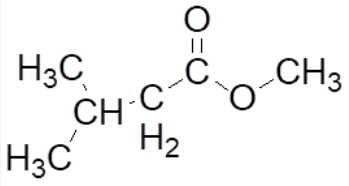
https://chem.libretexts.org/@go/page/36429



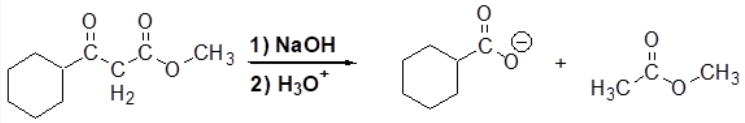
b)



c)

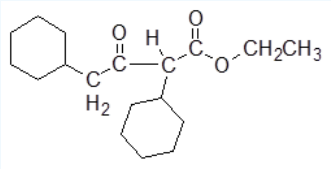


2) The beta-keto ester product of a claisen condensation can under hydrolysis with Sodium Hydroxide as shown in the reaction below. Please draw a curved arrow mechanism to explain how the products are formed. Also, explain why the ketone functional group preferably reacts with hydroxide instead of the ester.

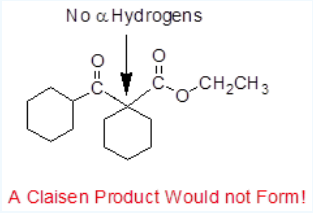


Answers

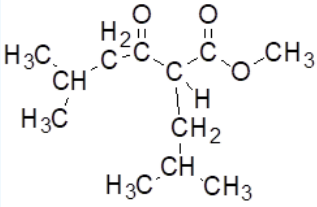
a)



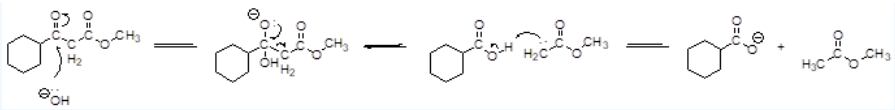
b)



c)



2) The carbonyl of the ketone is more likely to be attacked by the hydroxide nucleophile because is more reactive than the ester's



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23.8: MIXED CLAISEN CONDENSATIONS

OBJECTIVES

After completing this section, you should be able to

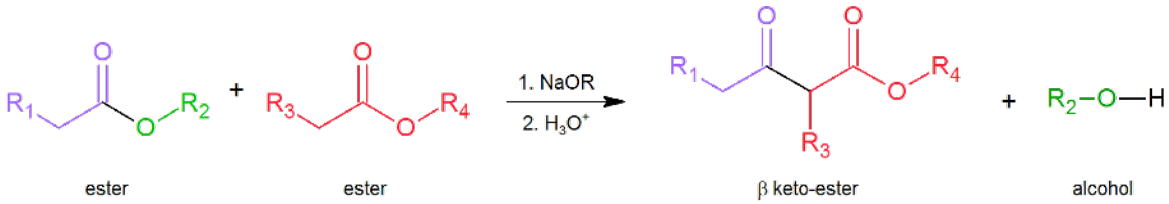
1. write an equation to illustrate a mixed Claisen condensation.
2. identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
3. determine whether a given pair of esters is likely to produce a good yield of a single product when subjected to a mixed Claisen condensation.
4. identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
5. identify the esters that should be used to produce a given *β*-keto ester by a mixed Claisen condensation.
6. write an equation to illustrate the formation of a *β*-diketone through a mixed Claisen-type condensation between an ester and a ketone.
7. identify the *β*-diketone formed as the result of a mixed Claisen-type condensation between a given ester and a given ketone.
8. identify the reagents necessary to synthesize a given *β*-diketone by a mixed Claisen-type condensation between an ester and a ketone.
9. write detailed mechanisms for mixed Claisen reactions and reactions that are related to the mixed Claisen reaction, including those in which both reacting moieties are present in the same compound.

STUDY NOTES

Just as we can react together two different aldehydes or ketones in a mixed aldol condensation, so can we react together two different esters in a mixed (or “crossed”) Claisen condensation. Again, by carefully selecting our substrates we can obtain a good yield of the desired product and minimize the number of possible by-products. Note that even if we replace one of the esters with a ketone, the reaction is still referred to as Claisen condensation. The important thing to realize as you study these reactions is that they all take place by essentially the same mechanism—attack by an enolate anion on a carbonyl group.

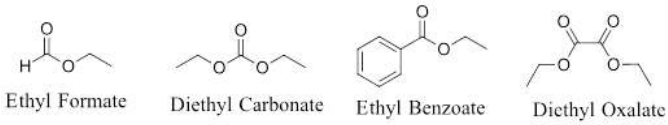
CROSSED CLAISEN CONDENSATION

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as Claisen donors and Claisen acceptors generally give complex mixtures which are difficult to separate.



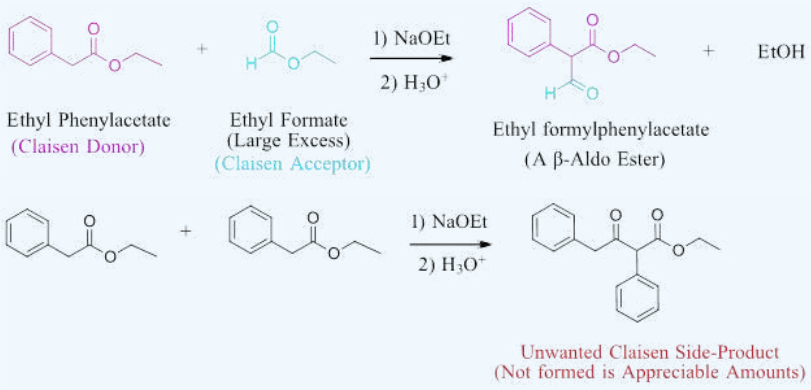
General Reaction for a Crossed Claisen

To avoid complex mixtures most Crossed Claisen reactions are usually not successful unless one of the two esters has no alpha-hydrogens as in the following examples.



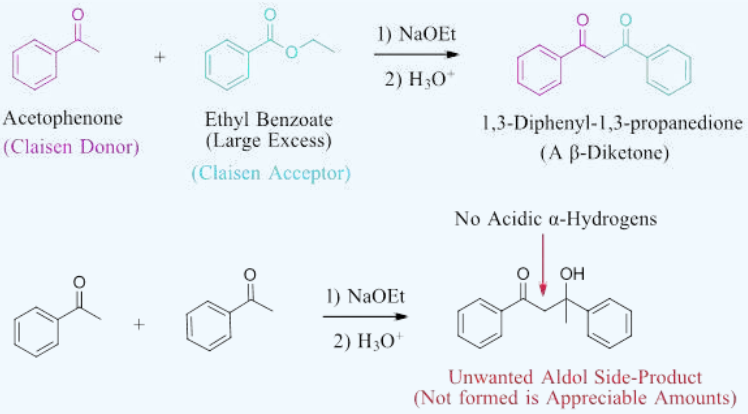
This forces the ester with alpha-hydrogens to be the Claisen donor (enolate) and the ester without alpha-hydrogens to be the Claisen acceptor (electrophile). Even with this differentiation, it is possible for the ester with alpha-hydrogens to undergo a Claisen Condensation with itself to produce an unwanted side-product. This is typically partially prevented by using the ester without alpha-hydrogens in a large excess.

EXAMPLE: NO ALPHA HYDROGENS



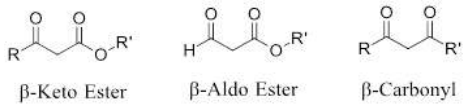
Another type of crossed Claisen condensation occurs when a ketone is reacted with an ester. The use of an ester without alpha-hydrogens is not necessary due to the greater reactivity of the ketone. The alpha-hydrogens of the ketone are much more acidic (pKa~20) than those of the ester (pKa~25). The alpha hydrogens of ketone will be preferably deprotonated to make it the enolate Claisen donor. The ester will therefore be the electrophilic Claisen acceptor and is likewise commonly used in a large excess. There is still a possibility of the ketone reacting with itself to form the product of an aldol reaction however the equilibrium is unfavorable. Also, the formation of the aldol product is reversible due to its lack of an acidic alpha hydrogen. The beta-diketone Claisen product can be irreversibly deprotonated due to its more acidic alpha-hydrogens, making it the reaction's main product.

EXAMPLE: ESTER WITH KETONE

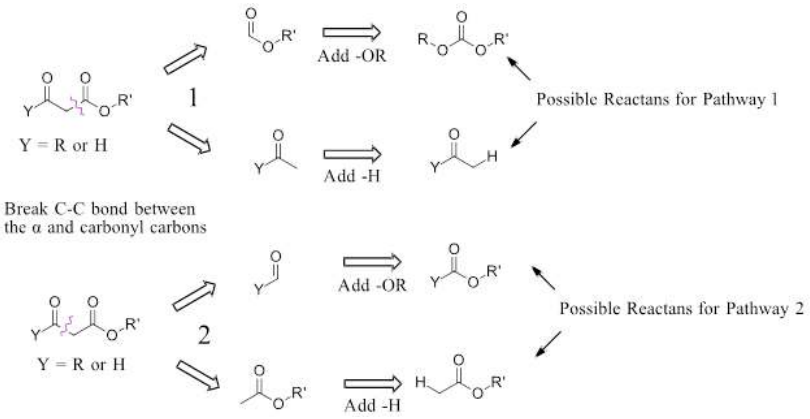


PLANING A SYNTHESIS USING A CLAISEN OR CROSSED CLAISEN-LIKE REACTION

A Claisen reaction should be considered for a synthesis pathway if the target molecule contains a beta-keto esters, a beta-aldo ester or a beta-dicarbonyl.



A beta-keto ester or a beta-aldo ester could possibly be made by a Claisen condensation of two esters. A beta-dicarbonyl could possibly be made by a Claisen-like condensation between a ketone and an ester. Here, the key bond cleavage is a C-C bond between one of the carbonyls and the alpha-carbon which lies between the carbonyl. In each of these situations there are two such C-C bonds so there will be two possible pathways to consider. After the C-C bond cleavage the fragment with the alpha-carbon will gain a hydrogen. The fragment with the bare carbonyl will gain an –OR group to become an ester. The –OR group added will be the same as any ester present in the target molecule. If none are present $–OCH_2CH_3$ is typically used.

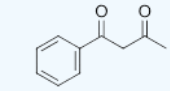


Analysis for Beta-Keto and Aldo Esters

A similar analysis can be performed on a 1,3-diketone and will be presented in the worked example below.

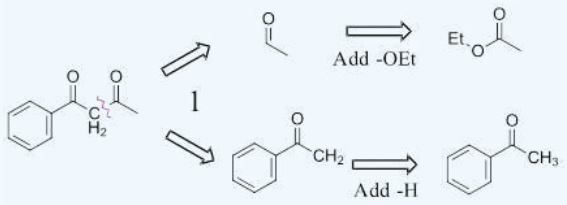
EXAMPLE 23.8.1

Show how the following molecule can be made using a Claisen-like condensation.

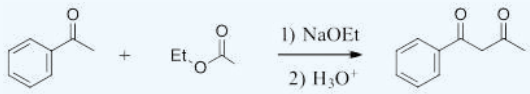


1-Phenyl-1,3-butanedione

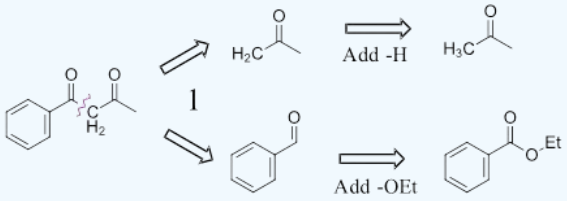
Pathway 1



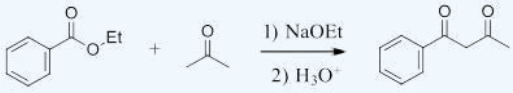
Answer Pathway 1



Pathway 2



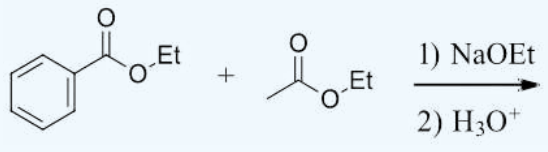
Answer Pathway 2



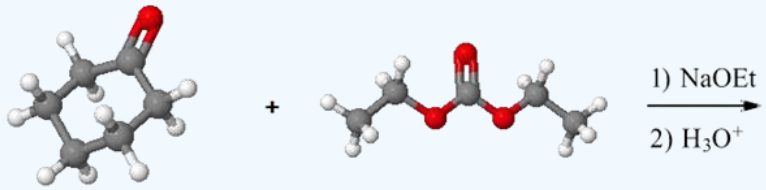
EXERCISE 23.8.1

Draw the product of the following reactions:

a.

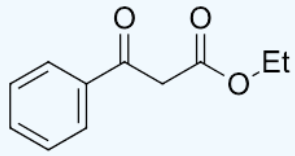


b.

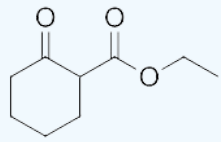


Answers

a.



b.



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23.9: INTRAMOLECULAR CLAISEN CONDENSATIONS - THE DIECKMANN CYCLIZATION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate an internal Claisen condensation, that is, a Dieckmann cyclization.
2. identify the product formed when a 1,6- or 1,7-diester undergoes an internal Claisen condensation.
3. identify the diester needed to prepare a given cyclic β-keto ester by an internal Claisen condensation.
4. identify the structural features present in a diester that lead to the formation of more than one product in an internal Claisen condensation.

KEY TERMS

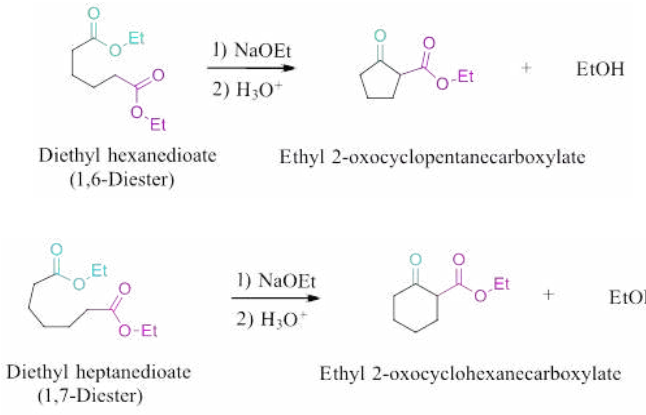
- Dieckmann cyclization

STUDY NOTES

Essentially no new material is introduced in this section; Dieckmann cyclizations are intramolecular Claisen condensations. These reactions occur for 1,6- and 1,7-diesters, as these substances result in the formation of compounds containing five- and six-membered rings, respectively. You may recall that the formation of such ring systems is favoured because they are relatively free of strain.

THE DIECKMANN CYCLIZATION

Diesters can undergo an intramolecular reaction, called the Dieckmann condensation, to produce cyclic beta-keto esters. This reaction works best with 1,6-diesters, which produce five-membered rings, and 1,7-diesters which produce six membered rings.

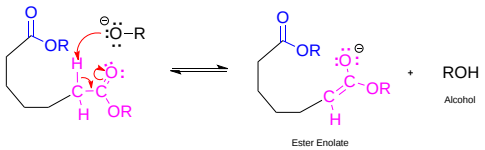


Examples of the Dieckmann Cyclization reaction.

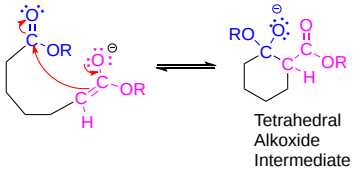
MECHANISM

The mechanism of the Dieckmann condensation is the same as a Claisen condensation. An alkoxide base removes an alpha-hydrogen from one of the esters to form an ester enolate. The enolate then adds to the carbonyl carbon of the other ester to form a tetrahedral alkoxide intermediate. The alkoxide reforms the carbonyl bond which causes the elimination of the –OR leaving group and forms a cyclic beta-keto ester. The high acidity of the beta-keto ester allows it to be deprotonated by the reactions base to form a second enolate. Like the Claisen condensation, this deprotonation step drives the equilibrium towards the products and is required for the reaction to occur. A full equivalent of base is necessary during this reaction.

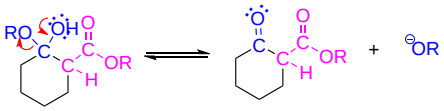
STEP 1: ENOLATE FORMATION



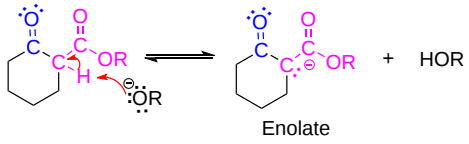
STEP 2: NUCLEOPHILIC ATTACK



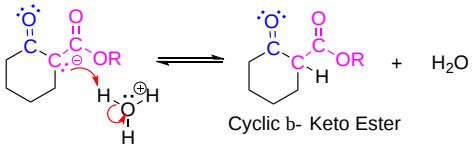
STEP 3: REMOVAL OF LEAVING GROUP



STEP 4: DEPROTONATION

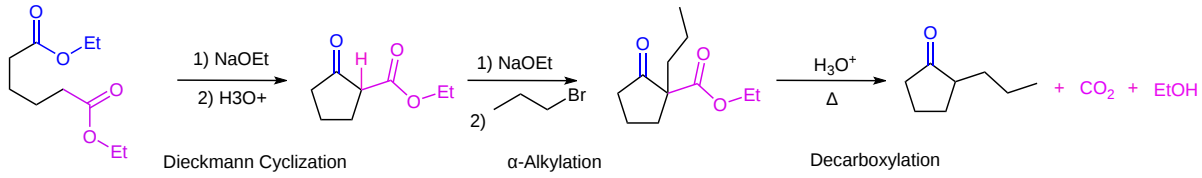


STEP 5: PROTONATION



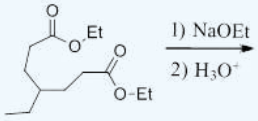
FURTHER REACTIONS OF THE DIECKMANN CYCLIZATION PRODUCT

The cyclic beta-keto ester product of a Dieckmann cyclization can be modified by reaction similar to those used in the acetoacetic ester synthesis (Section 22-7). The acidic alpha-hydrogens of the beta-keto ester allow it to easily be deprotonated and alkylated in an alpha-substitution reaction. Having a carbonyl group in the beta position allows the ester to be removed through decarboxylation. The combination of these three reactions (1) Dieckmann cyclization, (2) alpha alkylation, and (3) decarboxylation provides an efficient method for preparing 2-substituted cyclopentanones and cyclohexanones.

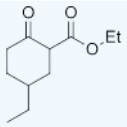


? EXERCISE 23.9.1

Draw the expected product for the following reaction:

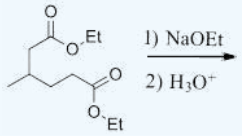


Answer

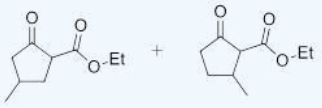


EXERCISE 23.9.2

The Dieckmann cyclization of the following molecule is expected to give a mixture of two cyclized products. Draw the structure of the two products and briefly explain why a mixture is formed.



Answers



Each has the ability to act as a Claisen donor and a Claisen acceptor. The reaction should produce a roughly 50/50 mixture where each ester acts as a Claisen acceptor.

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23.10: CONJUGATE CARBONYL ADDITIONS - THE MICHAEL REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Michael reaction.
2. write a detailed mechanism for a given typical Michael reaction.
3. identify the product formed in a given Michael reaction.
4. identify the reagents necessary to synthesize a given compound by a Michael reaction.

KEY TERMS

- Michael reaction

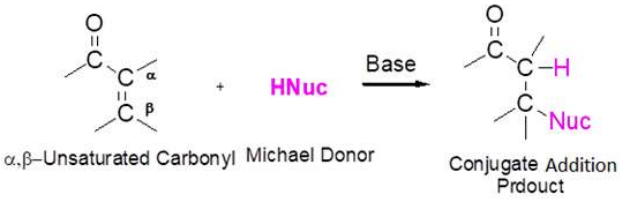
STUDY NOTES

Before studying this section in detail, you should review conjugate addition to *α,β*-unsaturated carbonyl compounds (Section 19.13).

Notice the wide variety of compounds that can take part in a Michael reaction. As usual, you should not feel overwhelmed by the number of different compounds that can be used, just keep in mind that in all cases the mechanism is essentially the same.

MICHAEL REACTION

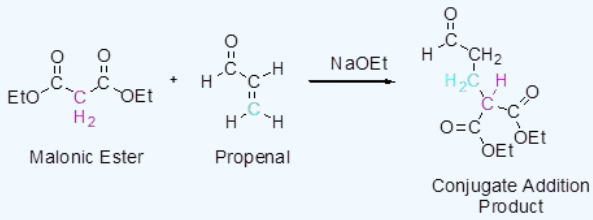
Certain nucleophiles undergo conjugate addition with the alkene of an α, β-unsaturated carbonyl compounds rather than undergo direct nucleophilic addition with the carbonyl. During conjugate addition, a nucleophile adds to the electrophilic β-alkene carbon to from a C-Nuc bond. If the starting materials contains an ester the corresponding alkoxide is used as the base in the reaction. Otherwise a hydroxide base, such as sodium or potassium hydroxide, is commonly used.



General Reaction of the Michael Reaction

When enolate nucleophiles undergo conjugate addition with an α, β-unsaturated carbonyl the process is called a Michael Reaction. The Michael reaction works best with particularly acidic enolate donors such as malonic esters, β-keto esters, etc. Enolates which are weaker acids tend to undergo nucleophilic addition to the carbonyl rather than conjugate addition. For example, malonic ester's acidic alpha-hydrogens can be easily deprotonated by sodium ethoxide to form an enolate. The enolate adds to propenal to form the conjugate addition product.

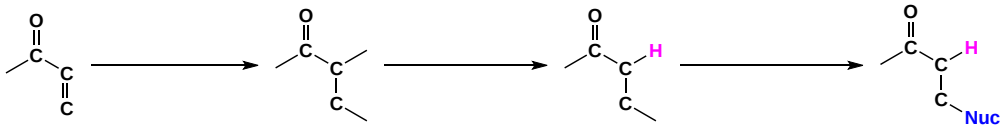
EXAMPLE 23.10.1



PREDICTING THE PRODUCT OF A MICHAEL REACTION

During the is reaction the C=C pi bond of the α, β-unsaturated carbonyl is broken. An C-H bond is formed on the carbon in the α-position from the carbonyl. An acidic hydrogen is removed from the nucleophile and then it is used to form a C-C bond with the carbon in the beta

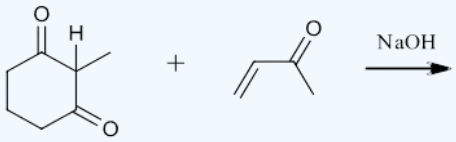
position from the carbonyl.



a. In the first step, remove the double bond and add two single bonds
b. Add a hydrogen to the bond adjacent to the carbonyl
c. Add the nucleophile to the other end of the double bond (remember to remove a hydrogen from the nucleophile)

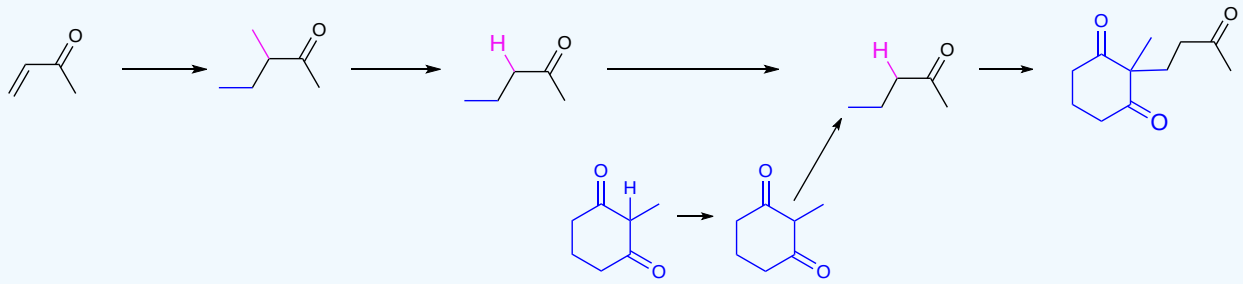
? WORKED EXAMPLE 23.10.1

What would be the product of the following conjugate addition?



Solution

1. Break the double bond and add two single bonds
2. Add a hydrogen to the bond adjacent to the carbonyl
3. Remove a hydrogen from the nucleophile.
4. Add the nucleophile to the other end of the double bond.



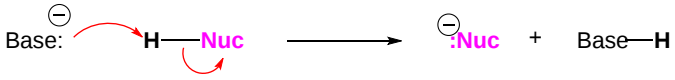
MECHANISM OF MICHAEL REACTION

During a Michael reaction the enolate acts as a nucleophilic donor and the α, β-unsaturated carbonyl acts as the electrophilic acceptor. The mechanism is a mixture of an alpha-substitution for the enolate and a conjugate addition for the α, β-unsaturated carbonyl.

Notice that the Michael Reaction does not require the deprotonation of the product to push the reaction towards completion. The reaction is thermodynamically favorable because the C-C bond formed in the product is stronger than the C=C bond in the starting material. This means that, unlike the Claisen condensation, this reaction only requires a catalytic amount of reaction base.

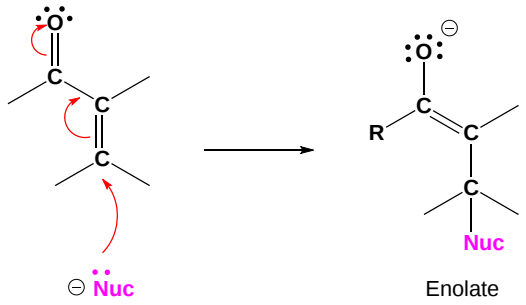
STEP 1: DEPROTONATION

The alkoxide base removes an alpha-hydrogen to from an enolate nucleophile.



STEP 2: NUCLEOPHILIC ATTACK ON THE CARBON B TO THE CARBONYL

The enolate nucleophile then adds to the electrophilic β-carbon of the α, β-unsaturated carbonyl. Conjugation pushes the C=C pi bond electrons onto the carbonyl oxygen, forming a new enolate enolate.



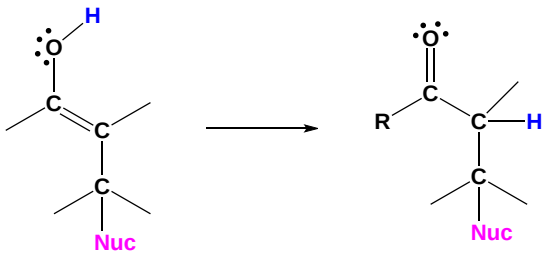
Enolate

STEP 3: PROTONATION

The alkoxide is protonated, forming an enol.

STEP 4: TAUTOMERIZATION

Tautomerization converts the enol back into a carbonyl forming the neutral conjugate addition product.



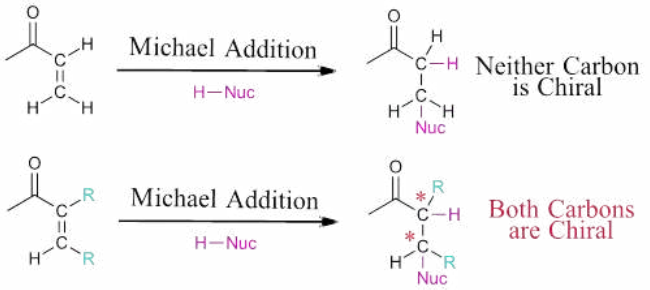
The Michael reaction can be performed with a wide variety of α, β-unsaturated carbonyl electrophilic acceptors and enolate donors. Michael acceptors such as α, β-unsaturated ketones, aldehydes, esters, amides, and nitro compounds can all participate in this reaction. Michael donors with particularly acidic α-hydrogens, such as β-diketones, β-keto esters, β-keto nitriles, α-nitro ketones, malonic esters, and nitro compounds can be used.

Michael Donors (aka nucleophile)	Michael Acceptors (aka electrophile)
β-diketone	α,β-unsaturated aldehyde
β-ketoester	α,β-unsaturated ketone
β-keto nitrile	α,β-unsaturated ester
α-nitro ketone	α,β-unsaturated amide
malonic esters	α,β-unsaturated nitrile
nitro compound	nitroethylene

Table 23.10.1: Possible Donors and Acceptors Which can be used in a Michael Reaction

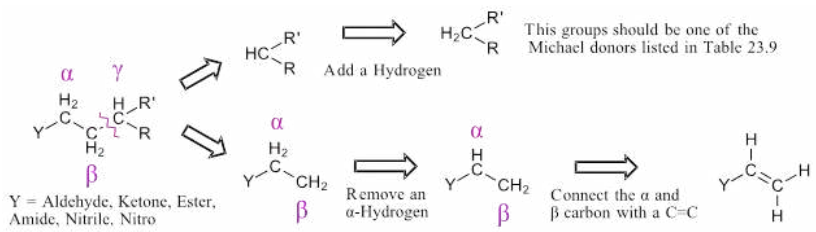
STEREOCHEMICAL CONSIDERATION OF MICHEAL REACTIONS

During a Michael reaction two sp^2 hybridized carbons are both converted to sp^3 hybridization. Both of them have the possibility of creating a chiral carbon. Michael reactions are often performed using an α, β-unsaturated carbonyl with only hydrogen substituents on the alkene to prevent the formation of chiral carbons. If either carbon in the alkene has an alkyl substituent it will likely form a chiral carbon in the Michael reaction product. The α-carbon of the enolate donor also has the possibility of forming a chiral carbon as discussed in **Section 22-6.**



PLANNING A SYNTHESIS USING A MICHAEL REACTION

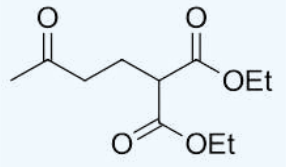
The true utility of the Michael reaction is seen when considering it use in a synthesis. The reaction can be used to prepare aldehydes, ketones, esters, amides, nitriles, and nitro compounds. A target molecule can possibly be made using a Michael reaction if it contains one of these functional groups and an alkyl chain at least three carbons long. The key bond cleavage is a C-C bond between β and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an α-hydrogen and then forms a C=C bond between the α and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic α-hydrogen and should be made up of Michael donor fragments such as those listed in **Table 23.10.1**. In some cases, there may be more than one fragmentation variation. Each variation should be investigated and the possible starting materials compared for viability.



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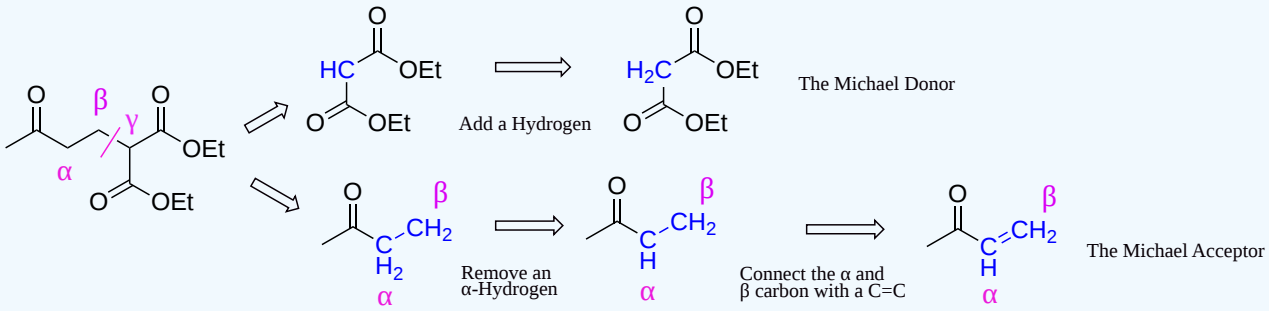
EXAMPLE

How could the following molecule be synthesized using a Michael Reaction?

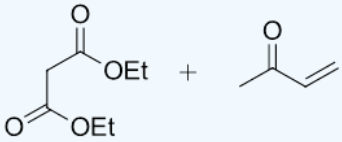


Answer

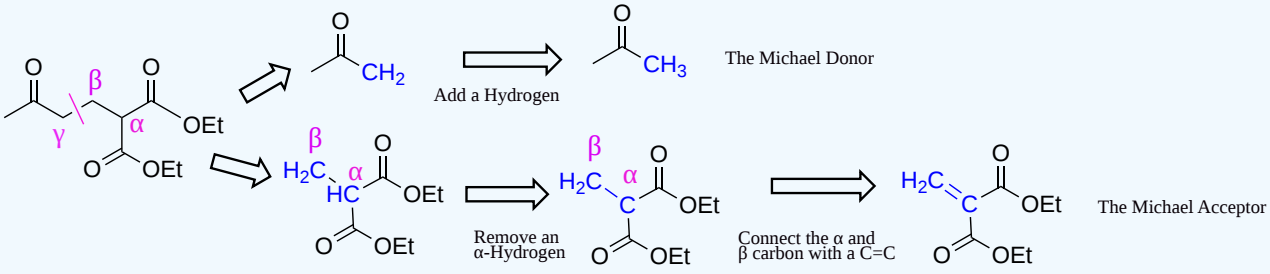
Pathway 1



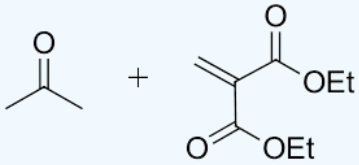
Starting Materials 1



Pathway 2

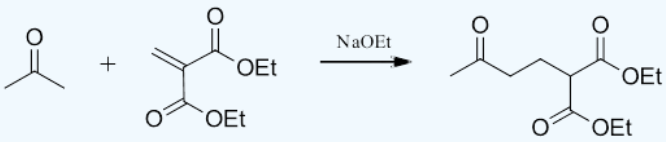


Starting Material 2



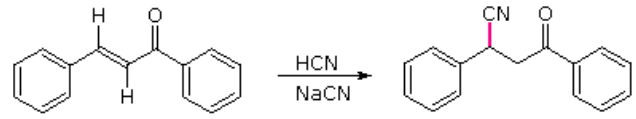
Solution

When comparing the two sets of possible starting materials of pathway 1 are preferred. The Michael enolate donor is particularly acidic because its conjugate base is stabilized by two carbonyls. The Michael enolate donor for pathway 2 does not have the same acidity. Consequently, the enolate would preferably undergo nucleophilic addition rather than conjugate addition. The makes the starting materials of pathway 1 preferred for the synthesis of the starting material.

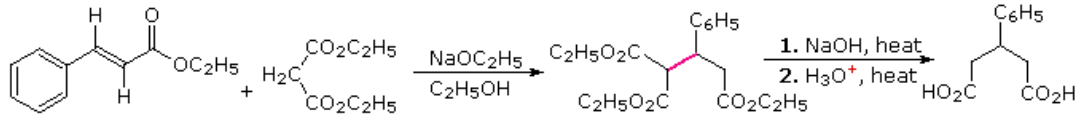


In combination with alkylations and condensations, the Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials. The carbon nucleophiles used in the following examples include cyanide ion, sodium diethylmalonate and the conjugate base of cyclohexane-1,3-dione. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would indicate preferential formation of 1,4-addition products. Cyanide addition does not always follow this rule, and aldehydes often give 1,2-products (cyanohydrins). In each case the initial reaction is a Michael addition, and the new carbon-carbon bond is colored magenta. Any subsequent bonds that are formed by other reactions are colored orange.

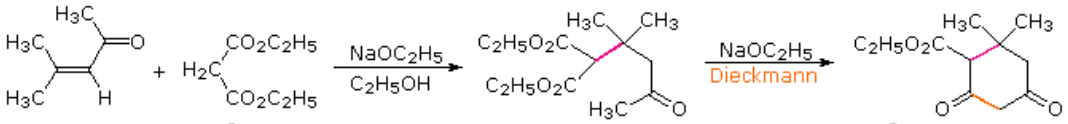
1.



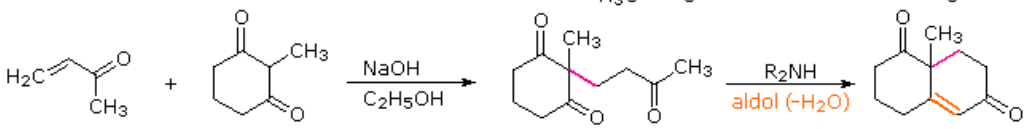
2.



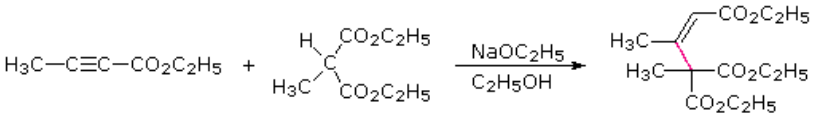
3.



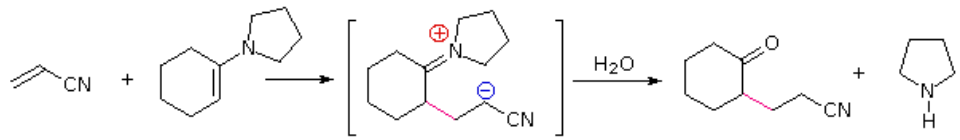
4.



5.

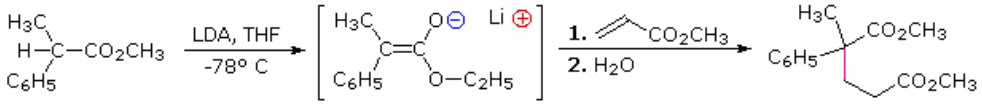


6.



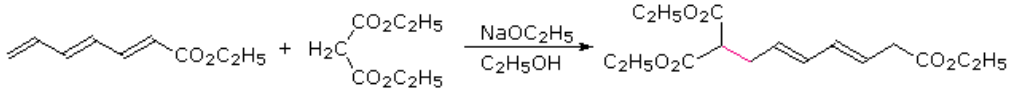
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.

7.



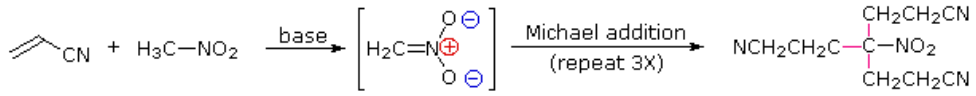
Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.

8.



Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).

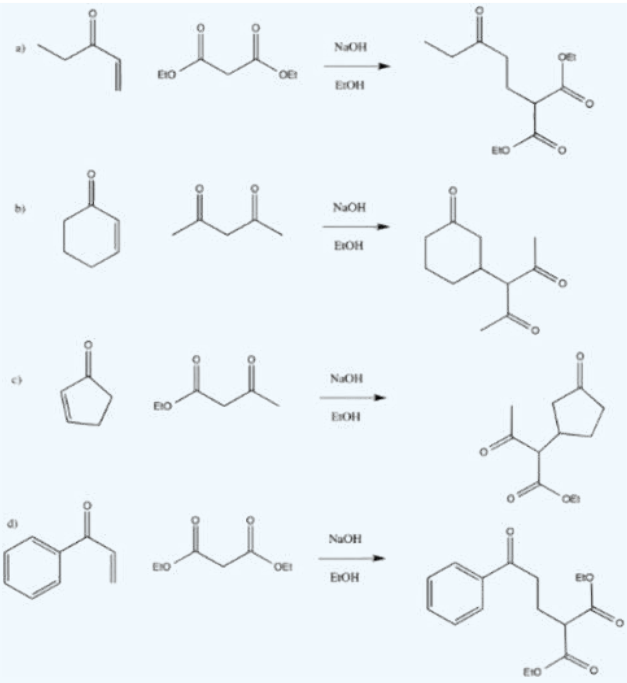
9.



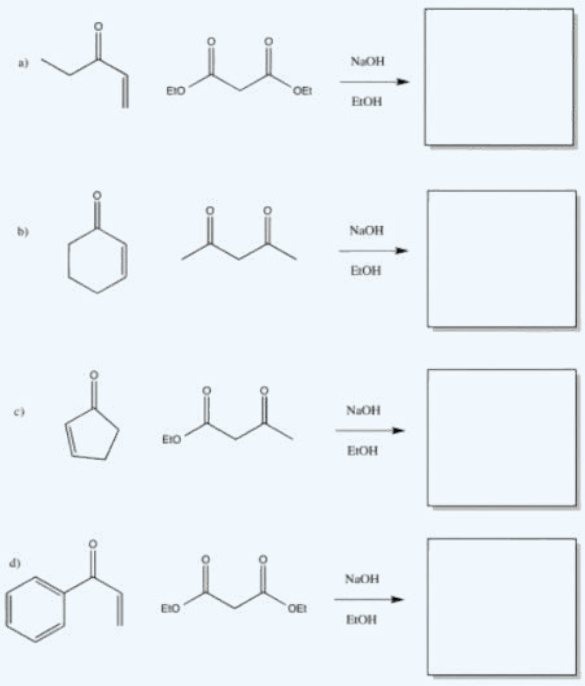
Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

? EXERCISE 23.10.1

Provide the products of the following Michael additions:

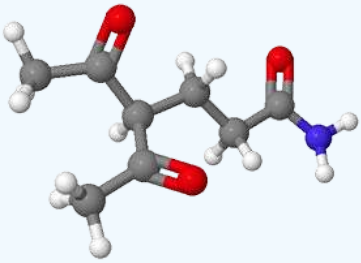


Answer

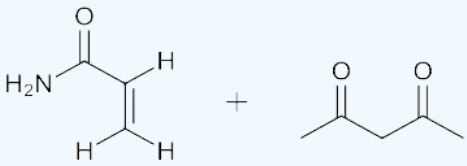


? EXERCISE 23.10.2

What would be the starting materials required to make the following molecule using a Michael reaction? Red = Oxygen, Grey = Carbon, White = Hydrogen, Blue = Nitrogen.



Answers



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23.11: CARBONYL CONDENSATIONS WITH ENAMINES - THE STORK REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the three-step Stork enamine reaction.
2. write a detailed mechanism for each of the three steps of the Stork enamine reaction.
3. identify the product formed, and the various intermediates (i.e., the enamine, the Michael-type adduct), in a given Stork enamine reaction.
4. identify the reagents needed to synthesize a given compound by a Stork enamine reaction.

KEY TERMS

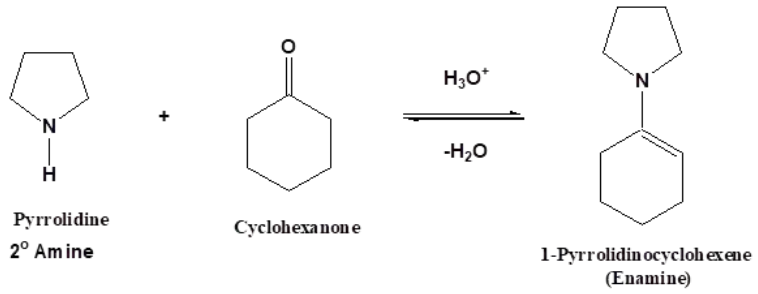
- Stork enamine reaction

STUDY NOTES

If we try to use a monoketone as a donor molecule in a Michael reaction, we will obtain a poor yield. An alternative route to the product that would be expected from such a synthesis is via the Stork enamine reaction. You may wish to review the formation of enamines (from ketones and secondary amines) before you proceed with this section; if so, review Section 19.8.

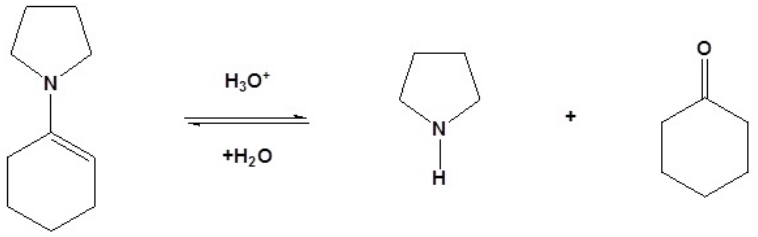
SYNTHESIS OF ENAMINES

As previously seen in **Section 19.8**, aldehydes and ketones react with 2° amines to reversibly form enamines. Enamines can add to acid halides to form 1,3-diketones and α, β-unsaturated Michael acceptors to from 1,5-dicarbonyls.

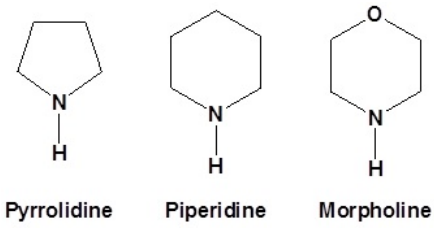


General Reaction

REVERSIBILITY

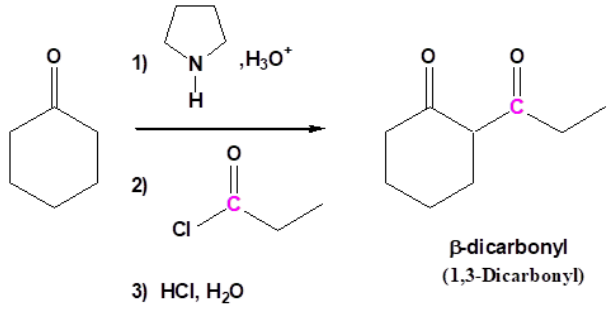


Typically the following 2° amines are used for enamine reactions

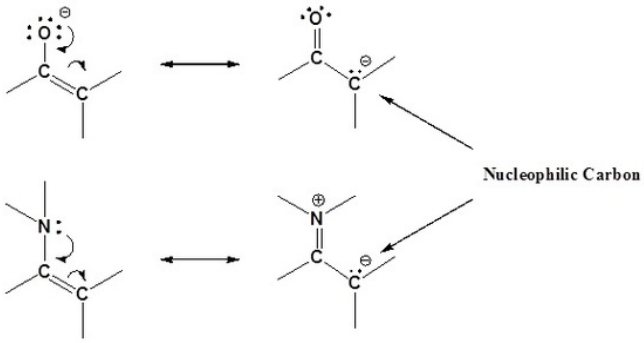


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Enamines have resonance structures similar to enolates. The lone pair electrons on the nitrogen are conjugated with the double bond and can donate electron density to the α-carbon. This allows the α-carbon of enamines to be nucleophilic in much the same fashion as enolates. The increased electron density of the α-carbon enamine, N,N-Dimethylaminoethylene, is shown as a yellow/green color in its electrostatic map. This is analogous to the increased electron density of the α-carbon of an enolate.

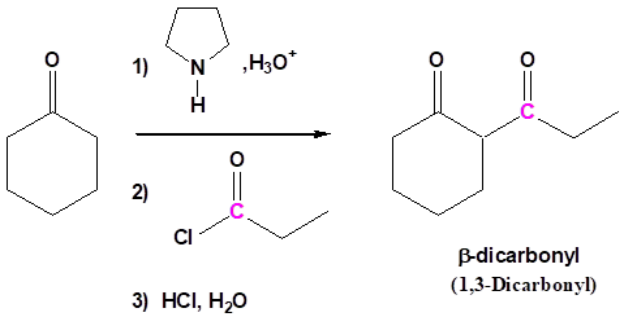


Enamines act as nucleophiles in a fashion similar to enolates. Because of this enamines can be used as synthetic equivalents as enolates in many reactions. This process requires a three steps: 1) Formation of the enamine, 2) Reaction with an electrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone. Some of the advantages of using an enamine over an enolate are enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. Also, enamine are more effective at the Michael reaction compared to a mono-carbonyl enolate.



ACYLATION OF ENAMINES

Acylation of Enamines involves the addition of an acyl group (RCO^-) to an enamines, resulting in the formation of an α-acylated product.

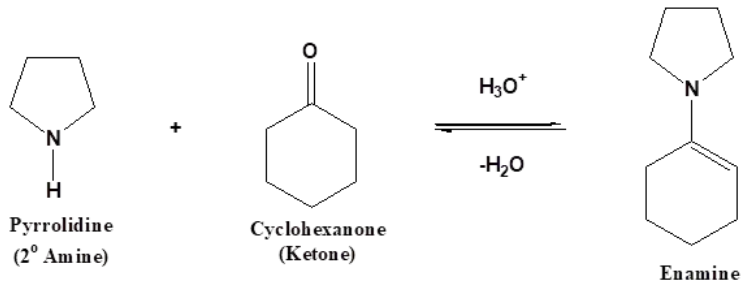


Example of an acylation of of an enamine.

MECHANISM ON ENAMINE ACYLATION

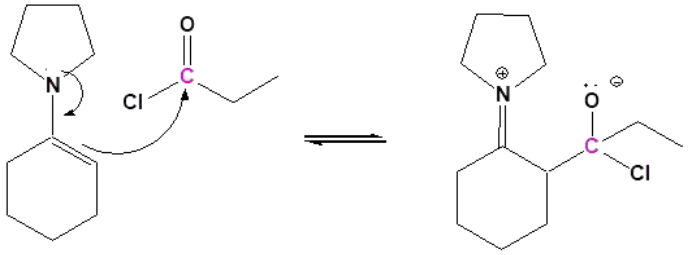
STEP 1 FORMATION OF THE ENAMINE

The mechanism starts with the formation of an enamine.



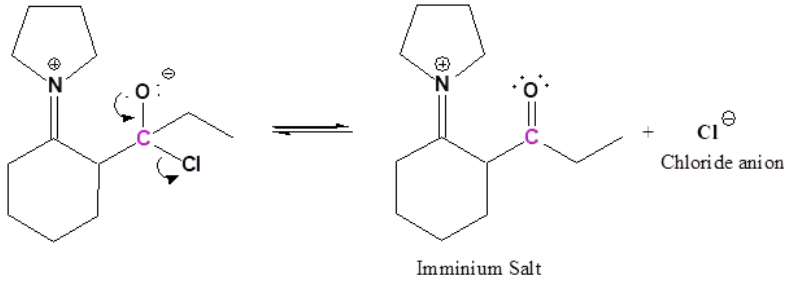
STEP 2: NUCLEOPHILIC ATTACK

The enamine adds to the electrophilic carbonyl carbon of the acid halide to form an iminium bond with tetrahedral alkoxide as an intermediate.



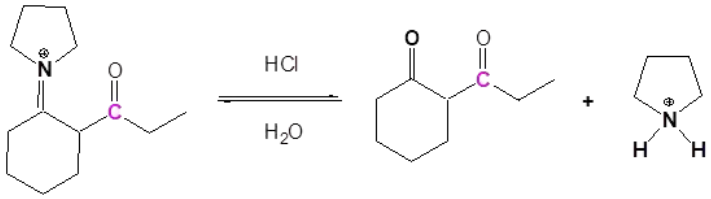
STEP 3: LEAVING GROUP REMOVAL

The alkoxide reforms the carbonyl bond and eliminate a halide anion as a leaving group.



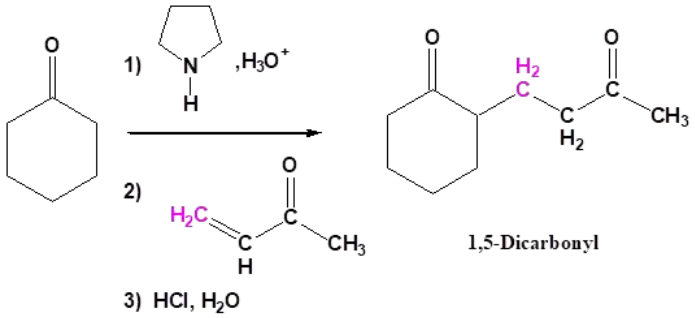
STEP 4: REFORM THE CARBONYL BY HYDROLYSIS

The iminium bond is then hydrolyzed to reform the carbonyl to create a 1,3-dicarbonyl compound as the product of a nucleophilic acyl substitution.



MICHAEL REACTION USING ENAMINES: THE STORK REACTION

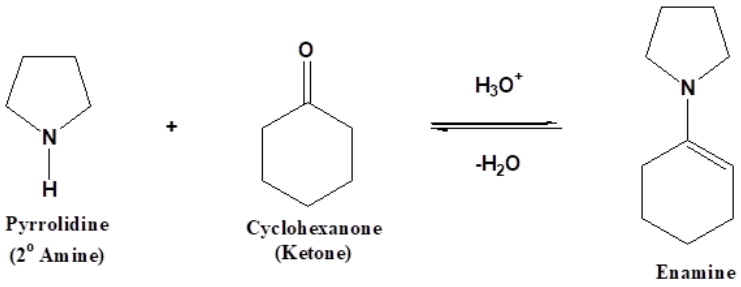
Enamines add to α, β-unsaturated carbonyls in a Michael-like reaction. The net reaction is the addition of a ketone to a α, β-unsaturated carbonyl to product a 1,5 dicarbonyl compound as the end product. This reaction is commonly known as the Stork enamine reaction after Gilbert Stork of Columbia University who originated the work.



Example of a The Stork Reaction

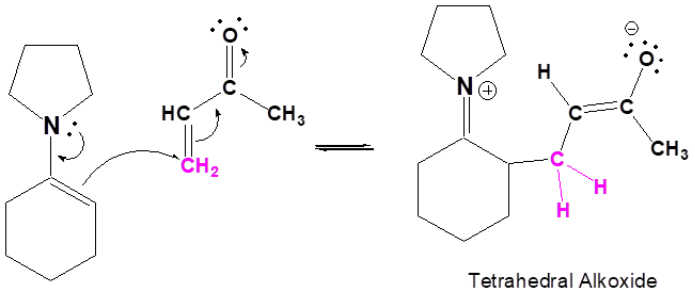
MECHANISM OF THE STORK REACTION

STEP 1: FORMATION OF THE ENAMINE



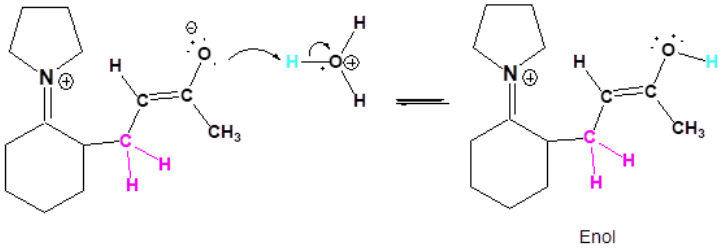
STEP 2: NUCLEOPHILIC ATTACK ON THE CARBON B TO THE CARBONYL

After formation, the enamine adds to the electrophilic alkene carbon of the a α, β-unsaturated carbonyl form an iminium bond. The pi electrons of the alkene are pushed onto the oxygen through conjugation to form an alkoxide as an intermediate.



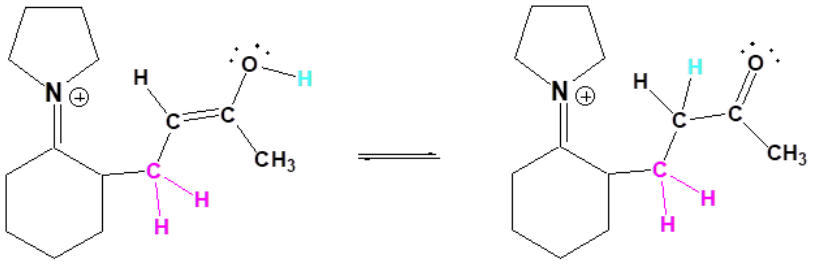
STEP 3: PROTONATION

Protonation of the alkoxide forms an enol.



STEP 4: TAUTOMERIZATION

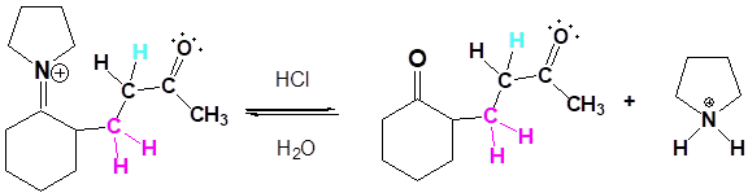
The enol undergoes tautomerization to reform the ketone.



Conjugate Additon Product

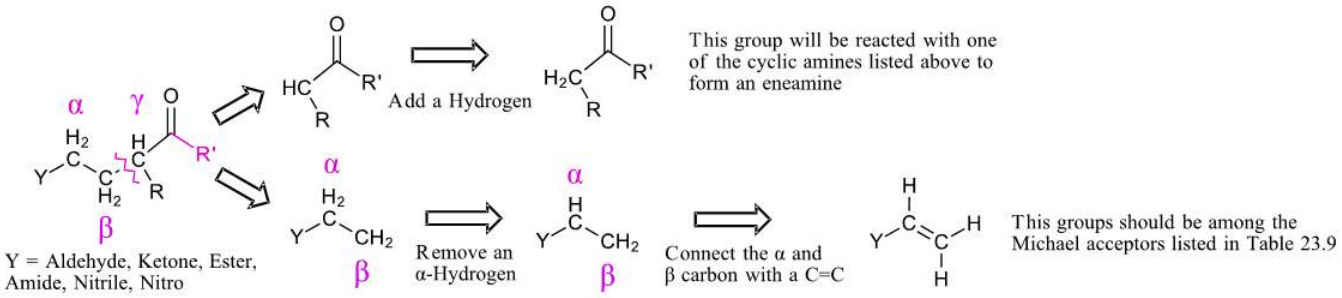
STEP 4: REFORM THE CARBONYL BY HYDROLYSIS

In the last step of the mechanism, the iminium bond is hydrolyzed to reform the carbonyl to create a 1,5-dicarbonyl compound as the product of a Michael-like reaction.



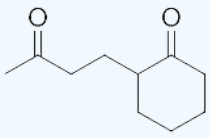
PLANNING A SYNTHESIS USING THE STORK ENAMINE SYNTHESIS

Planning a synthesis using a Stork enamine reaction is very similar to that of a Michael reaction (Section 23-10). A target molecule can possibly be made using a Stork enamine reaction if it contains a 1,5-dicarbonyl. Like the Michael reaction, the key bond cleavage is a C-C bond between beta and gamma carbons from a carbonyl-like group. The fragment with the Y group loses an alpha-hydrogen and then forms a C=C bond between the alpha and beta carbon. The carbon of the other fragment gains a hydrogen. This fragment should possess an acidic alpha-hydrogen and should be made up of Michael donor fragments.



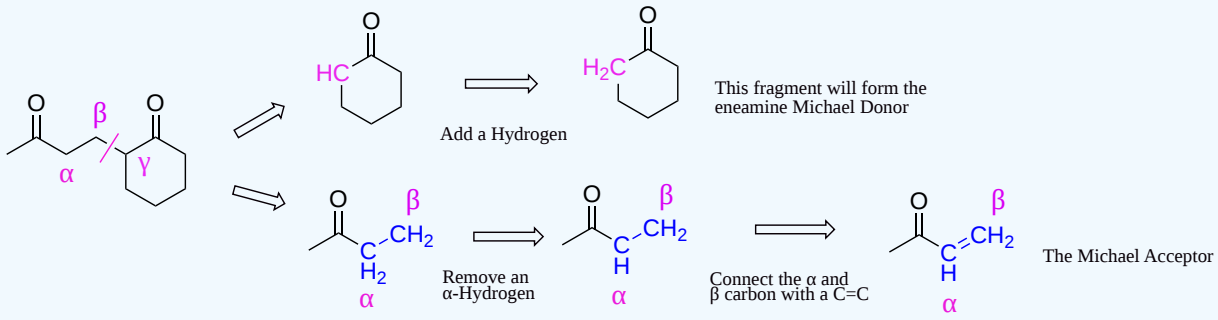
? WORKED EXAMPLE

How could the following molecule be made using a Michael Reaction?

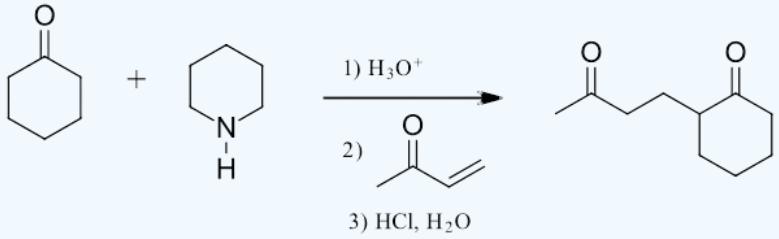


Answer

Pathway 1



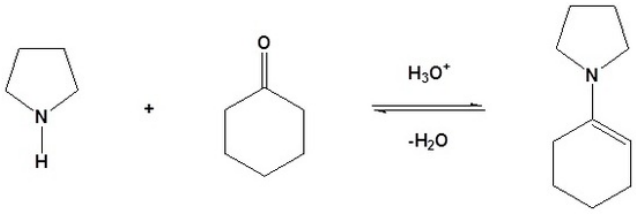
Solution



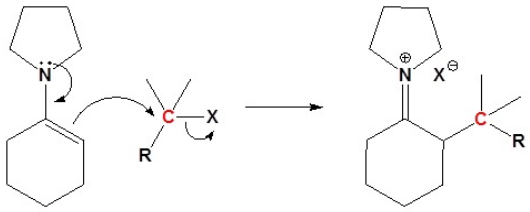
ALKYLATION OF AN ENAMINE

Enamines undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl. The individual steps are below.

STEP 1: FORMATION OF AN ENAMINE

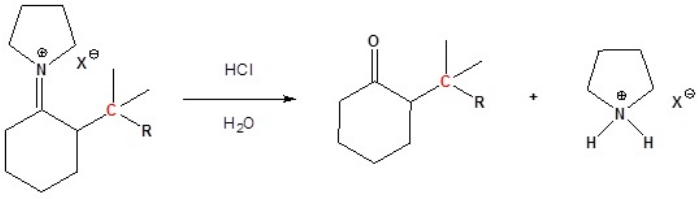


STEP 2: S_N2 ALKYLATION

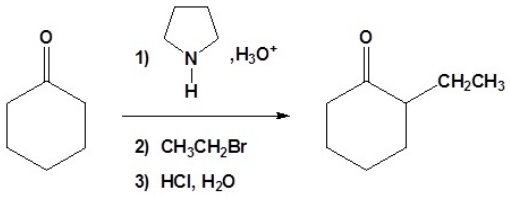


Iminium Salt

STEP 3: REFORM THE CARBONYL BY HYDROLYSIS

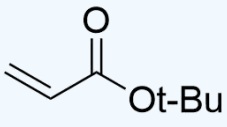


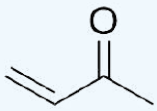
All three steps together:

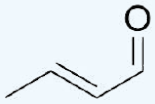


EXERCISE 23.11.1

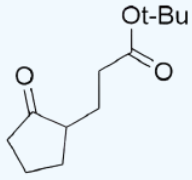
Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

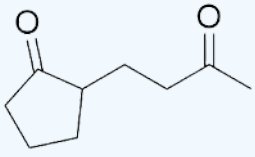
a. 

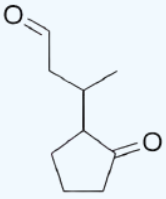
b. 

c. 

Answer

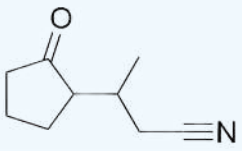
a. 

b. 

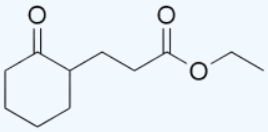
c. 

EXERCISE 23.11.2

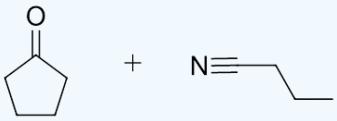
What would be the starting materials necessary to make the following molecules during a Stork enamine reaction.

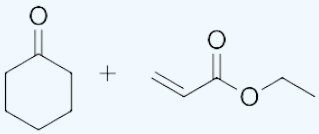
1. 

https://chem.libretexts.org/@go/page/36433

2. 

Answers

a. 

b. 

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23.12: THE ROBINSON ANNULATION REACTION

OBJECTIVES

After completing this section, you should be able to

1. write an equation to illustrate the Robinson annulation reaction.
2. identify the cyclic product formed when a 1,5-diketone is treated with base.
3. identify the carbonyl compounds and any other reagents needed to synthesize a given cyclic compound by a series of reactions, one of which is a Robinson annulation.

KEY TERMS

- Robinson annulation reaction

STUDY NOTES

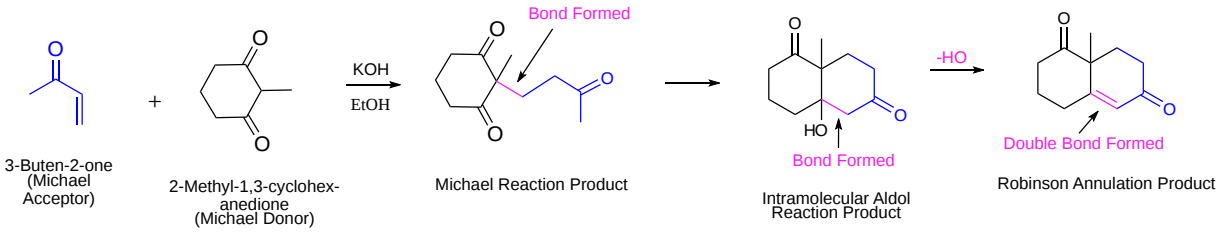
The building of an alicyclic compound from acyclic starting materials can present an interesting challenge to the synthetic organic chemist. One route by which such a synthesis can be achieved is through the use of the Robinson annulation reaction. This reaction, which may at first look very complex, can be readily understood once you realize that it simply involves a Michael reaction followed by an intramolecular aldol condensation. Both of these steps involve attack by enolate anions.

As in some of the other syntheses that you have studied, when you are simply given the structure of a compound and asked how it could have been prepared, it can be difficult to recognize which reactions might have been used. In this instance, keep in mind that you have studied relatively few reactions which have resulted in the formation of an alicyclic compound. Thus, when asked how such a compound might be prepared, you should keep the possibility of using a Robinson annulation reaction in mind.

THE ROBINSON ANNULATION

Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for ring annulus. The reaction is named after English chemist Sir Robert Robinson (1886-1975) who developed it. He received the Nobel prize in chemistry in 1947. Remember that during annulations five and six membered rings are preferred.

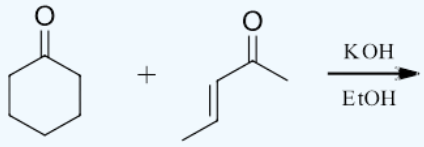
The nucleophilic enolate donor is typically an enolate ion or enamine of a cyclic ketone, β-keto ester or β-diketone. The electrophilic acceptor is usually an α, β-unsaturated ketone. In the example below, 2-methyl-1,3-cyclohexanedione is deprotonated to form an enolate which affects a Michael reaction addition on 3-buten-2-one forming a C-C bond. The product contains a 1,5-diketone fragment which can undergo an intramolecular aldol condensation. This occurs through creation of a new enolate at the methyl ketone which undergoes an intramolecular aldol reaction. A new C-C bond is formed to one of the ring carbonyls, creating a new six-membered ring. In the last step, the resulting alcohol is eliminated to form a α, β-unsaturated ketone as the final Robinson annulation product. Because the Robinson Annulation involves an aldol reaction, a full equivalent of base is required.



Example

EXAMPLE

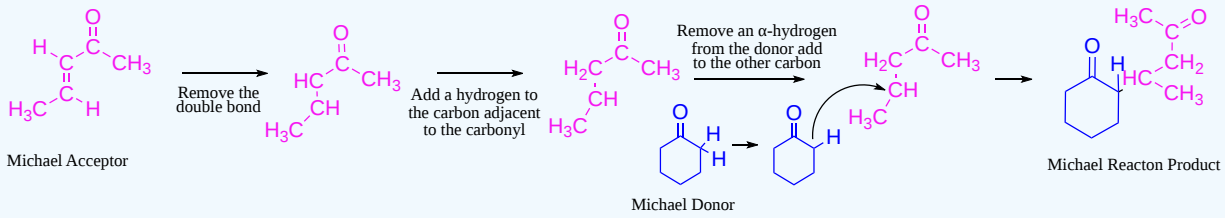
Draw the product of the following Robinson Annulation.



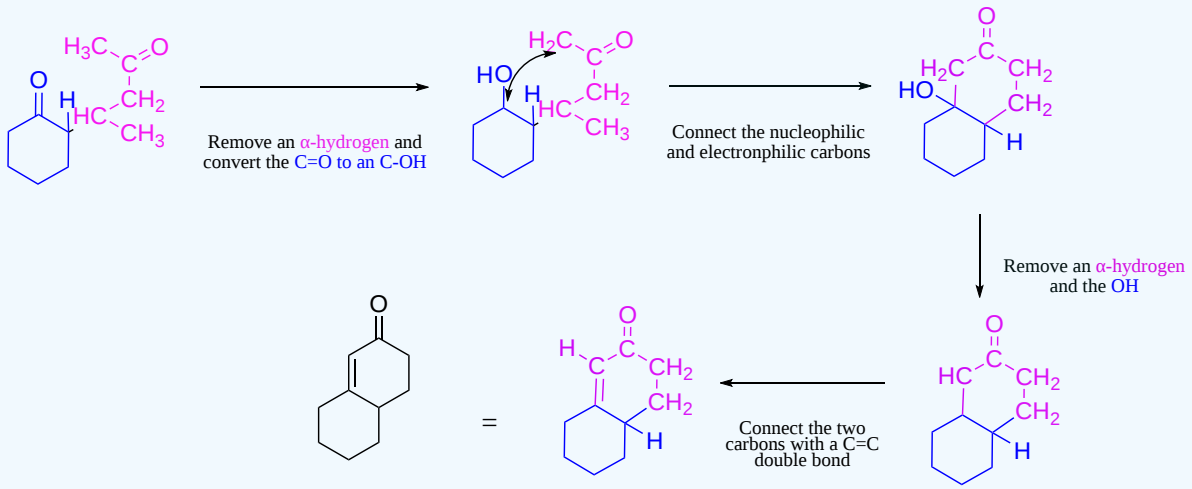
ANALYSIS

When considering the product of a Robinson annulation it is usually best to consider each reaction individually. Use the steps discussed in Section 23.10 to convert the starting materials into the product of a Michael reaction, then into the product of an intramolecular aldol condensation. If the starting materials are drawn in a skeletal structure it may be helpful to convert to a condensed formula to better keep track of carbons and hydrogens.

Formation of the Michael reaction product

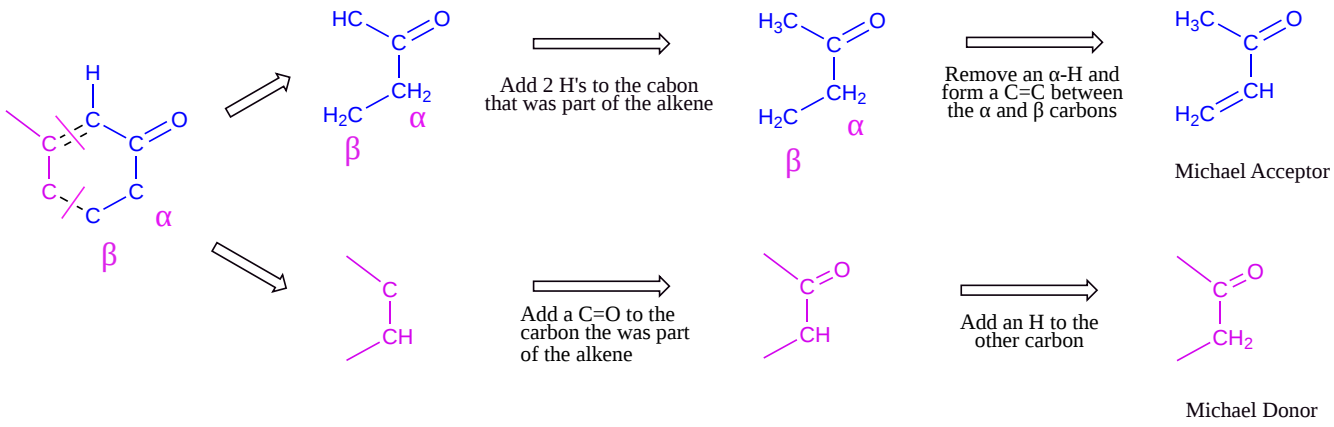


Formation of the intramolecular Aldol condensation product



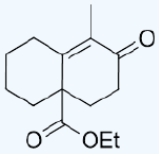
PLANNING A SYNTHESIS USING A ROBINSON ANNULATION

The presence of a cyclic, six-membered α, β-unsaturated ketone in a target molecule suggest that a Robinson Annulation may be utilized in its synthesis. The key bond cleavages are the C=C bond of the α, β-unsaturated ketone and the C-C bond between carbons in the a and g on the opposite alkyl chain of the ketone.

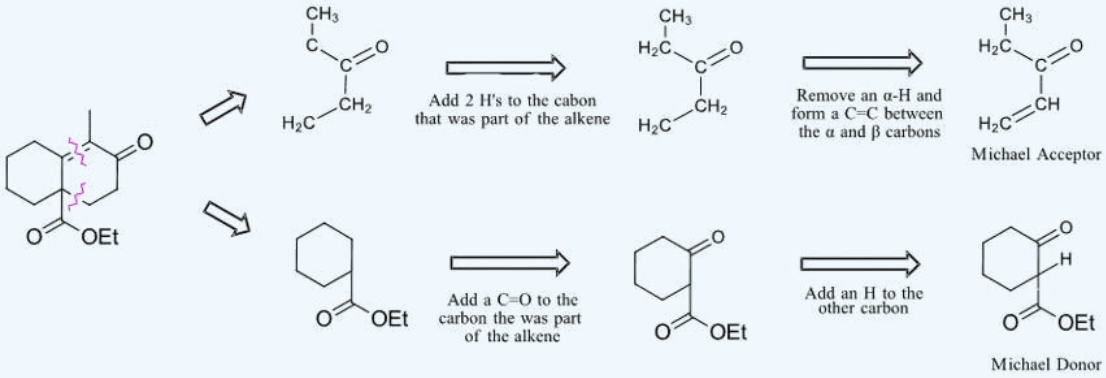


EXAMPLE

What would be the starting materials used if the following molecule was made using a Robinson annulation?

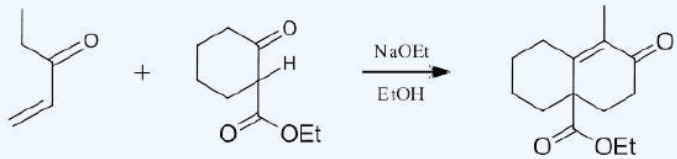


ANALYSIS



SOLUTION

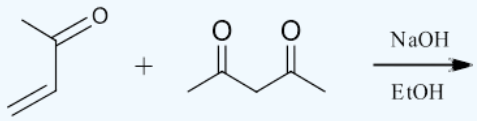
It is necessary to use sodium ethoxide as the reaction base due to the presence of an ester.



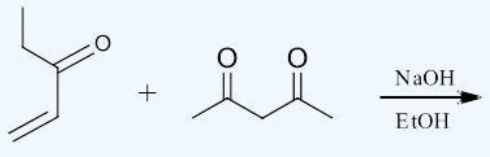
EXERCISE 23.12.1

Provide products of the following Robinson annulations.

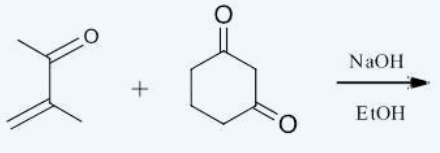
a.



b.

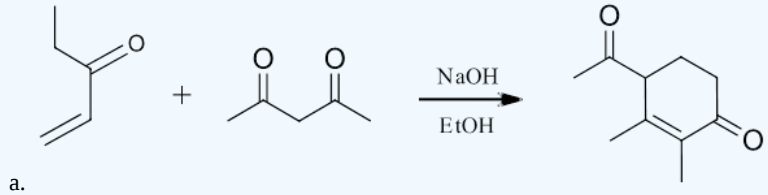


c.

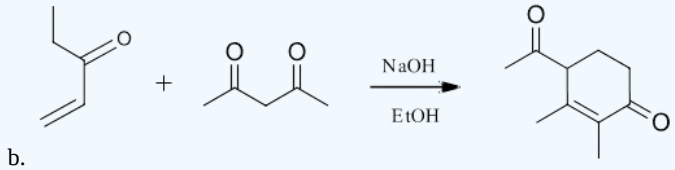


Answer

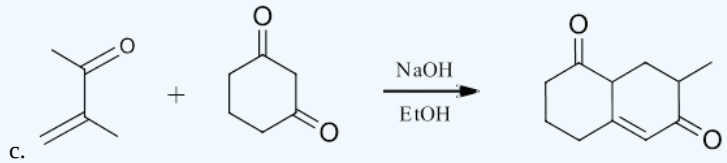
a.



b.

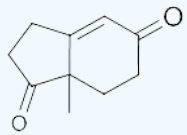


c.

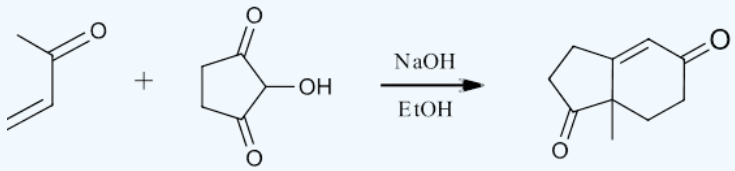


EXERCISE 23.12.2

What would be the starting materials required to make the following molecule using a Robinson annulation?



Answer



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23.13: SOME BIOLOGICAL CARBONYL CONDENSATION REACTIONS

OBJECTIVES

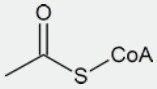
After completing this section, you should be able to

1. identify acetyl coenzyme A as an important biomolecule which undergoes carbonyl condensation reactions.
2. identify aldoases as enzymes that catalyze aldol reactions in biological systems.
3. identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

STUDY NOTES

Carbonyl condensation reactions occur in biological systems; for example, in the biosynthesis of citric acid.

You first met acetyl coenzyme A in Section 21.8. Again, we stress that it is not essential that you know the detailed structure of this compound (or other large biochemical stuctures discussed), but you should know that it may be represented as



and that it has the ability to behave just as any other acetyl-containing compound.

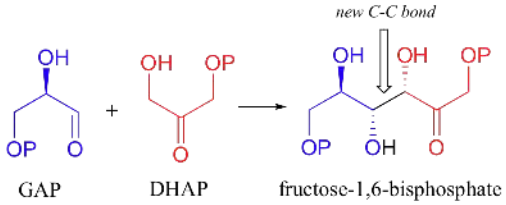
ALDOL REACTIONS IN NATURE

So far, we have examined the non-enzymatic reaction of an aldehyde or ketone with itself (a so-called 'self-condensation' reaction, where 'condensation' means the formation of one larger molecule from two smaller ones). However, aldol reactions occur in several biological pathways, most commonly in the metabolism of carbohydrates (sugars). The enzymes that catalyze aldol reactions are called, not surprisingly, '**aldolases**'. They occur in all organisms, but note that **Class I aldoases** are usually found in animals and higher plants, while **Class II aldoases** normally appear in bacteria and fungi.

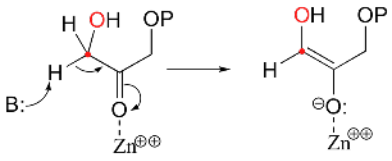
TYPICAL ALDOLASE REACTIONS - THREE VARIATIONS ON A THEME

The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion. Nature has evolved several distinct strategies to stabilize the intermediate that results. Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate, while others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

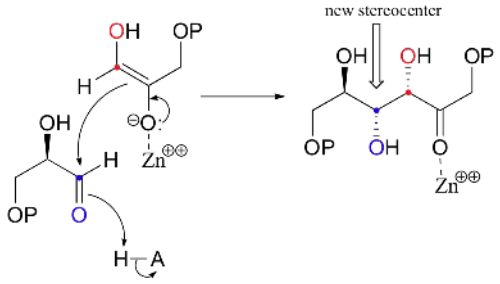
Let's examine first a reaction catalyzed by a so-called '**Class II' aldolase**, in which a metal cation - generally Zn^{2+} - bound in the active site serves to stabilize the negative charge on an enolate intermediate. Fructose 1,6-bisphosphate aldolase is an enzyme that participates in both the glycolytic (sugar burning) and gluconeogenesis (sugar building) biochemical pathways. For now, we will concentrate on its role in the gluconeogenesis pathway, but we will see it again later in its glycolytic role. The reaction catalyzed by fructose 1,6-bisphosphate aldolase is a condensation between two 3-carbon sugars, glyceraldehyde-3-phosphate (GAP) and dihydroxyacetone phosphate (DHAP), forming a six-carbon product (which leads, after three more enzymatic steps, to glucose).



In the first step of the condensation, an alpha-carbon on DHAP is deprotonated, leading to an enolate intermediate. The strategy used to stabilize this key intermediate is to coordinate the negatively-charged enolate oxygen to an enzyme-bound zinc cation.

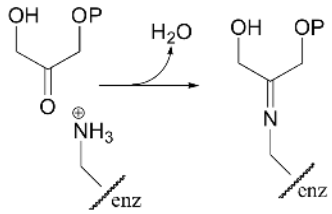


Next, the deprotonated a-carbon attacks the carbonyl carbon of GAP in a nucleophilic addition reaction, and protonation of the resulting alcohol leads directly to the fructose 1,6-bisphosphate product.

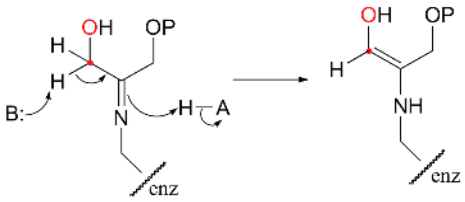


As with many other nucleophilic carbonyl addition reactions, a new stereocenter is created in this reaction, as a planar, achiral carbonyl group is converted to a tetrahedral, chiral alcohol. The enzyme-catalyzed reaction, not surprisingly, is completely stereospecific: the DHAP substrate is positioned in the active site so as to attack the *re* (front)face of the GAP carbonyl group, leading to the *R* configuration at the new stereocenter.

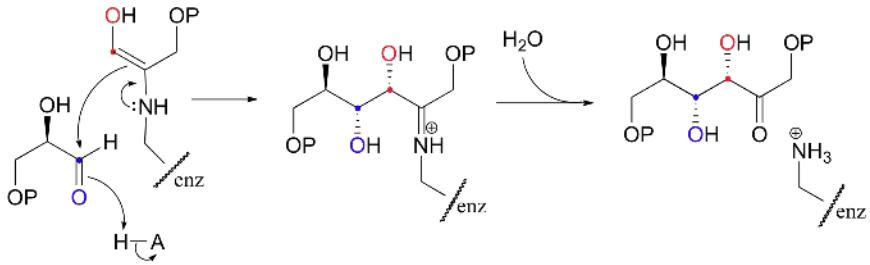
Interestingly, it appears that in bacteria, the fructose bisphosphate aldolase enzyme evolved separately from the corresponding enzyme in plants and animals. In plants and animals, the same aldol condensation reaction is carried out by a significantly different mechanism, in which the key intermediate is not a zinc-stabilized enolate but an enamine. The nucleophilic substrate (DHAP) is first linked to the enzyme through the formation of an imine (also known as a Schiff base) with a lysine residue in the active site.



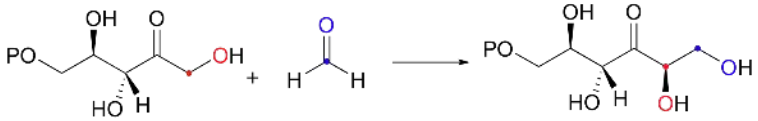
The alpha-proton is then abstracted by an active site base to form an enamine.



In the next step, the alpha-carbon attacks the carbonyl carbon of GAP, and the new carbon-carbon bond is formed. In order to release the product from the enzyme active site and free the enzyme to catalyze another reaction, the imine is hydrolyzed back to a ketone group.



There are many more examples of **'Class I' aldolase** reactions in which the key intermediate is a lysine-linked imine. Many bacteria are able to incorporate formaldehyde, a toxic compound, into carbohydrate metabolism by condensing it with ribulose monophosphate. The reaction proceeds through imine and enamine intermediates.



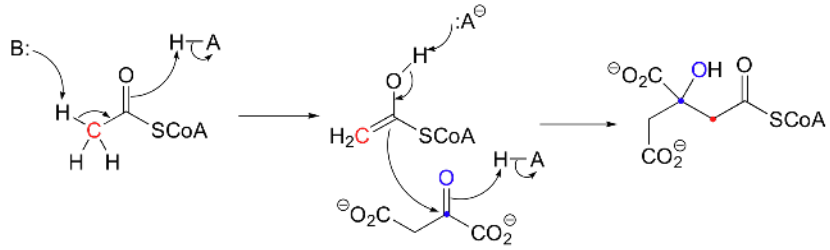
ribulose-5-phosphate formaldehyde hexulose-6-phosphate

EXAMPLE 23.13.1

a. Propose a complete mechanism for the condensation reaction shown above.
b. Propose a complete mechanism for the conversion of hexulose-6-phosphate (formed from the condensation of ribulose-5-phosphate and formaldehyde) into fructose-6-phosphate.

Solution

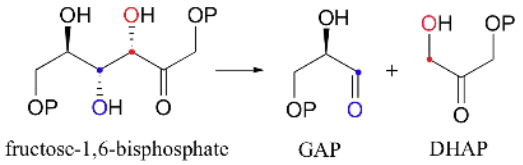
Along with aldehydes and ketones, esters and thioesters can act as the nucleophilic partner in aldol condensations. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA.



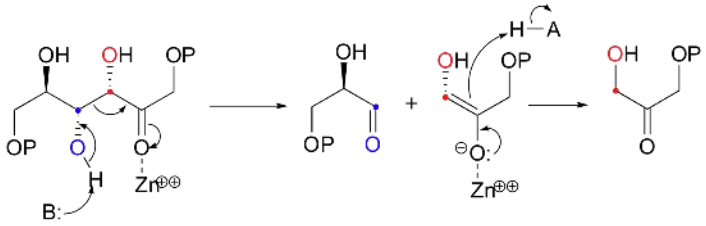
Notice that in this aldol reaction, the nucleophilic intermediate is stabilized by protonation, rather than by formation of an imine (as in the Class I aldolases) or by a metal ion (as in the Class II aldolases).

GOING BACKWARDS: THE RETROALDOL REACTION

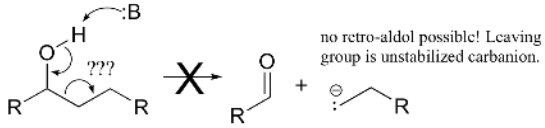
Although aldol reactions play a very important role in the formation of new carbon-carbon bonds in metabolic pathways, it is important to emphasize that they are also highly reversible: in most cases, the energy level of starting compounds and products are very close. This means that, depending on metabolic conditions, aldolases can also catalyze **retro-aldol** reactions (the reverse of aldol condensations, in which carbon-carbon bonds are *broken*). Recall that fructose 1,6-bisphosphate aldolase (section 13.3B) is active in the direction of sugar breakdown (glycolysis) as well as sugar synthesis (gluconeogenesis). In the glycolytic direction, the enzyme catalyzes - either by zinc cation or by imine/enamine mechanisms, depending on the organism - the retro-aldol cleavage of fructose bisphosphate into DHAP and GAP.



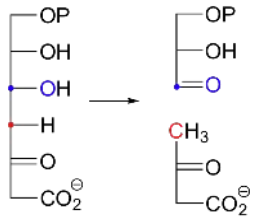
The mechanism is the exact reverse of the condensation reaction. Shown below is the mechanism for a Zn^{2+} - dependent (Type II) retroaldol cleavage. Notice that in the retroaldol reaction, the enolate intermediate is the *leaving group*, rather than the nucleophile.



The key thing to keep in mind when looking for a possible retro-aldol mechanism is that, when the carbon-carbon bond breaks, the electrons must have some place to go, where they will be stabilized by resonance. Generally, this means that there *must* be a carbonyl or imine group on the next carbon. If there is no adjacent carbonyl or imine group, the carbon-carbon bond is not free to break.



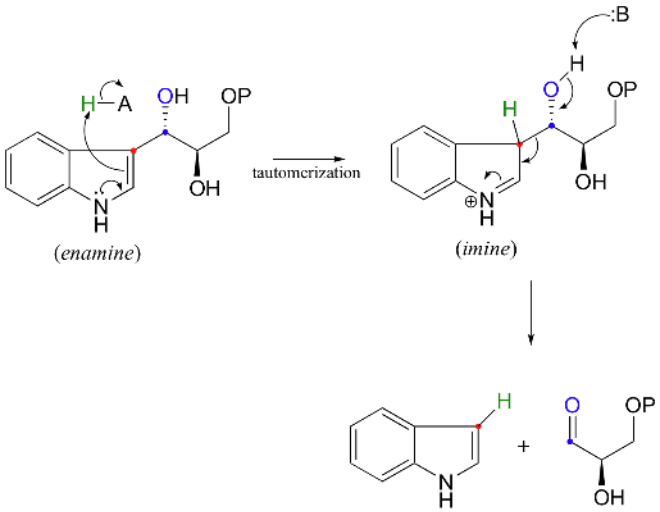
Here are two more examples of retro-aldol reactions. Bacterial carbohydrate metabolism involves this reversible, class I retro-aldol cleavage: (*Proc. Natl. Acad. Sci* **2001**, *98*, 3679).



EXAMPLE 23.13.2

Draw the structure of the enamine intermediate in the retroaldol reaction shown above.

Another interesting example is the retro-aldol cleavage of indole-3-glycerol phosphate, a step in the biosynthesis of tryptophan.



Look carefully at this reaction - how is the leaving group stabilized? There is an imine group involved, but no participation by an enzymatic lysine. The imine is 'built into' the starting compound, available from the initial tautomerization of the cyclic enamine group in indole-3-glycerol phosphate.

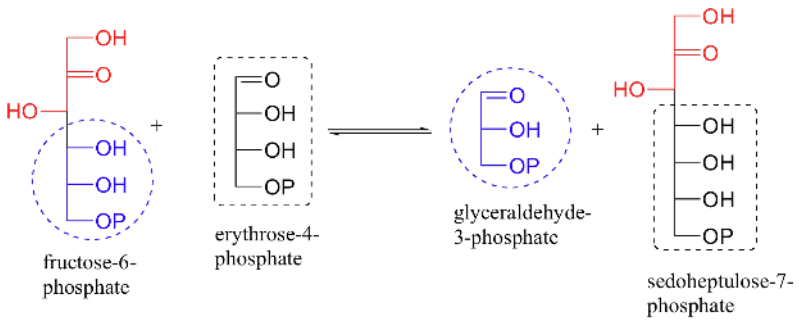
EXAMPLE 23.13.3

Draw the reverse (aldol condensation) direction of the reaction above.

Solution

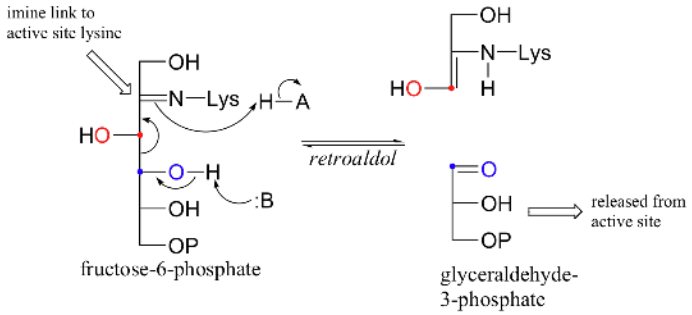
GOING BOTH WAYS: TRANSALDOLASE

An enzyme called transaldolase, which is part of the 'pentose phosphate pathway' of carbohydrate metabolism, catalyzes an interesting combination of class I aldol and retro-aldol reactions. The overall reaction, which can proceed in either direction depending on metabolic requirements, converts 3- and 7-carbon sugars into 6- and 4-carbon sugars. Essentially, a 3-carbon unit breaks off from a ketone sugar (ketose) and then is condensed directly with an aldehyde sugar (aldose).

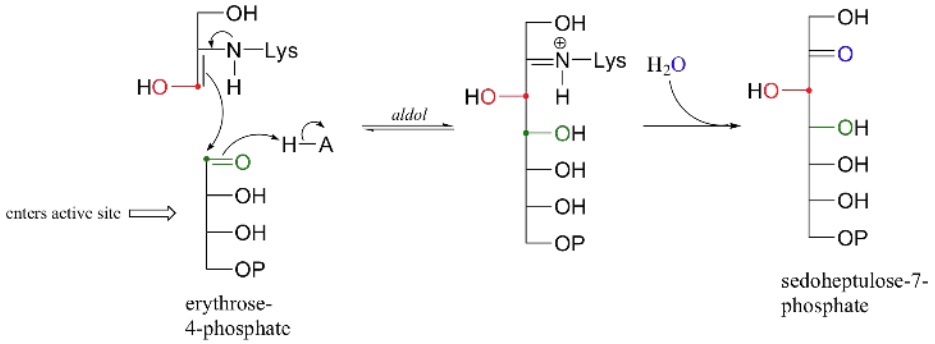


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Let's follow the progress of the reaction in the left-to-right direction as depicted above. Because this is a class I aldolase, the first step is the formation of an imine linkage between the ketone carbon of fructose-6-phosphate (F6P) and a lysine group from the enzyme. The enzyme-substrate adduct then undergoes a retro-aldol step to free glyceralde-3-phosphate (GAP), which leaves the active site.



The second substrate, erythrose 4-phosphate (E4P), enters the active site, and an aldol condensation occurs between E4P and the 3-carbon fragment remaining from the cleavage of fructose-6-phosphate.



The final step is hydrolysis of the imine and subsequent dissociation of sedoheptulose 7-phosphate from the active site.

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23.S: CARBONYL CONDENSATION REACTIONS (SUMMARY)

CONCEPTS & VOCABULARY

- Design multi-step syntheses in which the reactions introduced in this unit are used in conjunction with any of the reactions described in previous units.
- Solve road-map problems that require a knowledge of carbonyl condensation reactions.
- Define, and use in context, any of the key terms introduced.

23.1 Carbonyl Condensations - The Aldol Reaction

- A carbon-carbon bond forming reaction at the alpha carbon through an enolate nucleophile.
- The Aldol Reaction proceeds by first making an enolate nucelophile on an aldehyde (or ketone).
- The enolate nucleophile then dimerizes by attacking the carbonyl of the same aldehyde (or ketone).
- The final product is a beta-hydroxy aldehyde (or ketone).

23.2 Carbonyl Condensations versus Alpha Substitutions

- Carbonyl condensation reactions are a type of alpha substitution reaction.
- Both involve an enolate nucleophile and end with an alpha substitution product.
- In carbonyl condensations, the electrophile is another carbonyl compound.
- Carbonyl condensations are reversible and use a catalytic amount of base.
- The electrophile is already present in the reaction as the enolate is formed in carbonyl condensations.
- Alpha substitution reactions are more directional by design, since a full equivalent of base is used to generate the enolate.
- The electrophile is introduced after the enolate is generated.

23.3 Dehydration of Aldol Products - Synthesis of Enones

- The aldol reaction can undergo a dehydration (loss of water) to yield an α,β-unsaturated aldehyde or ketone.
- The additional stability provided by the conjugated carbonyl system makes some of the products thermodynamically driven.
- The of small products, such as water in this case, are termed condensations, so this reaction is aldol condesation.
- Heat promotes the condensation reactions.
- Under basic conditions, the β-elimination occurs through an E1cb mechanism.
- Under acidic conditions, the β-elimination occurs through an E1 or E2 mechanism.

23.4 Using Aldol Reactions in Synthesis

- If the target contains a β-hydroxy carbonyl compound or an α,β-unsaturated carbonyl compound, then synthetically think aldol reaction or condensation.
- To reverse the aldol condensation, break the enone at the double bond.
- To reverse the aldol reaction, break the C-C bond between the alpha carbon and the carbon attached to the hydroxy group.

23.5 Mixed Aldol Reactions

- Aldol condensations between different reactants are called mixed or crossed Claisen reactions.
- Multiple products are possible, so the success of the mixed aldol reactions depends on two things:
  - The electrophile (or acceptor) is an aldehyde.
  - The aldehyde acceptor has no alpha protons.
- Mixed aldols in which both reactants can serve as donors and acceptors generally give complex mixtures of both dimeric (homo) aldols and crossed aldols.
- The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the Claisen-Schmidt reaction.

23.6 Intramolecular Aldol Reactions

- Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction.
- In these intramolecular reactions, two sets of α-hydrogens need to be considered and most ring forming reaction five and six membered rings are preferred.

23.7 The Claisen Condensation Reaction

- Esters can contain α hydrogens, so can undergo a condensation reaction similar to the aldol reaction called a Claisen Condensation.
- One ester reacts as a nucleophile while the other reacts as an electrophile.
- A new C-C bond is formed in the reaction to form a β-keto ester product.

- An alkoxide that matches the ester group is used to help prevent side reactions in the Claisen Condensation.
- There is a thermodynamic driving step forming an enolate, which is followed by a protonation to obtain the neutral product.

23.8 Mixed Claisen Condensation Reactions

- Claisen condensations between different ester reactants are called Crossed Claisen reactions.
- Crossed Claisen reactions in which both reactants can serve as donors and acceptors generally give complex mixtures.
- Because of this most Crossed Claisen reactions are usually not performed unless one reactant has no alpha hydrogens.

23.9 Intramolecular Claisen Condensation Reactions - The Dieckmann Cyclization

- A diester can undergo an intramolecular reaction called a Dieckmann condensation.

23.10 Conjugate Carbonyl Additions - The Michael Reaction

- In 1,4 additions the nucleophile is added to the carbon β to the carbonyl while the hydrogen is added to the carbon α to the carbonyl.
- Enolates undergo 1,4 addition to α, β-unsaturated carbonyl compounds (product of the Aldol condensation) is a process called a Michael addition.
- A new C-C bond is formed between an enolate and the 4-C of the α, β-unsaturated carbonyl compound.
- The product is a 1,5-dicarbonyl species.

23.11 Carbonyl Condensations with Enamines - The Stork Reaction

- Aldehydes and ketones react with 2° amines to reversibly form enamines.
- Enamines act as nucleophiles similar to enolates.
- This process requires a three steps:
  - Formation of the enamine
  - Reaction with an eletrophile to form an iminium salt
  - Hydrolysis of the iminium salt to reform the aldehyde or ketone
- Advantages of using an enamine over an enolate
  - Neutral
  - Easier to prepare
  - Prevent overreaction issue that occurs when using enolates.
- Enamines undergo an S_N2 reaction with alkyl halides to yield the iminium salt.
- Enamines can react with acid halides to form β-dicarbonyls.
- Enamines can also be used as a nucleophile in a Michael reaction.

23.12 The Robinson Annulation Reaction

- Forms a cyclic product from acyclic starting materials by first creating a new C-C bond followed by ring formation.
- The Robinson Annulation reaction starts with a Michael reaction followed by an intramolecular Aldol condensation.
- The formation of 5 or 6 membered rings is preferred.

23.13 Some Biological Carbonyl Condensation Reactions

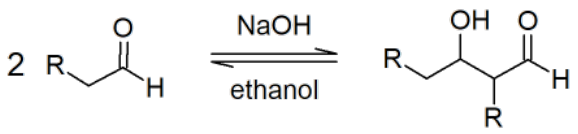
- Aldol reactions occur in several biological pathways.
- Enzymes that catalyze aldol reactions are called, not surprisingly, 'aldolases'.
- The first step in an aldolase reaction is the deprotonation of an alpha-carbon to generate a nucleophilic carbanion.
- Nature has evolved several distinct strategies to stabilize the intermediate that results.
  - Some aldolases use a metal ion to stabilize the negative charge on an enolate intermediate.
  - Others catalyze reactions that proceed through neutral Schiff base or enol intermediates.

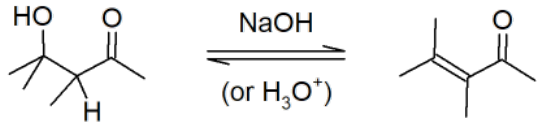
SKILLS TO MASTER

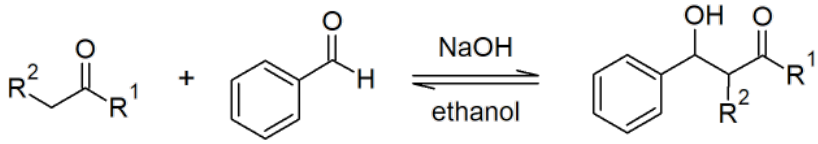
- Skill 23.1 Identify the product of an aldol reaction.
- Skill 23.2 Write the detailed mechanism for the aldol reaction.
- Skill 23.3 Describe the difference between a carbonyl condensation reaction and an alpha-substitution reaction.
- Skill 23.4 Know what an enone is.
- Skill 23.5 Write a detailed mechanism for the aldol condensation under basic conditions.
- Skill 23.6 Write a detailed mechanism for the aldol condensation under acidic conditions.
- Skill 23.7 Determine the products of an aldol condensation reaction.
- Skill 23.8 Provide the reactants for a target aldol condensation product.

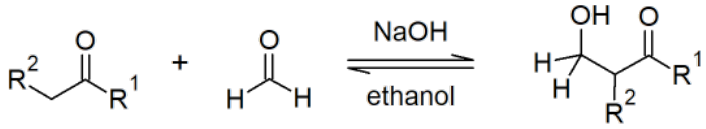
- Skill 23.9 Write an equation to illustrate a mixed aldol reaction.
- Skill 23.10 Identify the structural features necessary to ensure that two carbonyl compounds will react together in a mixed aldol reaction to give a single product rather than a mixture of products.
- Skill 23.11 Determine whether a given mixed aldol reaction is likely to produce a single product or a mixture of products.
- Skill 23.12 Identify the carbonyl compounds needed to produce a given enone or β-hydroxy aldehyde or ketone by a mixed aldol reaction.
- Skill 23.13 Write a detailed mechanism for the intramolecular aldol condensation.
- Skill 23.14 Write an equation to illustrate a Claisen condensation reaction.
- Skill 23.15 Write a detailed mechanism for a Claisen condensation reaction or its reverse.
- Skill 23.16 Identify the ester and other reagents needed to form a given β-keto ester by a Claisen condensation reaction.
- Skill 23.17 Write an equation to illustrate a mixed Claisen condensation.
- Skill 23.18 Identify the structural features that should be present in the two esters if a mixed Claisen condensation is to be successful.
- Skill 23.19 Identify the product formed when a given pair of esters is used in a mixed Claisen condensation.
- Skill 23.20 Identify the esters that should be used to produce a given β-keto ester by a mixed Claisen condensation.
- Skill 23.21 Write detailed mechanisms for mixed Claisen condensation.
- Skill 23.22 Write a detailed mechanism for an intramolecular Claisen condensation.
- Skill 23.23 Write a detailed mechanism for a given typical Michael reaction.
- Skill 23.24 Identify the product formed in a given Michael reaction.
- Skill 23.25 Identify the reagents necessary to synthesize a given compound by a Michael reaction.
- Skill 23.26 Write a detailed mechanism for each of the three steps of the Stork enamine reaction.
- Skill 23.27 Identify the reagents needed to synthesize a given compound by a Stork enamine reaction.
- Skill 23.28 Write a detailed mechanism for the Robinson Annulation reaction.
- Skill 23.29 Identify the product from an enone and an dicarbonyl under basic conditions.
- Skill 23.30 Identify the steps in which a carbonyl condensation reaction has occurred, given a general outline of a specific biosynthesis.

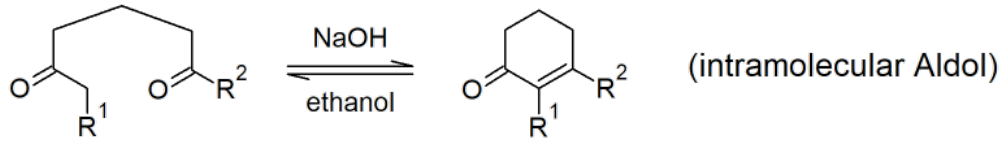
SUMMARY OF REACTIONS

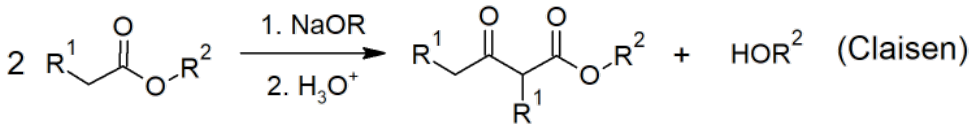


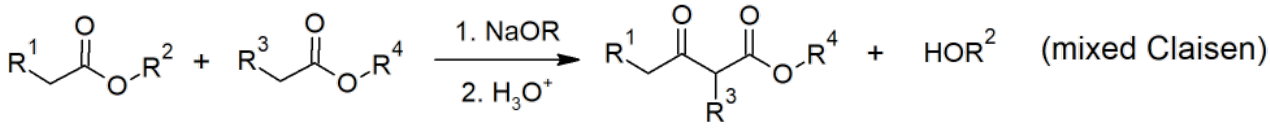




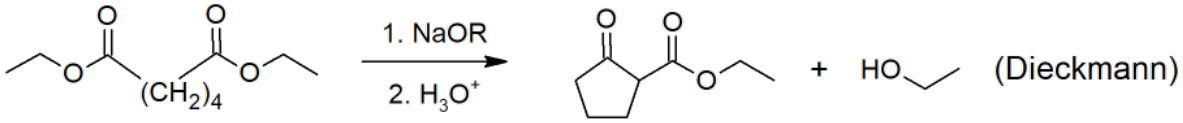


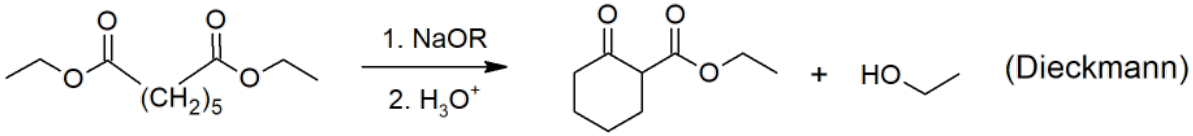


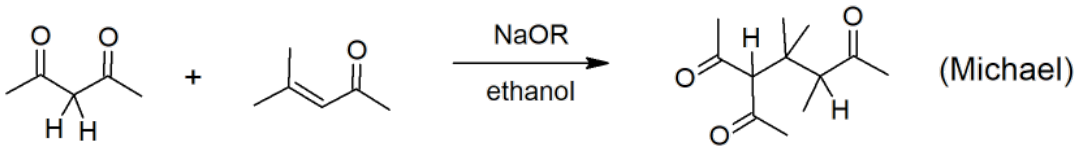




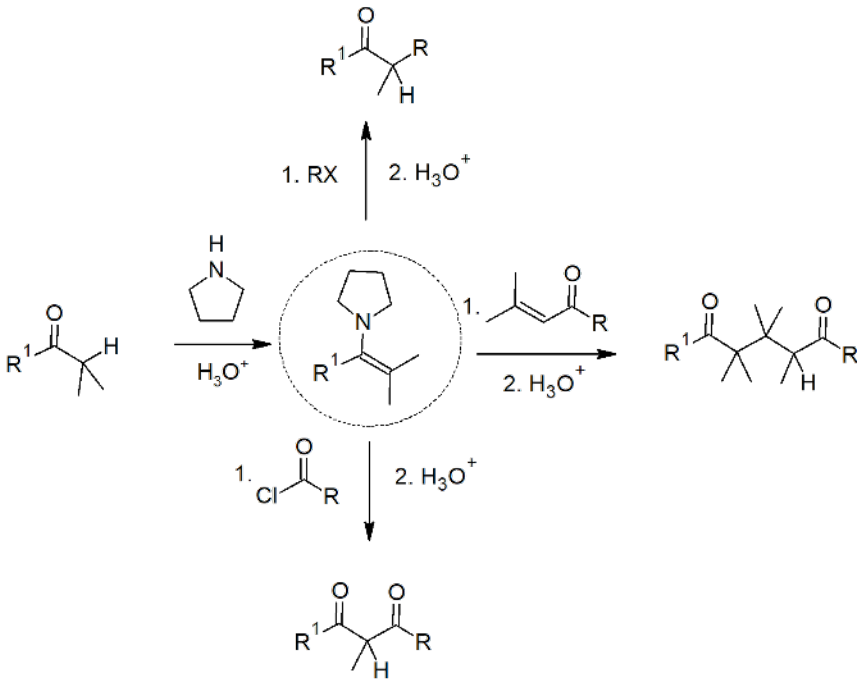
https://chem.libretexts.org/@go/page/207030







Stork Enamine Reactions



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CHAPTER OVERVIEW

24: AMINES AND HETEROCYCLES

LEARNING OBJECTIVES

When you have completed Chapter 24, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis that involves the use of any of the reactions described in this unit, and any of the reactions described in any previous unit.
3. solve road-map problems that require a knowledge of amine chemistry in addition to any of the chemistry discussed in previous units.
4. define, and use in context, the key terms introduced.

Amines are the first nitrogen-containing compounds that we study in detail in this course. We begin the chapter with an explanation of the differences in structure among primary, secondary and tertiary amines. We explain the nomenclature of aliphatic and arylamines, and examine the structure and bonding of these compounds, relating these features to their physical properties and basicity. We describe the use of amines to resolve racemic mixtures of chiral carboxylic acids.

Amines may be prepared by a number of different synthetic methods. We describe each of these methods and assess the relative merits of each. After a description of the reactions of aliphatic amines, we devote sections to a discussion of the use of tetraalkylammonium salts as phase-transfer agents. The chapter concludes with a summary of the spectroscopic properties of amines.

24.0: Chapter Objectives
24.1: Naming Amines
24.2: Structure and Properties of Amines
24.3: Basicity of Amines
24.4: Basicity of Arylamines
24.5: Biological Amines and the Henderson-Hasselbalch Equation
24.6: Synthesis of Amines
24.7: Reactions of Amines
24.8: Reactions of Arylamines
24.9: Heterocyclic Amines
24.10: Spectroscopy of Amines
24.S: Amines and Heterocycles (Summary)

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24.0: CHAPTER OBJECTIVES

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24.1: NAMING AMINES

OBJECTIVES

After completing this section, you should be able to

1. classify a given amine as being primary, secondary or tertiary.
2. explain, briefly, the difference in meaning of the terms primary, secondary and tertiary when they are applied to the structures of amines and alcohols.
3. determine whether a given structure represents a quaternary ammonium cation.
4. provide an acceptable IUPAC name for an amine, given its Kekulé, condensed or shorthand structure.
5. draw the structure of an amine, given its IUPAC name.
6. give the name and structure of one typical heterocyclic amine (e.g., pyridine).

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- amine
- primary amine
- secondary amine
- quaternary ammonium cation
- tertiary amine

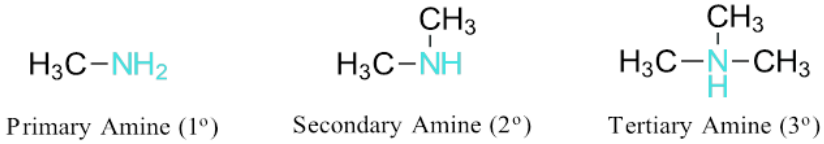
STUDY NOTES

You should recognize that heterocyclic amines—compounds in which the nitrogen atom occurs as part of a ring—are very common in organic chemistry. Be prepared to meet such compounds throughout this, and subsequent chapters, but do not try to memorize all of the names and structures givenin the reading. You should, however, commit the structures of pyridine and pyrrole to memory.

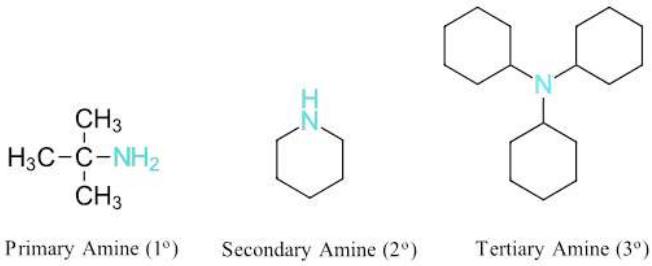
CLASSIFICATION OF AMINES

Amines are made up of an sp^3 hybridized nitrogen and are either alkyl substituted (alkylamines) or aryl substituted (arylamines).

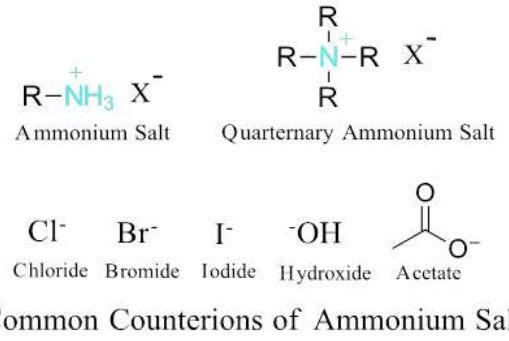
Amines are classified as primary, secondary, or tertiary based on the number or organic substituents directly attached to the nitrogen. An amine attached to one substituent is primary (1°), two substituents is secondary (2°), and three substituents is tertiary (3°).



EXAMPLE



Amines attached to 4 substituents and at least one substituent is a hydrogen are called ammonium salts. Amines attached to 4 alkyl substituents are called quaternary ammonium salts. The nitrogen in ammonium salts lacks lone pair electrons and carries a formal positive charge. Ammonium salts are also require a negatively charged counter-ion which can vary in composition.

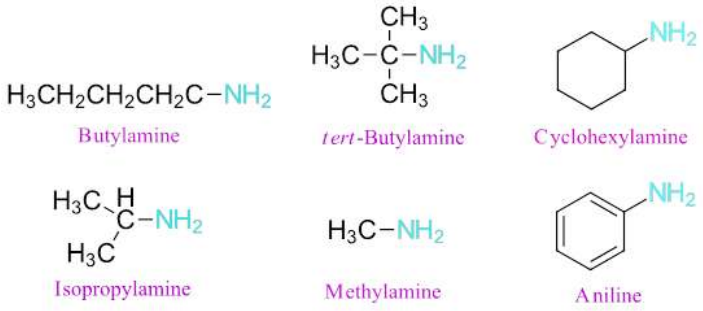


Common Counterions of Ammonium Salts

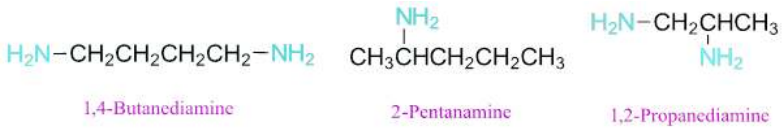
NOMENCLATURE OF AMINES

NOMENCLATURE OF PRIMARY AMINES

Primary amines are named in two main ways using the IUPAC system. They can either be named as alkylamines or as alkanamines. Most 1° amines which are attached to linear alkanes, cycloalkanes, and alkyl groups with common names (Section 3.3), tend to be named as alkylamines. The alkyl groups is named as a substituent (**prefix + yl**) then the suffix -amine is added. Many amines have common names that are used by IUPAC, for example the primary arylamine ($C_6H_5NH_2$) is called aniline.



Other primary amines tend to be named as alkanamines. The alkyl group is named as an alkane (**prefix+ane**) and –e ending is replaced with the suffix **-amine**. The –e ending is not removed for diamines.



NOMENCLATURE OF SYMMETRICAL SECONDARY AND TERTIARY AMINES

Symmetrical 2° and 3° amines (where all substituents are identical) are named as alkylamines and the prefix di- or tri -added to indicate the number of substituents.



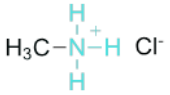
NOMENCLATURE OF UNSYMMETRICAL SECONDARY AND TERTIARY AMINES

Unsymmetrical 2° and 3° amines are named with the largest chain being the base chain (**prefix+yl+amine**). The other alkyl groups are named as N-substituents. This notation is used to indicate that the substituent is attached to the amine nitrogen and not an alkyl carbon.

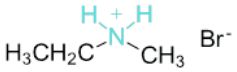


NOMENCLATURE OF AMMONIUM SALTS

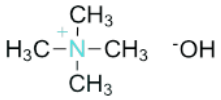
Ammonium salts and quaternary ammonium salts are named using the same rules as 2º and 3º amines except the –amine suffix is replaces with -ammonium + the name of the counter ion. The counter ion name is separated with a space.



Methylammonium Chloride

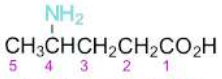


N-Methylethylammonium Bromide

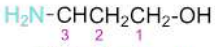


Tetramethylammonium Hydroxide

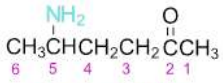
Amines have one of the lower functional group priorities in the IUPAC nomenclature system. When present in a compound with a functional group of higher priority, the amine group is named as a substituent called **"amino."**



4-Aminopentanoic Acid



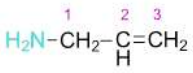
3-Amino-1-propanol



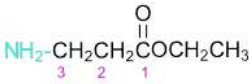
4-Amino-2-Butanone



2,4-Diaminobenzoic Acid

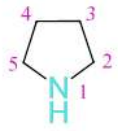


2-Propen-1-amine
(NH_2 Has Priority)

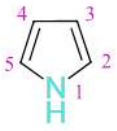


Ethyl 3-aminopropionate

Heterocyclic amine have one or more nitrogens as part of the ring and can be aliphatic or aromatic. Most heterocyclic amine ring systems have a common name and are numbered such that a nitrogen always gets position 1. An amine attached to a heterocyclic ring is named as an amino substituent.



Pyrrolidine



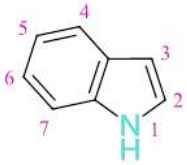
Pyrrole



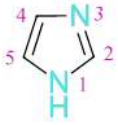
Piperidine



Pyridine



Indole



Imidazole



Quinoline

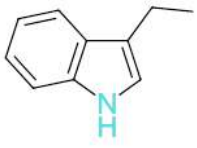


Pyrimidine

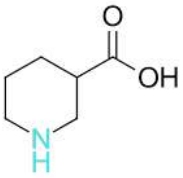
EXAMPLE



1-Methylpyrrolidine



3-Ethylindole

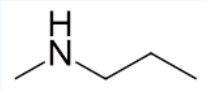


3-Piperidinecarboxylic acid

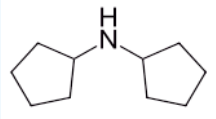
EXERCISES 24.1.1

Name the following compounds:

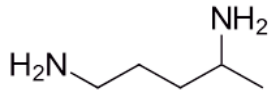
a)



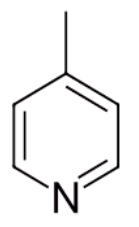
b)



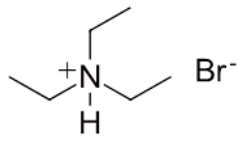
c)



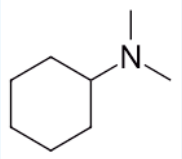
d)



e)



f)



Answers

a. N-Methylpropylamine
b. Dicyclopentylamine
c. 1,4-Pentanediamine
d. 4-Methylpyridine
e. Triethylammonium Bromide
f. N,N-Dimethylcyclohexylamine

EXERCISE 24.1.1

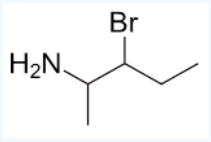
Draw the structures corresponding to the following names:

a. 3-Bromo-pentan-2-amine

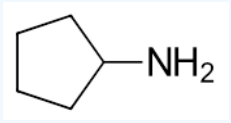
b. Cyclopentanamine
c. *Trans*-3-ethylcyclohexanamine
d. *Sec*-butyl-*tert*-butyl amine
e. N,N-Dimethyl-3-pentanamine
f. 4-Methyl-2-hexanamine
g. 6-Bromo-4-amino-2-heptanol3)

Answer

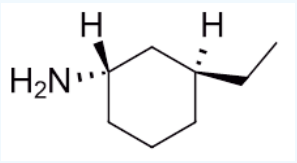
a)



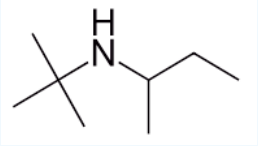
b)



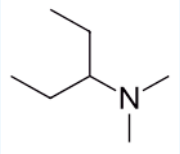
c)



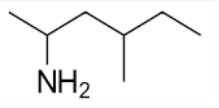
d)



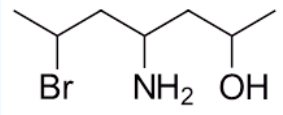
e)



f)



g)



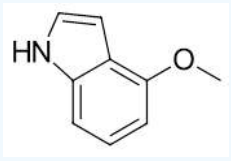
EXERCISE 24.1.3

Draw the structures of the following heterocyclic compounds:

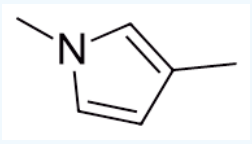
a. 4-Methoxyindole
b. 1,4-Dimethylpyrrole
c. 3-(N,N-Dimethylamino)pyridine
d. 2-Aminopyrimidine

Answer

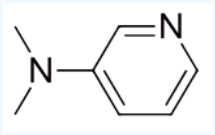
a)



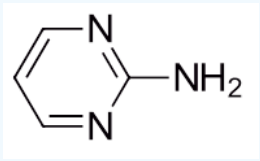
b)



c)



d)



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24.2: STRUCTURE AND PROPERTIES OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. describe the geometry and bonding of simple amines.
2. explain why most chiral amines cannot be resolved into their two enantiomers.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

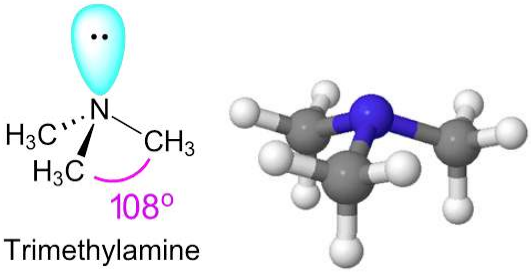
- pyramidal inversion

STUDY NOTES

Molecular models may help you to understand pyramidal inversion.

BONDING, SHAPE, AND HYBRIDIZATION OF AMINES

The nitrogen atom in most amines is sp^3 hybridized. Three of the sp^3 hybrid orbitals form sigma bonds with the fourth orbital carrying the lone pair electrons. Single-bonded nitrogen is trigonal pyramidal in shape, with the non-bonding lone electron pair pointing to the unoccupied corner of a tetrahedron. Due to crowding by the lone pair electrons, the C-N-C bond angle between alkyl substituents on an amine is roughly 108º which is slightly less than the 109.5º bond angle for a perfect tetrahedral geometry.

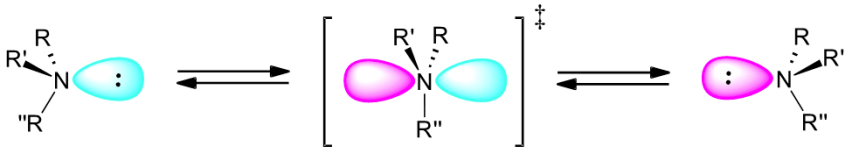


Trimethylamine

The C-N bonds (147 pm) of non-conjugated amines is shorter than C-C bond (154 pm) in alkanes, and longer than the C-O bond (143 pm) present in alcohols. This difference in bond length is expected given that the relative atom sizes are C > O > N.

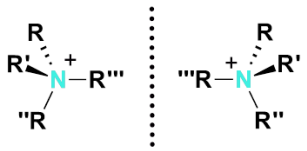
CHIRALITY OF AMINES

Due to their tetrahedral configuration, amines with three different substituents are chiral. The R and S enantiomeric forms of a chiral amine cannot be resolved due to their rapid interconversion by a process called pyramidal or nitrogen inversion. During the inversion, the sp^3 hybridized amine momentarily rehybridizes to a sp^2 hybridized, trigonal planar, transition state where the lone pair electrons occupy a p orbital. The nitrogen then returns to a tetrahedral sp^3 hybridization causing the lone pair electrons to return to a sp^3 orbital on the opposite side of the nitrogen. During this process substituents invert to form the enantiomer. The thermodynamic barrier for this inversion (~25 kJ/mol) is low enough to allow rapid inversion at room temperature, leading to a mixture of interconverting R and S configurations. At room temperature a nitrogen atom exists as a racemic mixture of R and S configurations at equilibrium.



sp^3-Hybridized (Tetrahedral) **sp^2-Hybridized (Trigonal Planar)** **sp^3-Hybridized (Tetrahedral)**

Quarternary amines lack lone pair electrons and therefore do not undergo pyramidal inversions. Quarternary amines with four different substituents are chiral and are readily resolved into separate enantiomers.

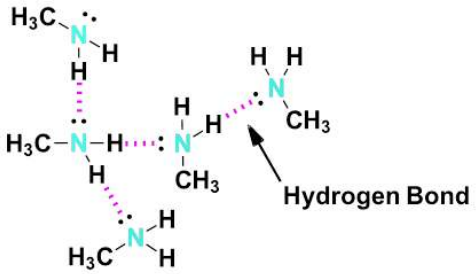


Enantiomers of a Chiral Quarternary Amine

BOILING POINT AND WATER SOLUBILITY

Methyl, dimethyl, trimethyl, and ethyl amines are gases under standard conditions. Most common alkyl amines are liquids, and high molecular weight amines are, quite naturally, solids at standard temperatures.

It is instructive to compare the boiling points and water solubility of amines with those of corresponding alcohols and ethers. The dominant factor here is hydrogen bonding, and the first table below documents the powerful intermolecular attraction that results from -O-H---O- hydrogen bonding in alcohols (light blue columns). Corresponding -N-H---N- hydrogen bonding is weaker, as the lower boiling points of similarly sized amines demonstrate. Alkanes provide reference compounds in which hydrogen bonding is not possible, and the increase in boiling point for equivalent 1º-amines is roughly half the increase observed for equivalent alcohols.



A Representation of the Hydrogen Bonding in Methyamine

Compound	CH_3CH_3	CH_3OH	CH_3NH_2	$CH_3CH_2CH_3$	CH_3CH_2OH	$CH_3CH_2NH_2$
Mol.Wt.	30	32	31	44	46	45
Boiling Point ºC	-88.6º	65º	-6.0º	-42º	78.5º	16.6º

The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher than isomeric 3º-amines (no hydrogen bonding). Indeed, 3º-amines have boiling points similar to equivalent sized ethers; and in all but the smallest compounds, corresponding ethers, 3º-amines and alkanes have similar boiling points. In the examples shown here, it is further demonstrated that chain branching reduces boiling points by 10 to 15 ºC.

Compound	$CH_3(CH_2)_2CH_3$	$CH_3(CH_2)_2OH$	$CH_3(CH_2)_2NH_2$	$CH_3CH_2NHCH_3$	$(CH_3)_3CH$	$(CH_3)_2CHOH$	$(CH_3)_2CHNH_2$	$(CH_3)_3N$
Mol.Wt.	58	60	59	59	58	60	59	59
Boiling Point ºC	-0.5º	97º	48º	37º	-12º	82º	34º	3º

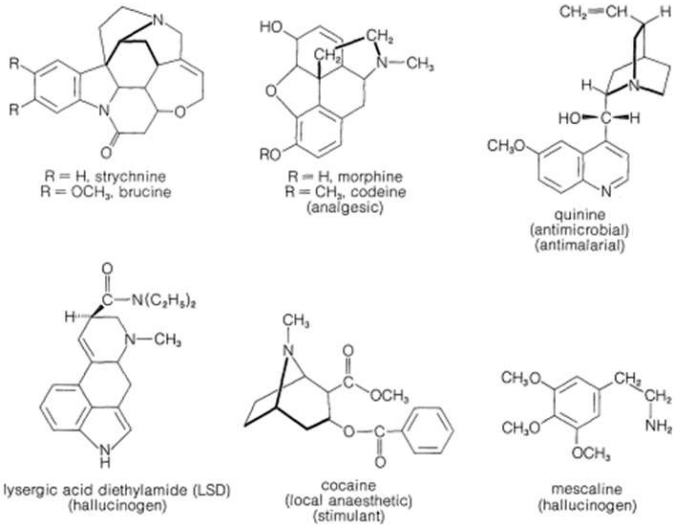
Most aliphatic amines display some solubility in water, reflecting their ability to form hydrogen bonds. Solubility decreases proportionally with the increase in the number of carbon atoms in the molecule – especially when the carbon atom number is greater than six. Aliphatic amines also display significant solubility in organic solvents, especially in polar organic solvents.

The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. The basicity of amines allows them to be dissolved in dilute mineral acid solutions, and this property facilitates their separation from neutral compounds such as alcohols and hydrocarbons by partitioning between the phases of non-miscible solvents.

NATURALLY OCCURRING AMINES

A large and widespread class of naturally occurring amines is known as alkaloids. The structures of the plant alkaloids are extraordinarily complex, yet they are related to the simple amines in being weak nitrogen bases. In fact, the first investigator to isolate an alkaloid in pure form was F. W. A. Sertürner who, in 1816, described morphine as basic, salt-forming, and ammonia-like. He used the term "organic alkali"

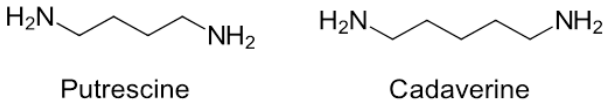
from which is derived the name alkaloid. Alkaloids include compounds that may be classified as antimicrobial (quinine), as analgesics (morphine, codeine), as hallucinogens (mescaline, LSD), and as topical anesthetics (cocaine).



Certain amines and ammonium compounds play key roles in the function of the central nervous system as neurotransmitters and the balance of amines in the brain is critical for normal brain functioning. The amines acetylcholine chloride, adrenalin, and serotonin play important roles in nerve function in the human body.



Most amines have “interesting” odors. The simple ones smell very much like ammonia. Higher aliphatic amines smell like decaying meat. The stench of rotting meat is due in part to two diamines: putrescine and cadaverine. They are made during the decarboxylation of the amino acids, ornithine and lysine, by bacteria.



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24.3: BASICITY OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. account for the basicity and nucleophilicity of amines.
2. explain why amines are more basic than amides, and better nucleophiles.
3. describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
4. explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids, and illustrate the synthetic usefulness of the strong bases that can be formed from these weak acids.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- amide

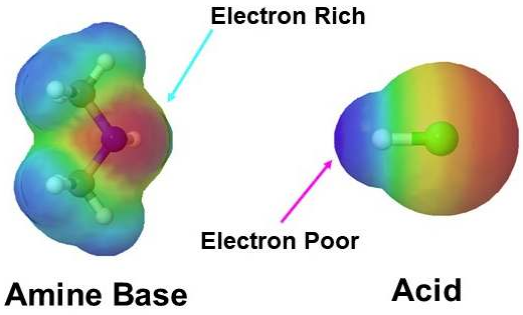
STUDY NOTES

The lone pair of electrons on the nitrogen atom of amines makes these compounds not only basic, but also good nucleophiles. Indeed, we have seen in past chapters that amines react with electrophiles in several polar reactions (see for example the nucleophilic addition of amines in the formation of imines and enamines in Section 19.8).

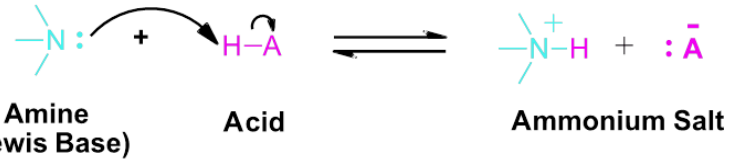
The ammonium ions of most simple aliphatic amines have a pK_a of about 10 or 11. However, these simple amines are all more basic (i.e., have a higher pK_a) than ammonia. Why? Remember that, relative to hydrogen, alkyl groups are electron releasing, and that the presence of an electron-releasing group stabilizes ions carrying a positive charge. Thus, the free energy difference between an alkylamine and an alkylammonium ion is less than the free energy difference between ammonia and an ammonium ion; consequently, an alkylamine is more easily protonated than ammonia, and therefore the former has a higher pK_a than the latter.

BASICITY OF NITROGEN GROUPS

In this section we consider the relative basicity of amines. When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic and nucleophilic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen. The lone pair electrons makes the nitrogen in amines electron dense, which is represents by a red color in the electrostatic potential map present below left. Amine are basic and easily react with the hydrogen of acids which are electron poor as seen below.



Amines are one of the only neutral functional groups which are considered basis which is a consequence of the presence of the lone pair electrons on the nitrogen. During an acid/base reaction the lone pair electrons attack an acidic hydrogen to form a N-H bond. This gives the nitrogen in the resulting ammonium salt four single bonds and a positive charge.



Amines react with water to establish an equilibrium where a proton is transferred to the amine to produce an ammonium salt and the hydroxide ion, as shown in the following general equation:

$$RNH2_{(aq)} + H_2O_{(l)} \rightleftharpoons RNH3^+_{(aq)} + OH^-_{(aq)} \tag{24.3.1}$$

The equilibrium constant for this reaction is the base ionization constant (K_b), also called the base dissociation constant:

$$K_b = \frac{[RNH3^+][OH^-]}{[NH2]} \tag{24.3.2}$$

$$pK_b = -\log K_b$$

Just as the acid strength of a carboxylic acid can be measured by defining an acidity constant K_a (Section 2-8), the base strength of an amine can be measured by defining an analogous basicity constant K_b. The larger the value of K_b and the smaller the value of pK_b, the more favorable the proton-transfer equilibrium and the stronger the base.

However, Kb values are often not used to discuss relative basicity of amines. It is common to compare basicity's of amines by using the K_a's of their conjugate acids, which is the corresponding ammonium ion. Fortunately, the K_a and K_b values for amines are directly related.

Consider the reactions for a conjugate acid-base pair, $RNH_3^+ - RNH_2$:

$$RNH_3^+(aq) + H_2O(l) \rightleftharpoons RNH_2(aq) + H_3O^+(aq) \quad K_a = \frac{[RNH2][H3O]}{[RNH3+]}$$

$$RNH_2(aq) + H_2O(l) \rightleftharpoons RNH_3^+(aq) + OH^-(aq) \quad K_b = \frac{[RNH3+][OH-]}{[RNH2]}$$

Adding these two chemical equations together yields the equation for the autoionization for water:

$$\cancel{RNH_3^+(aq)} + H_2O(l) + \cancel{RNH_2(aq)} + H_2O(l) \rightleftharpoons H_3O^+(aq) + \cancel{RNH_2(aq)} + OH^-(aq) + \cancel{RNH_3^+(aq)}$$

$$2\,H_2O(l) \rightleftharpoons H_3O^+(aq) + OH^-(aq)$$

Given that the *K* expression for a chemical equation formed from adding two or more other equations is the mathematical product of the input equations' *K* constants.

$$K_a \text{ X } K_b = \{2\ H_2O\} / (H_3O^+)\{OH^-\} = Kw$$

$$K_a = \frac{K_w}{K_b}$$

$$pK_a + pK_b = 14$$

Thus if the K_a for an ammonium ion is know the K_b for the corresponding amine can be calculated using the equation $K_b = K_w / K_a$. This relationship shows that as an ammonium ion becomes more acidic (K_a increases / pK_a decreases) the correspond base becomes weaker (K_b decreases / pK_b increases)

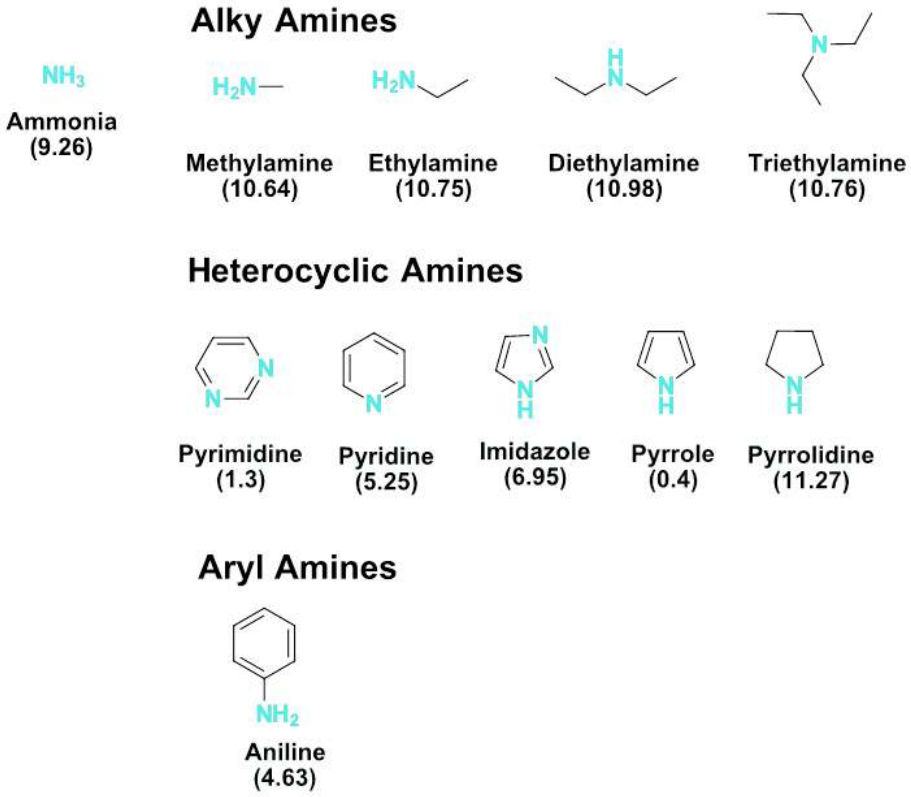
Weaker Base = Larger K_a and Smaller pK_a of the Ammonium ion

Stronger Base = Smaller K_a and Larger pK_a of the Ammonium ion

Like ammonia, most amines are Brønsted-Lowry and Lewis bases, but their base strength can be changed enormously by substituents. Most simple alkyl amines have pK_a's in the range 9.5 to 11.0, and their aqueous solutions are basic (have a pH of 11 to 12, depending on concentration).

Aromatic herterocyclic amines (such as pyrimidine, pyridine, imidazole, pyrrole) are significantly weaker bases as a consequence of three factors. The first of these is the hybridization of the nitrogen. In each case the heterocyclic nitrogen is sp^2 hybridized. The increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton compared to sp^3 hybridized nitrogens. The very low basicity of pyrrole reflects the exceptional delocalization of the nitrogen electron pair associated with its incorporation in an aromatic

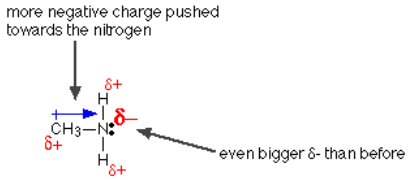
ring. Imidazole (pK_a = 6.95) is over a million times more basic than pyrrole because the sp^2 nitrogen that is part of one double bond is structurally similar to pyridine, and has a comparable basicity.



Basicity of common amines (pK_a of the conjugate ammonium ions)

INDUCTIVE EFFECTS IN NITROGEN BASICITY

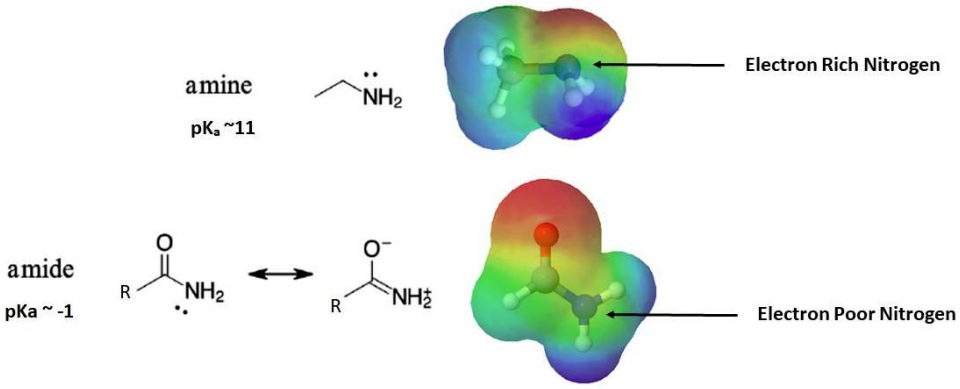
Alkyl groups donate electrons to the more electronegative nitrogen. The inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonia. The small amount of extra negative charge built up on the nitrogen atom makes the lone pair even more attractive towards hydrogen ions. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia.



Compound	pK_a
NH_3	9.3
CH_3NH_2	10.66
$(CH_3)_2NH$	10.74
$(CH_3)_3N$	9.81

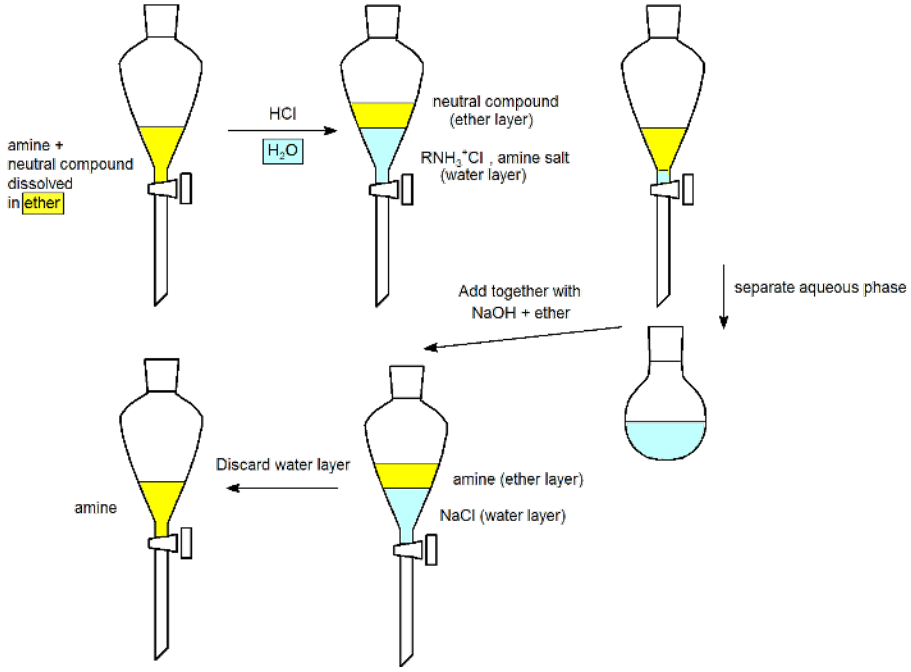
COMPARING THE BASICITY OF ALKYLAMINES TO AMIDES

The nitrogen atom is strongly basic when it is in an amine, but *not* significantly basic when it is part of an amide group. While the electron lone pair of an amine nitrogen is localized in one place, the lone pair on an amide nitrogen is delocalized by resonance. The electron density – in the form of a lone pair – is stabilized by resonance delocalization, even though there is not a negative charge involved. Here's another way to think about it: the lone pair on an amide nitrogen is not as available for bonding with a proton – these two electrons are too stable being part of the delocalized pi-bonding system. The electrostatic potential map shows the effect of resonance on the basicity of an amide. The map shows that the electron density, shown in red, is almost completely shifted towards the oxygen. This greatly decreases the basicity of the lone pair electrons on the nitrogen in an amide.



AMINE EXTRACTION IN THE LABORATORY

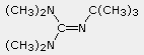
Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids are dissolved, and (2) the extracting solvent. The two immiscible liquids are then easily separated using a separatory funnel. For amines one can take advantage of their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water. The salt will extract into the aqueous phase leaving behind neutral compounds in the non-aqueous phase. The aqueous layer is then treated with a base (NaOH) to regenerate the amine and NaCl. A second extraction-separation is then done to isolate the amine in the non-aqueous layer and leave behind NaCl in the aqueous layer.



IMPORTANT REAGENT BASES

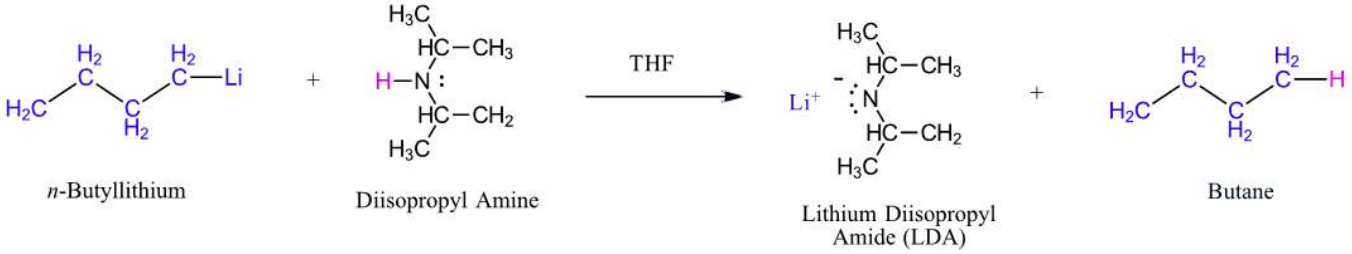
The significance of all these acid-base relationships to practical organic chemistry lies in the need for organic bases of varying strength, as reagents tailored to the requirements of specific reactions. The common base sodium hydroxide is not soluble in many organic solvents, and is therefore not widely used as a reagent in organic reactions. Most base reagents are alkoxide salts, amines or amide salts. Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amine bases, and fill the gap in base strength between amines and amide salts.

Basicity of common amines (pK_a of the conjugate ammonium ions)

Base Name	Pyridine	Triethyl Amine	Hünig's Base	Barton's Base	Potassium t-Butoxide	Sodium HMDS	LDA
Formula		$(C_2H_5)_3N$			$(CH_3)_3CO^{(-)}\ K^{(+)}$	$[(CH_3)_3Si]_2N^{(-)}\ Na^{(+)}$	$[(CH_3)_2CH]_2N^{(-)}\ Li^{(+)}$
pK_a of conjugate acid	5.3	10.7	11.4	14	19	26	35.7

Pyridine is commonly used as an acid scavenger in reactions that produce mineral acid co-products. Its basicity and nucleophilicity may be modified by steric hindrance, as in the case of 2,6-dimethylpyridine (pK_a=6.7), or resonance stabilization, as in the case of 4-dimethylaminopyridine (pK_a=9.7). Hünig's base is relatively non-nucleophilic (due to steric hindrance), and is often used as the base in E2 elimination reactions conducted in non-polar solvents. Barton's base is a strong, poorly-nucleophilic, neutral base that serves in cases where electrophilic substitution of other amine bases is a problem. The alkoxides are stronger bases that are often used in the corresponding alcohol as solvent, or for greater reactivity in DMSO. Finally, the two amide bases see widespread use in generating enolate bases from carbonyl compounds and other weak carbon acids.

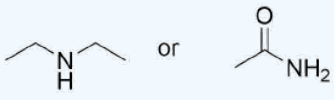
In addition to acting as a base, 1º and 2º amines can act as very weak acids. Their N-H proton can be removed if they are reacted with a strong enough base. An example is the formation of lithium diisopropylamide (LDA, $LiN[CH(CH_3)_2]_2$) by reacting *n*-butyllithium with diisopropylamine (pK_a 36) **(**Section 22-5**)**. LDA is a very strong base and is commonly used to create enolate ions by deprotonating an alpha-hydrogen from carbonyl compounds **(**Section 22-7**)**.

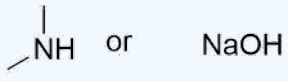


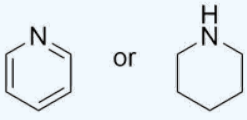
n-Butyllithium + Diisopropyl Amine → Lithium Diisopropyl Amide (LDA) + Butane

? EXERCISE 24.3.1

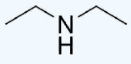
Select the more basic amine from each of the following pairs of compounds.

(a) 

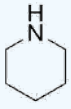
(b) 

(c) 

Answer

(a) 

(b) NaOH

(c) 

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EXERCISE 24.3.1

The 4-methylbenzylammonium ion has a pKa of 9.51, and the butylammonium ion has a pKa of 10.59. Which is more basic? What's the pKb for each compound?

Answer

The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

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24.4: BASICITY OF ARYLAMINES

OBJECTIVES

After completing this section, you should be able to

1. use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
2. arrange a given series of arylamines in order of increasing or decreasing basicity.
3. discuss, in terms of inductive and resonance effects, why a given arylamine is more or less basic than aniline.

STUDY NOTES

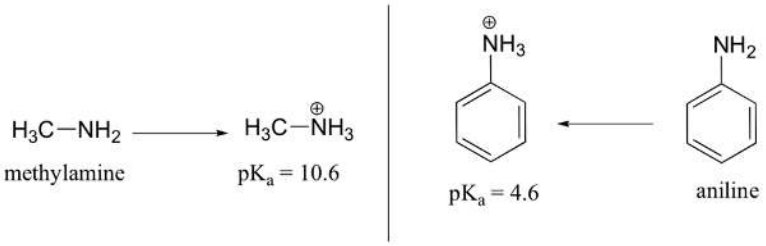
With reference to the discussion of base strength, the traditional explanation for the base-strengthening effect of electron-releasing (I) substituents is that such substituents help to stabilize the positive charge on an arylammonium ion more than they stabilize the unprotonated compound, thereby lowering $\Delta G°$.

The electron-withdrawing (i.e., deactivating) substituents decrease the stability of a positively charged arylammonium ion.

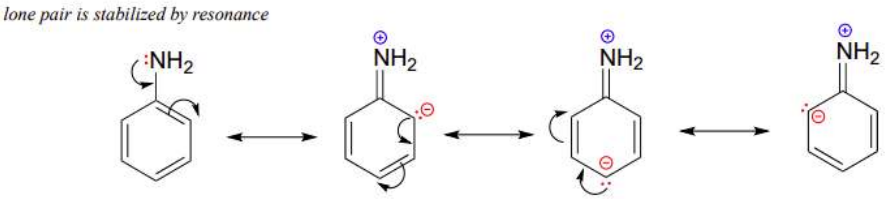
Note that the arylammonium ion derived from aniline, $PhNH_3^+$, is commonly referred to as the anilinium ion.

BASICITY OF ANILINE

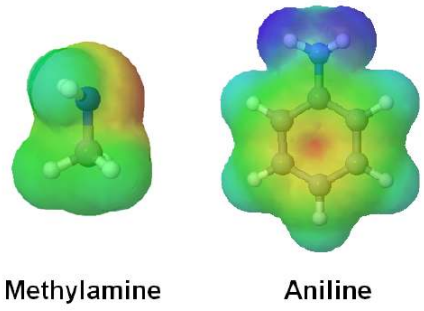
Aniline is substantially less basic than methylamine, as is evident by looking at the pK_a values for their respective ammonium conjugate acids (remember that the lower the pKa of the conjugate acid, the weaker the base).



This difference is basicity can be explained by the observation that, in aniline, the lone pair of electrons on the nitrogen are delocalized by the aromatic p system, making it less available for bonding to H^+ and thus less basic. The lone pair electrons of aniline are involved in four resonance forms making them more stable and therefore less reactive relative to alkylamines.

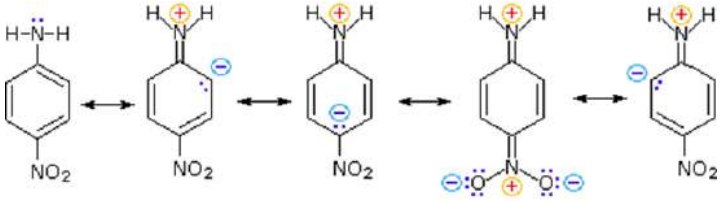


The effect of delocalization can be seen when viewing the electrostatic potential maps of aniline an methyl amine. The nitrogen of methyl amine has a significant amount of electron density on its nitrogen, shown as a red color, which accounts for it basicity compared to aniline. While the electron density of aniline's nitrogen is delocalized in the aromatic ring making it less basic.



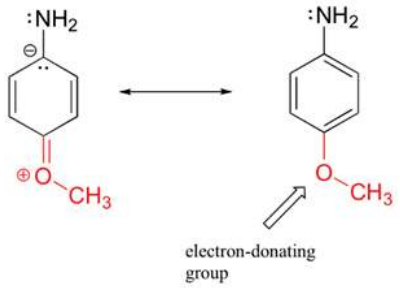
BASICITY OF SUBSTITUTED ARYLAMINES

The addition of substituents onto the aromatic ring can can make arylamines more or less basic. Substituents which are electron-withdrawing (-Cl, -CF_3, -CN, -NO_2) decrease the electron density in the aromatic ring and on the amine making the arylamine less basic. In particular, the nitro group of *para*-nitroaniline allows for an additional resonance form to be drawn, which further stabilizes the lone pair electrons from the nitrogen, making the substituted arylamine less basic than aniline. This effect is analogous to the one discussed for the acidity of substituted phenols in **Section 17.2**.



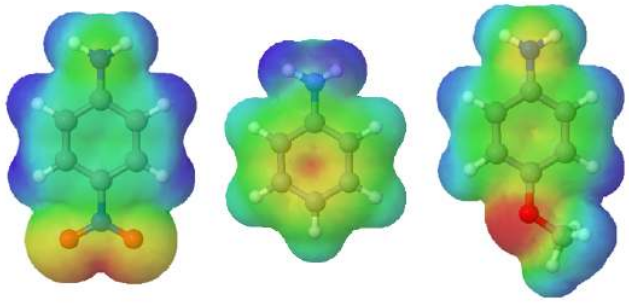
Reduced Basicity of *para*-Nitroaniline due to Electron Pair Delocalization

Substituents which are electron-donating (-CH_3, -OCH_3, -NH_2) increase the electron density in the aromatic ring and on the amine making the arylamine more basic. In the case of *para*-methoxyaniline, the lone pair on the methoxy group donates electron density to the aromatic system, and a resonance contributor can be drawn in which a negative charge is placed on the carbon adjacent to the nitrogen, which makes the substituted arylamine more basic than aniline.



Increased Basicity of para-Methoxyaniline due to Electron-Donation

The shifting electron density of aniline, *p*-nitroaniline, and *p*-methoxyaniline are seen in their relative electrostatic potential maps. For *p*-Nitroaniline virtually all of the electron density, shown as a red/yellow color. is pulled toward the electron-withdrawing nitro group. In *p*-methoxyaninline the electron donating methoxy group donates electron density into the ring. The amine in p-methoxyaniline is shown to have more electron density, shown as a yellow color, when compared to the amine in aniline.



***p*-Nitroaniline** **Aniline** ***p*-Methoxyaniline**

? EXERCISE S24.4.1

Using the knowledge of the electron donating or withdrawing effects of subsituents gained in Section 16.6, rank the following compound in order of decreasing basicity.

a. *p*-Nitroaniline, methyl p-aminobenzoate, *p*-chloroaniline
b. *p*-Bromoaniline, *p*-Aminobenzonitrile, *p*-ethylaniline
c. p-(Trifluoromethyl)aniline, *p*-methoxyaniline, *p*-methylaniline

Answers

a. *p*-Chloroaniline, methyl p-aminobenzoate, *p*-nitroaniline

b. *p*-Ethylaniline, *p*-Bromoaniline, *p*-aminobenzonitrile

c. *p*-Methoxyaniline, *p*-methylaniline, *p*-(trifluoromethyl)aniline

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24.5: BIOLOGICAL AMINES AND THE HENDERSON-HASSELBALCH EQUATION

OBJECTIVES

1. identify the form that amine bases take within living cells.
2. use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
3. explain why organic chemists write cellular amines in their protonated form and amino acids in their ammonium carboxylate form.

The Henderson-Hasselbalch equation is very useful relating the pKa of a buffered solution to the relative amounts of an acid and its conjugate base. In Section 20-3, we used the Henderson-Hasselbalch equation to show that under physiological pH, carboxylic acids are almost completely dissociated into their carboxylate ions.

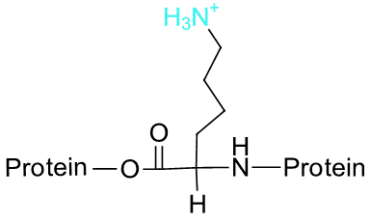
$$\mathrm{pH} = \mathrm{pK_a} + \log\left(\frac{\text{concentration of}}{\text{concentration of weak acid}}\right) \qquad \textbf{(Henderson-Hasselbalch equation)}$$

So, what does the side chain of a lysine amino acid residue look like if it is on the surface of a protein in an aqueous solution buffered pH 7.0? Is it protonated or deprotonated? The values in the Henderson-Hasselbalch can be used for an amine with the ammonium salt written as, HA = RNH_3^+, and the amine as being, A^- = RNH_2. With an approximate pK_a of 10.8 for the protonated amine HA, it should be >99% protonated, in the positively-charged, ammonium form:

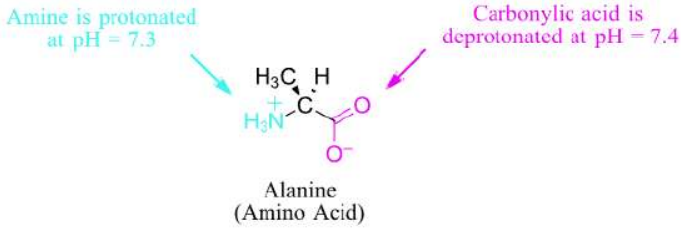
$$7.0 = 10.8 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]} = 1.6 \times 10^{-4}$$

So, $[\mathrm{RNH_3^+}] \gg [\mathrm{RNH_2}]$ at this pH. Consequently, in an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).



Alcohols are fully protonated and neutral at pH 7, as are thiols. The imidazole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.



EXERCISE 24.5.1

Would you expect an aromatic hetererocycle, pyrrole, to be protonated at pH = 7.3? Use the Henderson-Hasselbalch equation to determine your answer. pKa of protonated pyrrole is 0.4.

Answer

$$7.3 = 0.4 + \log\left(\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]}\right)$$

$$\frac{[\mathrm{RNH_2}]}{[\mathrm{RNH_3^+}]} = 7.9 \times 10^6$$

So, $[\mathrm{RNH_2}] \gg [\mathrm{RNH_3^+}]$. Thus pyrrole would be almost completely unprotonated at pH = 7.

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24.6: SYNTHESIS OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. write equations to illustrate the synthesis of amines by
   a. reduction of nitriles or amides and nitro compounds.
   b. reactions involving alkyl groups:
      i. S_N2 reactions of alkyl halides, ammonia and other amines.
      ii. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
      iii. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
   c. reductive amination of aldehydes or ketones.
   d. Hofmann or Curtius rearrangements.
2. write detailed mechanisms for each of the steps involved in the synthetic routes outlined in Objective 1.
3. identify the product or products formed when
   a. a given nitrile or amide is reduced using lithium aluminum hydride.
   b. a given alkyl halide is reacted with ammonia or an alkylamine.
   c. a given alkyl halide is reacted with azide ion and the resulting product is reduced.
   d. a given alkyl halide is reacted with potassium phthalimide and the resulting product is hydrolyzed.
   e. a given aldehyde or ketone is reacted with ammonia or an amine in the presence of nickel catalyst.
   f. a given amide is treated with halogen and base.
   g. a given acyl azide is heated and then hydrolyzed.
4. identify the starting material, the other reagents, or both, needed to synthesize a given amine by any of the routes listed in Objective 1.
5. write a general equation to illustrate the preparation of an arylamine by the reduction of a nitro compound, and balance such an equation.
6. identify the product formed from the reduction of a given aromatic nitro compound.
7. identify the organic compound, the inorganic reagents, or both, needed to prepare a given arylamine.

KEY TERMS

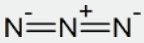
Make certain that you can define, and use in context, the key terms below.

- azide synthesis
- Curtius rearrangement
- Hofmann rearrangement
- Gabriel synthesis
- imide
- reductive amination

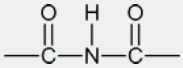
STUDY NOTES

You may wish to review the mechanism of S_N2 reactions which is discussed in some detail in Sections 11.2 and 11.3.

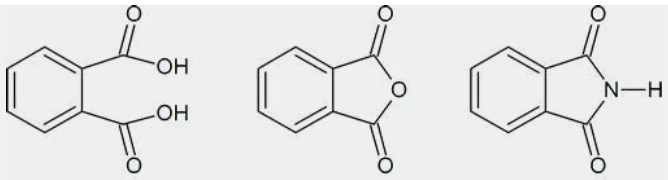
Azide synthesis is the first method on the table of synthesis of primary amines. The Lewis structure of the azide ion, N_3^-, is as shown below.



An “imide” is a compound in which an N$\ce{-}$H group is attached to two carbonyl groups; that is,



You should note the commonly used trivial names of the following compounds.



phthalic acid phthalic anhydride phthalimide

The phthalimide alkylation mentioned in the reading is also known as the Gabriel synthesis.

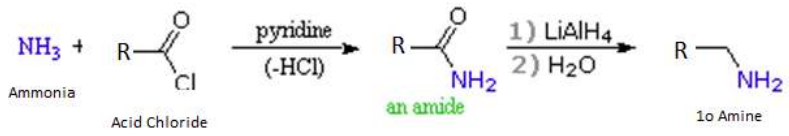
If necessary, review the reduction of nitriles (Section 20.7) and the reduction of amides (Section 21.7).

Before you read the section on reductive amination you may wish to remind yourself of the structure of an imine (see Section 19.8).

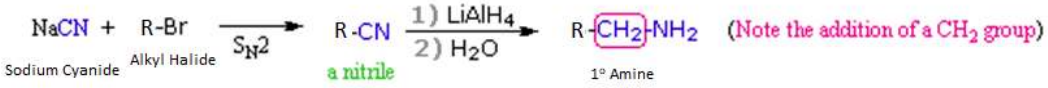
The Hofmann rearrangement is usually called the Hofmann degradation. In a true rearrangement reaction, no atoms are lost or gained; however, in this particular reaction one atom of carbon and one atom of oxygen are lost from the amide starting material, thus the term "rearrangement" is not really appropriate. There is a rearrangement step in the overall degradation process, however: this is the step in which the alkyl group of the acyl nitrene migrates from carbon to nitrogen to produce an isocyanate.

REDUCTION OF NITRILES, AMIDES, AND NITRO COMPOUNDS

Acid chlorides react with ammonia to give amides, by an addition-elimination path, and these are reduced to amines by $LiAlH_4$ (Section 21-7).

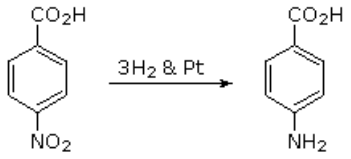


Alkyl halides can be converted to primary amines through a two-step process. First an S_N2 reaction with a cyanide anion converts the alkyl halide into a nitrile. Then the nitrile is reduced to a primary amine by $LiAlH_4$ (Section 20-7). During this reaction sequence an additional carbon atom is added.

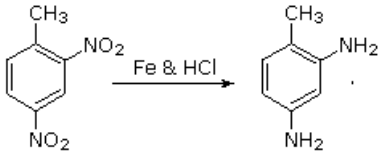


Arylamines are typically prepared by the reduction of a nitro group on an aromatic ring. Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + platinum catalyst), and zinc, iron, or tin(II) chloride in dilute mineral acid. The procedures described above are sufficient for most cases. Catalytic hydrogenation can be problematic because it is known to reduce other functional groups such as alkenes, alkynes, and some carbonyl groups.

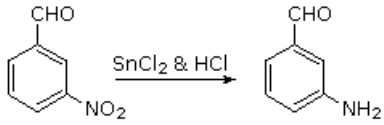
Nitro Group Reduction



p-Nitrobenzoic acid p-Aminobenzoic acid



2,4-Dinitrotoluene 2,4-Toluenediamine



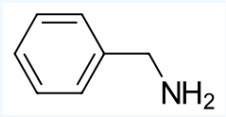
p-Nitrobenzaldehyde p-Aminobenzaldehyde

? EXERCISE 24.6.1

Propose structures of the starting materials needed to make the the following amines using the reduction of a nitrile or an amide:

a. $CH_3CH_2CH_2CH_2NH_2$

b. $(CH_3CH_2)_2NH$

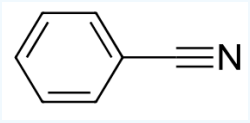
c. 

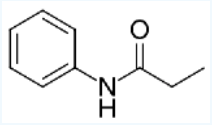
d. N-Propylaniline

Answer

a. $CH_3CH_2CH_2CONH_2$

b. $CH_3CONHCH_2CH_3$

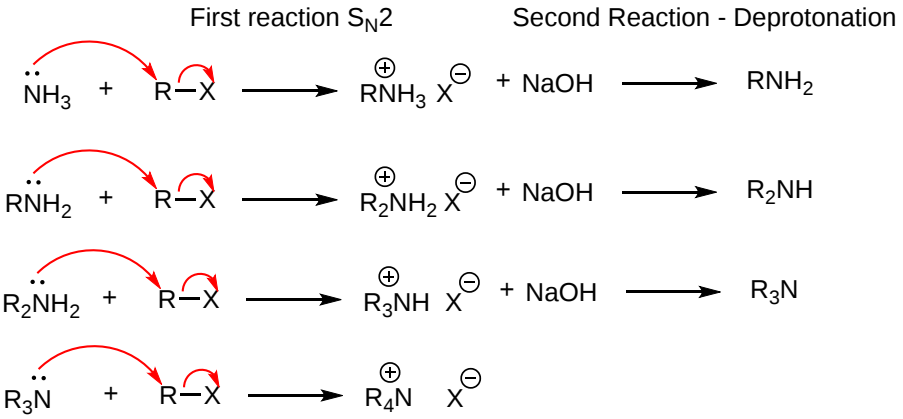
c. 

d. 

S_N2 REACTIONS OF ALKYL HALIDES

Because they posses lone pair electrons, ammonia and amines are considered good nucleophiles. Ammonia and amines can by alkylated by an S_N2 reaction with alkyl halides. The product of the reaction is an ammonium salt where the negative counter-ion is the halogen of the

alkyl halide. When the alkylated products are 1°, 2°, and 3° amines, they can be deprotonated with NaOH to produce the neutral amine. When a 3° amine is alkylated, a quaternary ammonium salt is produced.



Alkylation is an efficient method for the synthesis of 3° and 4° amines. However, when 1° and 2° amines are alkylated a mixture of products is typically produced. When ammonia is reacted with an alkylhalide an monoalkylammonium salt is formed.

$$RX + NH_3 \rightarrow RNH_3^+ + X^-$$

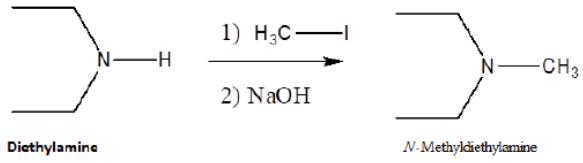
It is possible for any remaining ammonia present in the reaction to deprotonate the ammonium salt to produce the neutral monoalkyl amine.

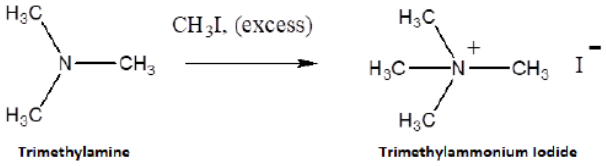
$$RNH_3^+ + NH_3 \rightarrow RNH_2 + NH_4^+$$

The monoalkyl amine is then free to react with a second alkyl halide creating a dialkylammonium salt. This process can be repeated to to eventually to create a tetralkylammonium salt. Typically when a alkyl halide is reacted with ammonia, a mixture of mostly 1° and 2° amines, with trace amounts of 3° amines and 4° ammonium salts, is produced.

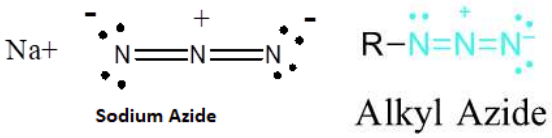
$$RNH_2 + RX \rightarrow R_2NH_2^+ + X^-$$

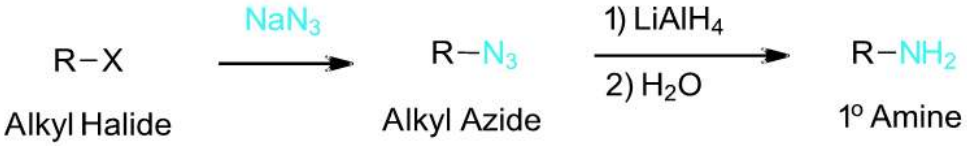
Example





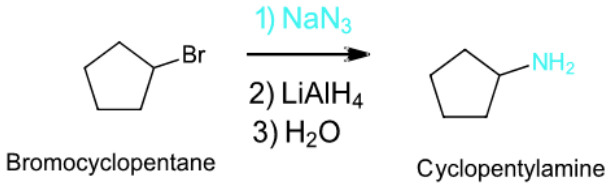
To synthesize a 1° or 2° amine, specific reactions are usually employed. A more efficient method starts with an S_N2 reaction between a 1° or 2° alkyl halide and the nucleophilic azide anion (N_3^-) to produce an alkyl azide. The alkyl azide is not nucleophilic so it cannot react with additional alkyl halide to produce overalkylation. Alkyl azide is then reduced with $LiAlH_4$ to produce a 1° amine.





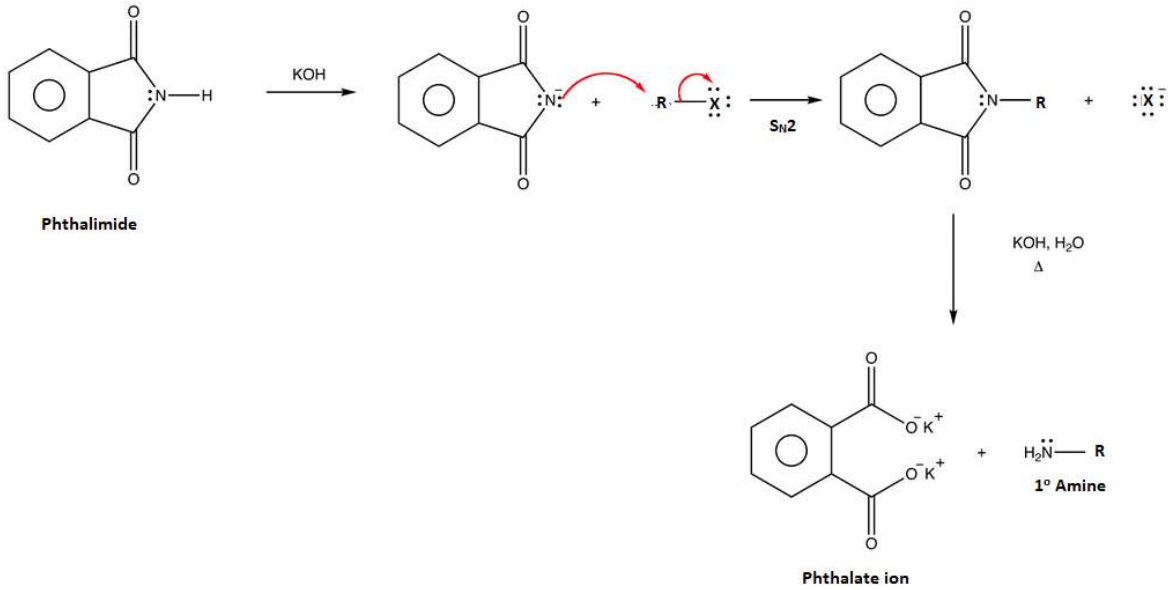
Example



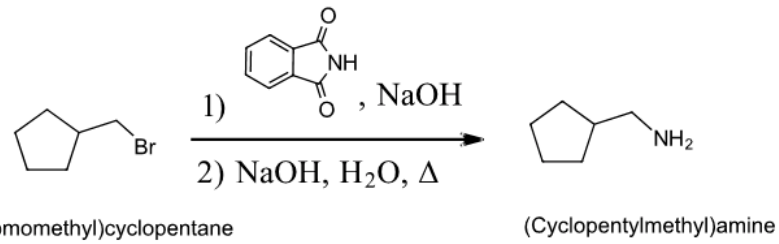


GABRIEL AMINE SYNTHESIS

Another common method for the synthesis of 1° amines is called the **Gabriel amine synthesis**. This reaction starts with the deprotonation of phthalimide by a hydroxide base such as potassium hydroxide (KOH). The N-H hydrogen of an imide functional group is acidic because its conjugate base is resonance stabilized by two carbonyl groups. The phthalimide anion is nucleophilic and easily alkylated through an S_N2 reaction with an alkyl halide. The resulting N-alkylated phthalimide then undergoes base hydrolysis to produce a 1° amine product. The mechanism for the base promoted hydrolysis of the N-alkylated phthalimide is analogous to the hydrolysis of an amide (Section 21-7).



Example

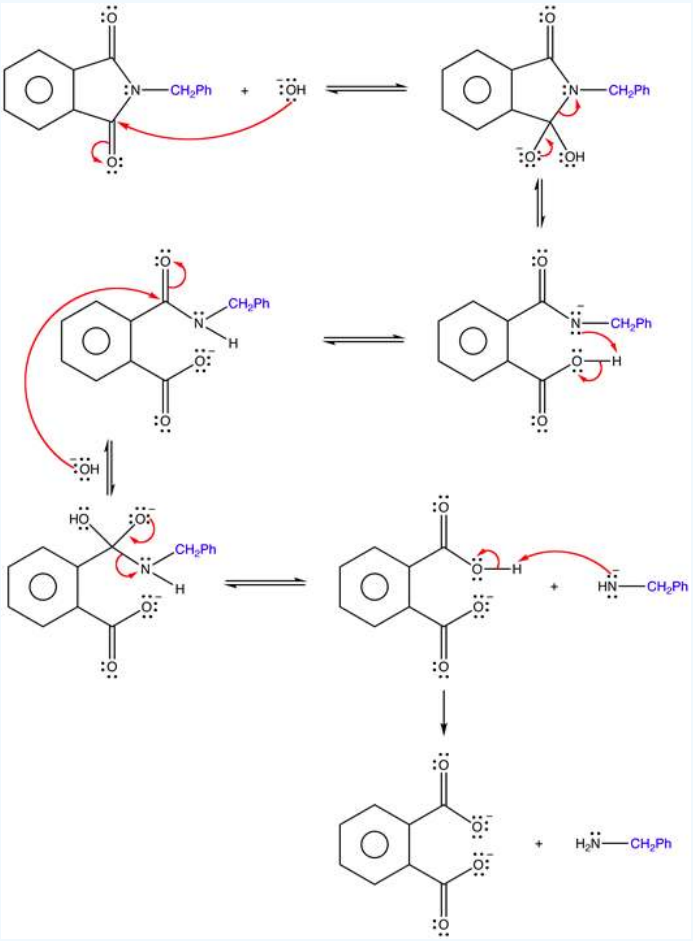


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EXERCISES 24.6.1

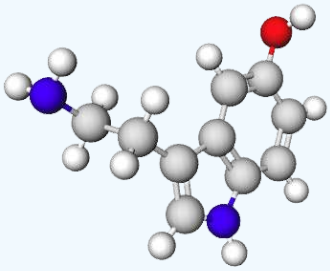
Write the mechanism for the base promoted hydrolysis of an N-alkyl phthalimide to create a 1° amine and the phthalate ion.2)

Answers

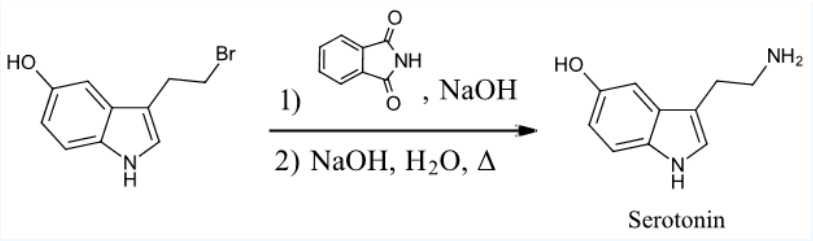


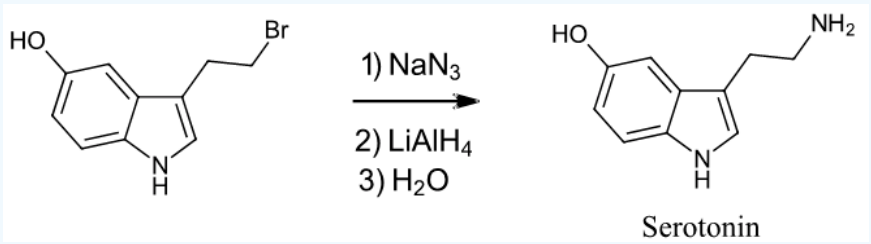
EXERCISE 24.6.2: SEROTONIN

Starting with any alkyl halide, show two methods to synthesize the neurotransmitter serotonin.



Answer

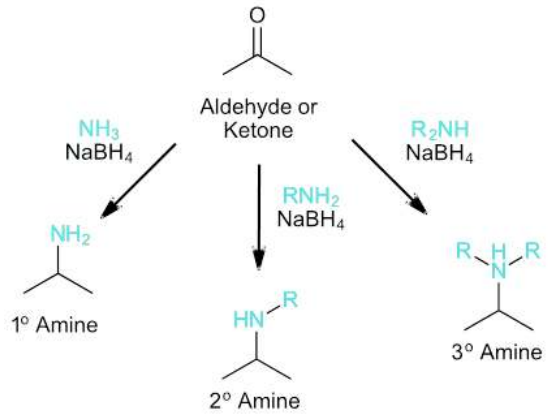




REDUCTIVE AMINATION

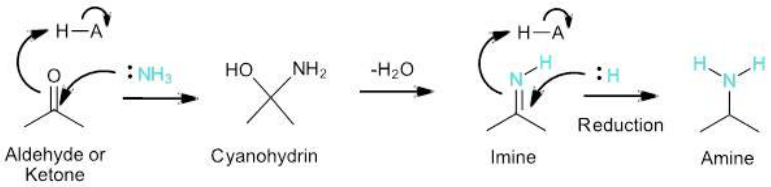
Aldehydes and ketones can be converted into 1°, 2° and 3° amines using **reductive amination**. The reaction takes place in two parts. The first step is the nucleophiic addition of ammonia, a 1° amine, or a 2° amine to a carbonyl group to form an imine **(**Section 19-8**)**. The second step is the reduction of the imine to an amine using a hydride reducing agent. Some common reducing agents used for this reaction are: sodium borohydride ($NaBH_4$), sodium cyanoborohydride ($NaBH_3CN$), $NaBH(OAc)_3$, or hydrogen gas (H_2) over a nickel catalyst.

General Reaction

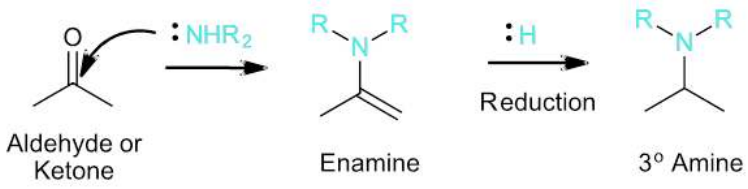


MECHANISM

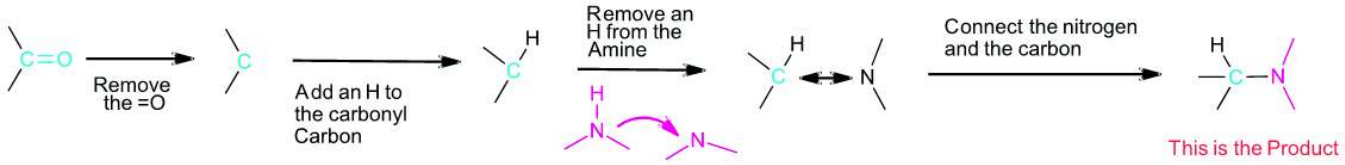
Reductive amination starts with the nucleophilic addition of ammonia or a 1° amine to an aldehyde or ketone forms a cyanohydrin intermediate. Subsequent dehydration forms an imine intermediate (Section 19-8). The imine undergoes hydride reduction in a similar fashion as C=O carbonyl bonds are reduced to an alcohol.



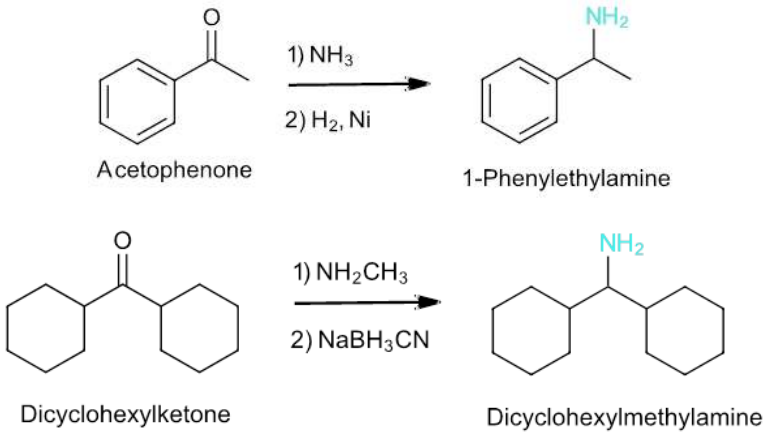
When a 2° amine is used for reductive amination, an enamine intermediate is formed which then undergoes hydride reduction to form a 3° amine.



PREDICTING THE PRODUCTS OF A REDUCTIVE AMINATION



Examples



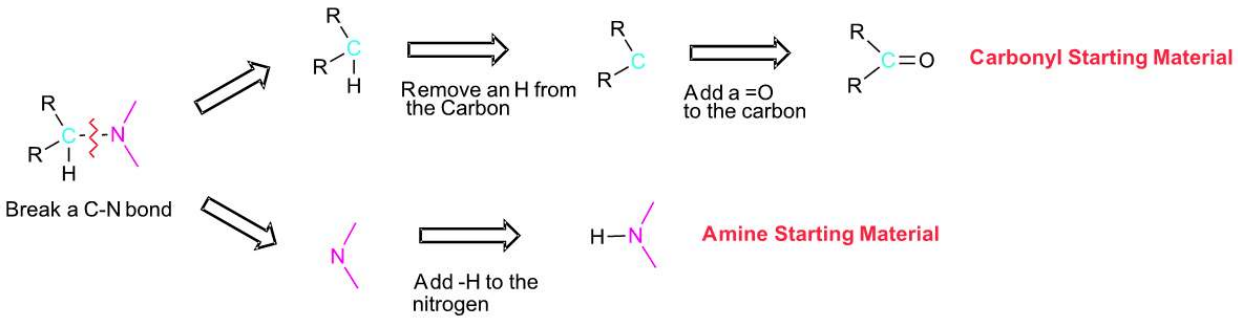
BIOLOGICAL REDUCTIVE AMINATIONS

Reductive amination is used in the biosynthesis of the amino acid proline. The enzyme pyrroline-5-carboxylate synthase (**P5CS)** catalyzes glutamate undergoing an intramolecular imine formation to produce 1-pyrrolinium 5-carboxylate. Then the enzyme pyrroline-5-carboxylate reductase **(PYCR)** catalyzed the nucleophilic hydride reduction of the C=N bond to produce proline. The biological hydride reducing agent for this sequence is reduced nicotinamide adenine dinucleotide **(NADH).**



PLANNING A SYNTHESIS USING A REDUCTIVE AMINATION

If you are trying to develop a synthesis of an amine molecule, the key bond break is a C-N bond in the target molecule. There may be multiple C-N bonds present, so each should be broken separately to produce a possible set of starting materials. Because the amine is commonly used in excess during a reductive animation, the pathway which provides the simplest amine starting material is preferred. The carbon from the broken C-N bond goes on to become a carbonyl starting material. The nitrogen gains a hydrogen to become the amine starting material.



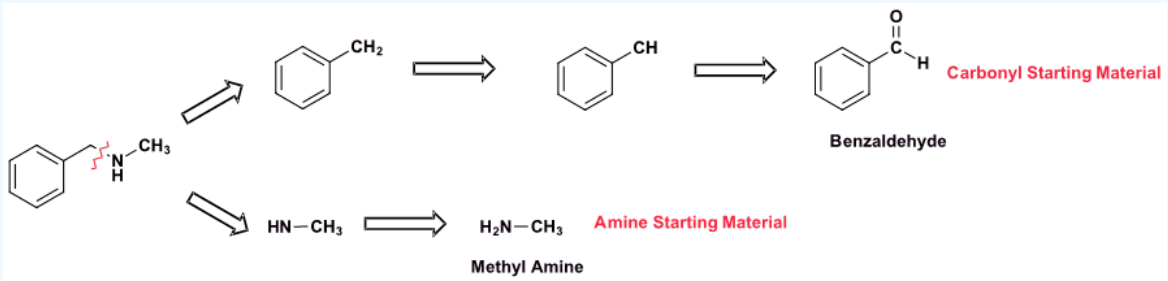
WORKED EXERCISE 24.6.1

Show how N-methylbenzylamine can be synthesized using a reductive amination. If more than one pathway is possible, draw them both and determine which one would be preferred.

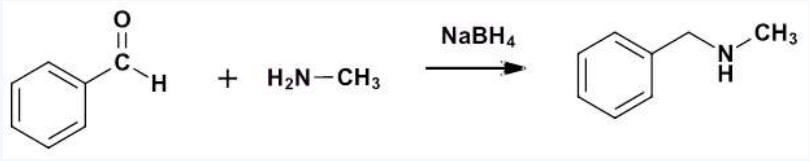


Answer

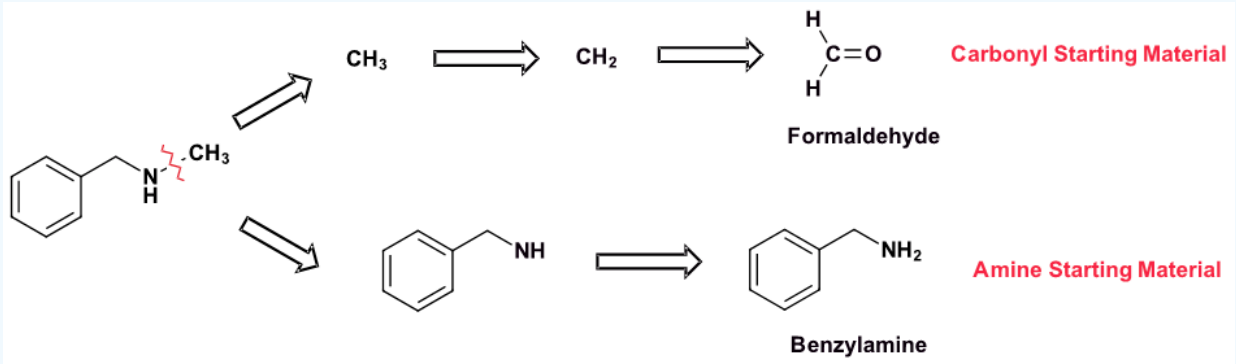
Pathway 1



Solution 1

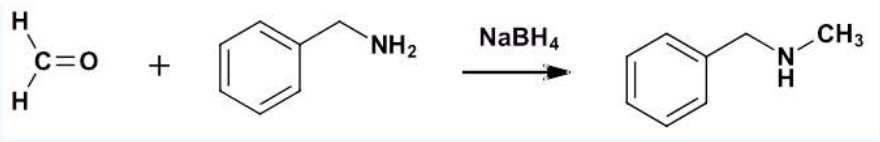


Pathway 2



Solution 2

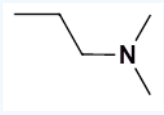
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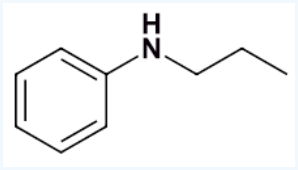


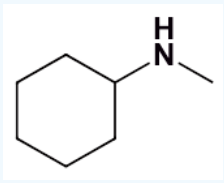
Because N-methylbenzylamine has two C-N bonds there are two possible synthesis pathways. Pathway 1 is most likely preferred because it uses the simplest amine starting material, methyl amine.

EXERCISE 24.6.1

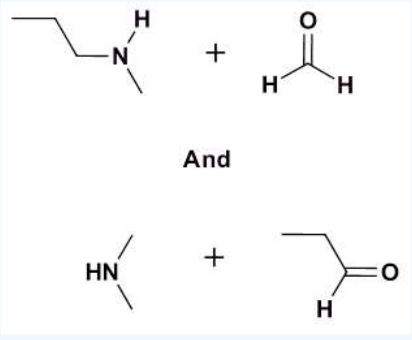
Provide starting materials which could be used to prepare the following compounds using a reductive amination. Show all possible pathways.

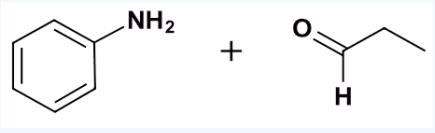
a. 

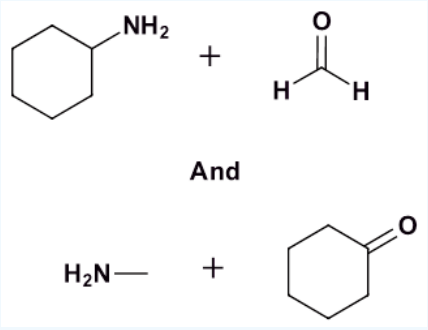
b. 

c. 

Answers

a. 

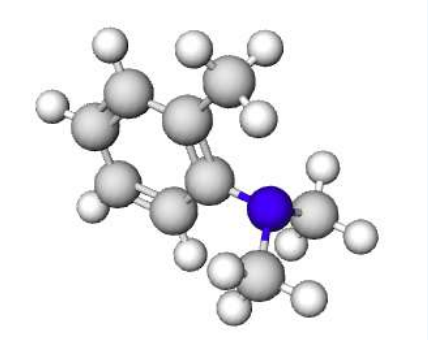
b. 

c. 

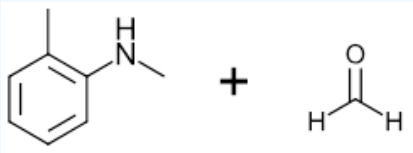
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EXERCISE 24.6.4

Identify the starting materials which could provide the following molecule using a reductive amination.



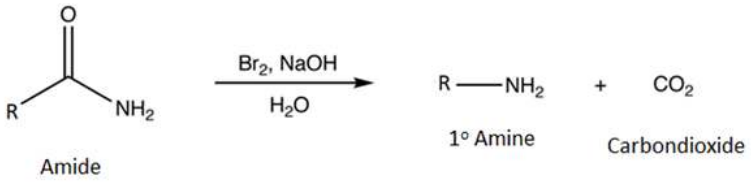
Answer



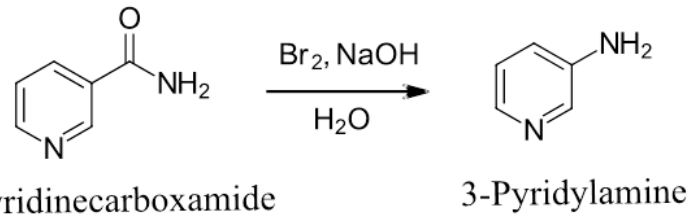
HOFMANN REARRANGEMENT

The Hofmann rearrangement occurs when a 1° amide is reacted with bromine (Br_2) and a base. The products are a 1° amine with one less carbon and carbon dioxide (CO_2).

General Reaction

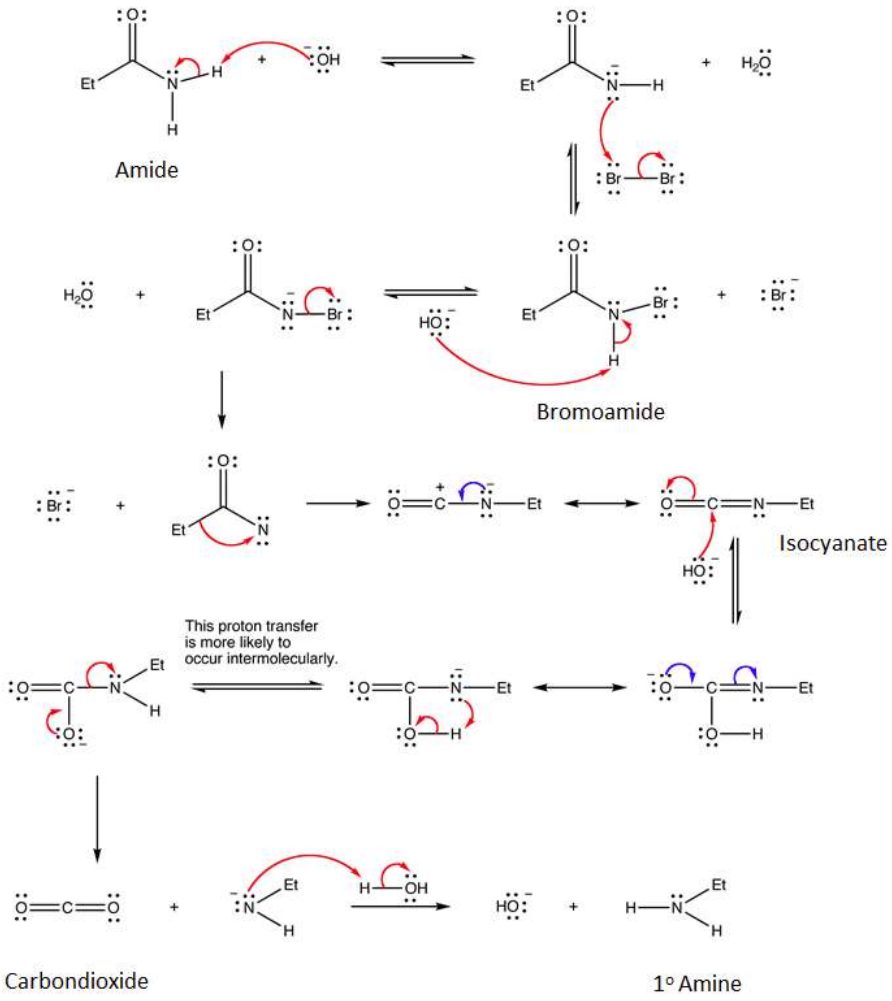


Example



Mechanism

The mechanism for the Hofmann rearrangement is quite complex. The mechanism starts with the deprontation of the primary amide by a base. The nitrogen is brominated during an S_N2 reaction with Br_2 to produce an N-bromoamide. Bromide is eliminated as a leaving group to produce a electron deficient nitrene-like nitrogen. Electrons from the adjacent C-C bond migrate to the nitrogen as part of a rearrangment to finally produce an isocyanate. The carbon in the isocyante is electrophilic and reacts with a nucleophilic hydroxide to create a C-O bond. After movement of electrons through resonance and a proton transfer a carbamate intermediate is formed. The carbamate decomposes to create an amide anion and a stable CO_2 molecule. Finally, water protonates the amide anion to produce a 1° amine.

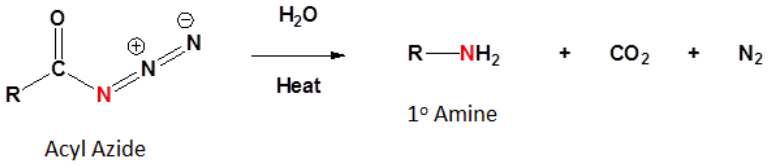


CURTIUS REARRANGEMENT

The Curtius Rearrangement is another method used to synthesize a 1° amine.

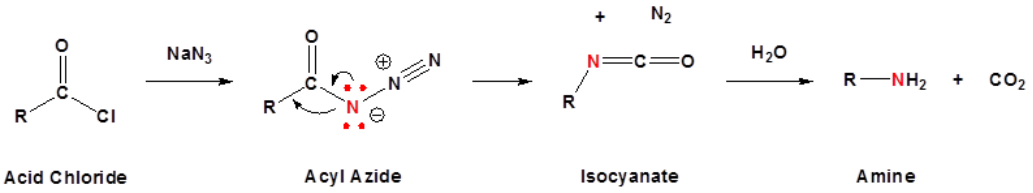
General Reaction

The Curtius rearrangement involves an acyl azide reacting with water and heat to produce a 1° amine along with CO_2 and N_2. The acyl azide is usually made by a nucleophilic substitution of an acid chloride with sodium azide (NaN_3)

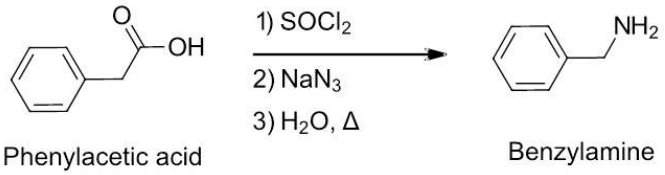


Mechanism

The mechanism of the Curtius rearrangement is quite similar to the Hoffman rearrangement. The loss of N_2 as a leaving group creates an electron deficient nitrogen. The adjacent -R group migrates to form an isocyanate. Reaction of the isocyanate forms a carbamate which decomposes to form a 1° amine and CO_2.

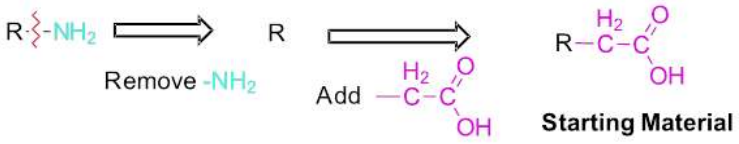


Example



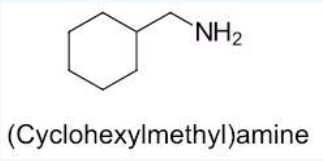
Planning a Synthesis using a Hoffman or Curtius Rearrangement

Because the amide and the acyl azide required for these rearrangements both are best made from an acid chloride, synthesis of amines using these reaction are best started from the corresponding carboxylic acid. For retrosynthetic analysis starting from the desired amine product - the key break is the C-NH_2 bond. The amine is removed and replaced with a -CH_2CO_2H fragment to provide the required carboxylic acid starting material.



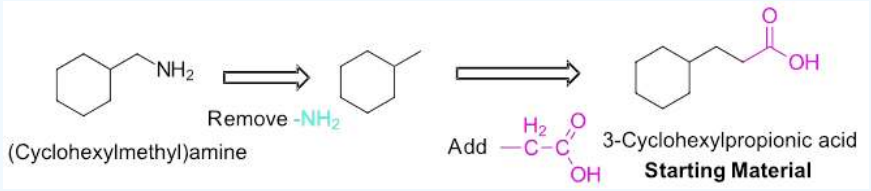
WORKED EXAMPLE 24.6.1

Show how the following molecule could be prepared from a carboxylic acid starting material using both the Hoffman and Curtius rearrangements.



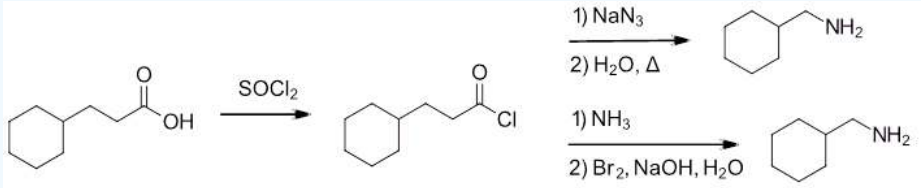
Answer

First determine the structure of the carboxylic acid starting material. This will be the starting material for both rearrangements. In the first step, convert the carboxylic acid into an acid halide using thionyl chloride ($SOCl_2$). Then use the required conditions for each rearrangement.



Solution

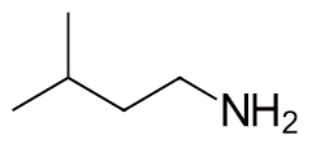
The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



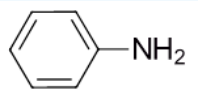
EXERCISES 24.6.1

1) Using a carboxylic acid starting material explain how to prepare the following molecules using both the Hoffman and Curtius rearrangements.

a)



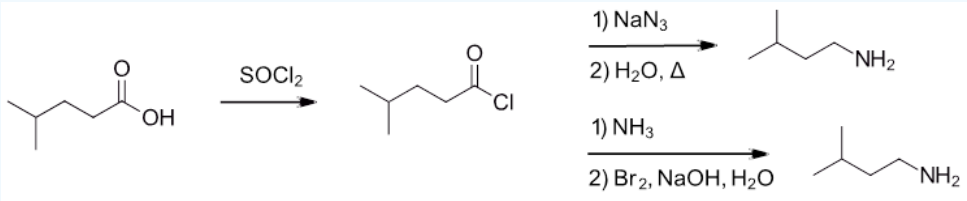
b)



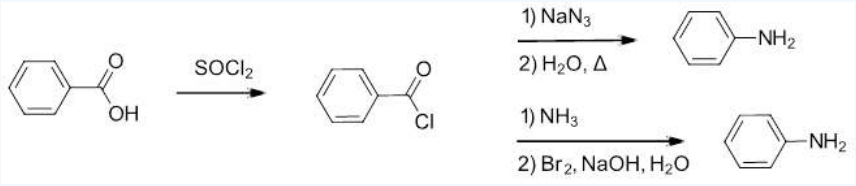
Answers

1)

a) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



b) The top solution shows the Curtius Rearrangement, while the bottom is an example using the Hofmann Rearrangement.



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24.7: REACTIONS OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
2. identify the product formed when a given amine reacts with a given acid chloride.
3. identify the amine, the acid chloride, or both, needed to synthesize a given amide.
4. write a reaction sequence to illustrate the overall conversion of an amine to an alkene via a Hofmann elimination.
5. identify the alkene most likely to be formed when a given quaternary ammonium salt is heated with moist silver oxide (or silver hydroxide).
6. deduce the structure of an unknown quaternary ammonium salt, given the identity of the alkene or alkenes produced when the salt is heated with moist silver oxide.

KEY TERMS

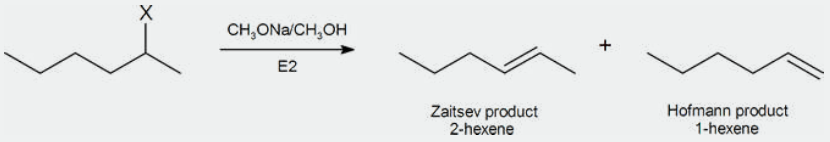
Make certain that you can define, and use in context, the key term below.

- Hofmann elimination

STUDY NOTES

The alkylation and acylation of amines have been dealt with in previous sections: alkylation in Section 24.6 and acylation in Sections 21.4 and 21.5. Review these sections if necessary.

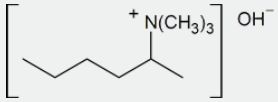
One explanation is given for Hofmann elimination further on in this reading. Another argument, based on the consideration of the structures of the possible transition states, has been suggested by Joseph Bunnett and is widely accepted. We can begin to understand Bunnett's reasoning by considering the elimination products formed from by the dehydrohalogenation of a number of substituted hexanes in the reaction



The table below describes the proportion of each product you would expect when X in the above reaction represents a given halogen.

X	% 2-hexene	% hexene
I	81	19
Br	72	28
Cl	67	33
F	30	70

As we descend this table, the electron-withdrawing ability of X increases, and the percentage of Hofmann product also increases. Given that the $(CH_3)_3N^+$ group is strongly electron-withdrawing, it is quite consistent for a compound of the type



to give 96% Hofmann product and 4% Zaitsev product in an E2 elimination reaction. But why does the proportion of Hofmann product increase as the electron-withdrawing ability of X increases? Bunnett suggests that the transition state in an E2 process can vary from being "carbocation-like" on one hand to "carbanion-like" on the other.

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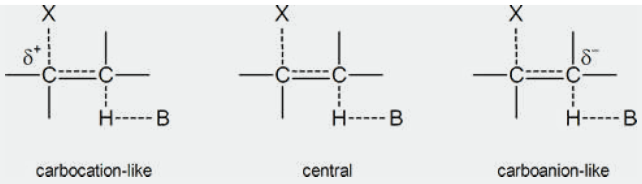
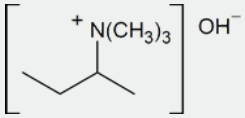


Figure 24.1 Various transition states for an E2 elimination reaction

In a carbocation-like transition state, the C-X bond is broken to a greater extent than the C-H bond; in the central transition state both, the C-X bond and the C-H bond are broken to an equal extent; and in the carbanion-like transition state, the C-H bond is broken to a greater extent than the C-X bond. In the latter case, a partial negative charge will develop on the carbon atom to which the hydrogen is attached, hence the term "carbanion-like." As we already know, any species or transition state bearing a full or partial negative charge is stabilized by the presence of electron-withdrawing groups and destabilized by the presence of electron-releasing groups.

Let us now consider the two possible transition states for an E2 elimination of $(CH_3)_3NH^+$ from a quaternary ammonium hydroxide,



One transition state leads to Zaitsev elimination, the other to Hofmann elimination.

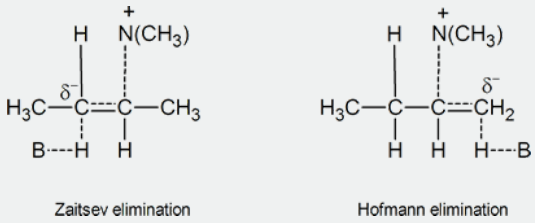
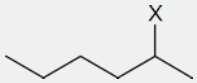


Figure 24.2 Possible carbanion-like transition states

In the transition state leading to the Zaitsev product, the carbon atom carrying the partial negative charge is bonded to an electron-releasing methyl group. This is clearly a less favourable situation than the one that exists in the transition state leading to Hofmann elimination, where there are no electron-releasing groups attached to the carbon atom bearing the partial negative charge. Bunnett's argument is that carbanion-like transition states are much more likely when the atom or group X in a compound such as



is strongly electron withdrawing, because the \(\ce{C-X}\) bond becomes stronger as the electron-withdrawing ability of X increases.

Thus, as we go along the series X = I, Br, Cl, F, $(CH_3)_3N^+$, the electron-withdrawing ability of X increases, the C-X bond becomes more difficult to break, the transition state becomes more carbanion-like in character, and Hofmann elimination becomes more pronounced.

ALKYLATION OF AMINES

It is instructive to examine these nitrogen substitution reactions using the common alkyl halide class of electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1°-amine, presumably by an S_N2 mechanism. The hydrogen bromide produced in the reaction combines with some of the excess ammonia, giving ammonium bromide as a by-product. Water does not normally react with 1°-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

$$\mathbf{2\,RCH_2Br + NH_3(large\ excess) \longrightarrow RCH_2NH_2 + NH_4^{(+)}Br^{(-)}}$$

It follows that simple amines should also be more nucleophilic than their alcohol or ether equivalents. If, for example, we wish to carry out an S_N2 reaction of an alcohol with an alkyl halide to produce an ether (the Williamson synthesis), it is necessary to convert the weakly nucleophilic alcohol to its more nucleophilic conjugate base for the reaction to occur. In contrast, amines react with alkyl halides directly to give N-alkylated products. Since this reaction produces HBr as a byproduct, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.

$$\mathbf{2\,RNH_2 + C_2H_5Br \longrightarrow RNHC_2H_5 + RNH_3^{(+)}Br^{(-)} \rightleftharpoons RNH_2C_2H_5^{(+)}Br^{(-)} + RNH_2}$$

Unfortunately, the direct alkylation of 1° or 2°-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember

that one equivalent of the strong acid HX is produced). If a 2:1 ratio of amine to alkylating agent is used, as in the above equation, the HX issue is solved, but another problem arises. Both the starting amine and the product amine are nucleophiles. Consequently, once the reaction has started, the product amine competes with the starting material in the later stages of alkylation, and some higher alkylated products are also formed. Even 3º-amines may be alkylated to form quaternary (4º) ammonium salts. When tetraalkyl ammonium salts are desired, as shown in the following example, Hünig's base (N,N-diisopropylethylamine) may be used to scavenge the HI produced in the three S_N2 reactions. Steric hindrance prevents this 3º-amine (Hünig's base) from being methylated.

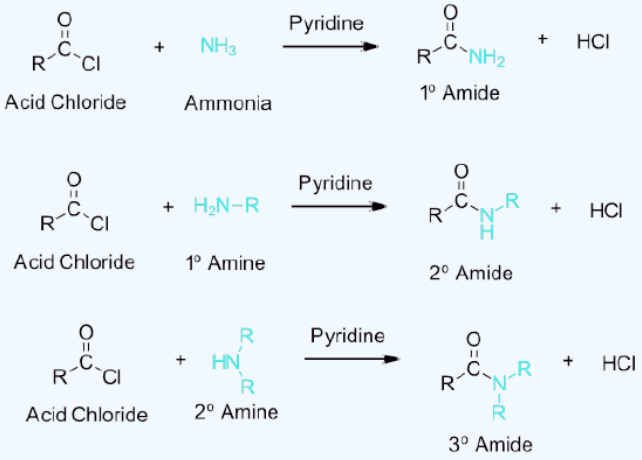
$$C_6H_5NH_2 + 3\,CH_3I + \text{Hünig's base} \longrightarrow C_6H_5N(CH_3)_3{}^{(+)}I^{(-)} + \text{HI salt of Hünig's base}$$

ACYLATION OF AMINES

Ammonia, 1º amines, and 2º amines react rapidly with acid chlorides or acid anhydrides to form 1º, 2º, and 3º amides respectively **(Sections 21-4 and 21.5)**. These reactions typically take place rapidly at room temperature and provide high reaction yields.

The reaction is commonly run with a base, such as NaOH or pyridine, to neutralize the HCl produced. Over-acylation does not occur because the lone pair electrons on the amide nitrogen are conjugated with the carbonyl making it less nucleophilic than an amine starting material.

EXAMPLE 24.7.1

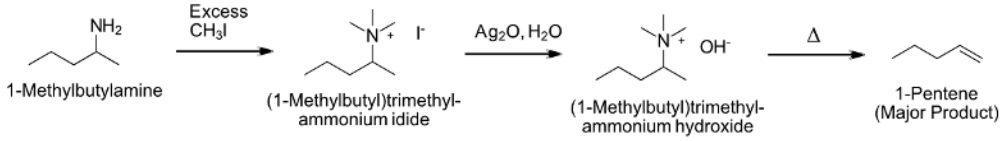


HOFMANN ELIMINATION

Amine functions seldom serve as leaving groups in nucleophilic substitution or base-catalyzed elimination reactions. Indeed, they are even less effective in this role than are hydroxyl and alkoxyl groups. As noted earlier, 1º and 2º-amines are much weaker acids than alcohols, so it is not surprising that it is difficult to force the nitrogen function to assume the role of a leaving group. In this context we note that the acidity of the potential ammonium leaving group is at least ten powers of ten less than that of an analogous oxonium species. However, amines can be turned into a good leaving group by alkylation with an alkyl halide to form a quaternary ammonium salt. Upon elimination the quarternary ammonium salt produces a stable 3º amine as a leaving group.

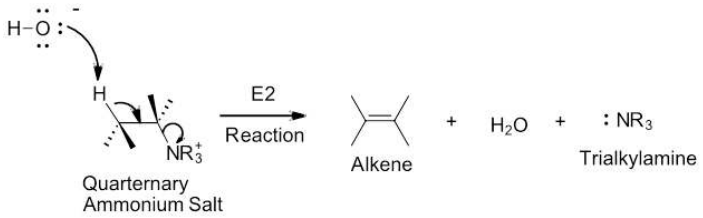
Elimination reactions of 4º-ammonium salts are termed **Hofmann eliminations**. Since the counter anion in most 4º-ammonium salts is halide, this is often replaced by the more basic hydroxide ion through reaction with silver hydroxide (or silver oxide). The resulting hydroxide salt must then be heated (100 - 200 ºC) to affect the E2-like elimination of a 3º-amine. For an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, which is similar to elimination reactions of alkyl halides. Simple amines are easily converted to the necessary 4º-ammonium salts by exhaustive alkylation, usually with methyl iodide (methyl has no beta-hydrogens and cannot compete in the elimination reaction).

General Reaction



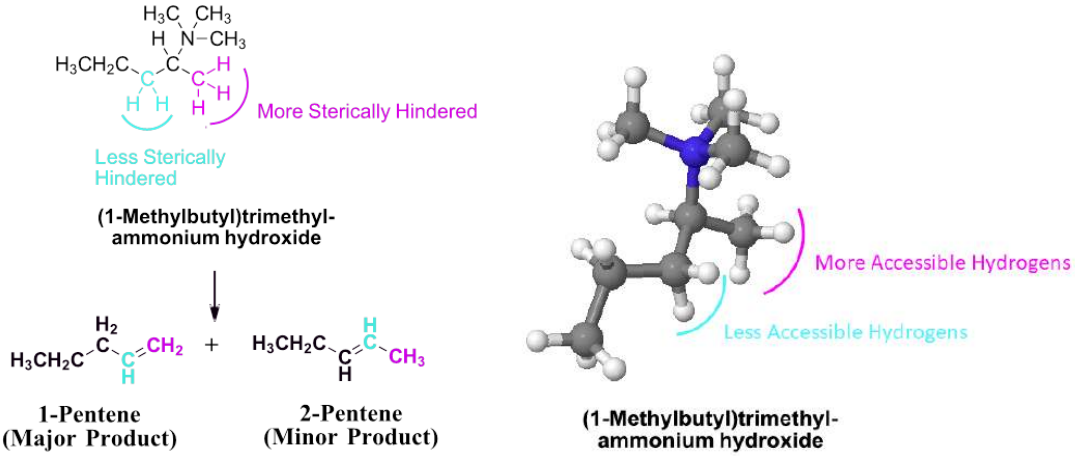
MECHANISM

During the Hofmann elimination, the hydroxide counter ion acts as a base to remove a beta-hydrogen and cause an E2 elimination to form an alkene. A trialkyl amine is eliminated as a leaving group during this reaction.

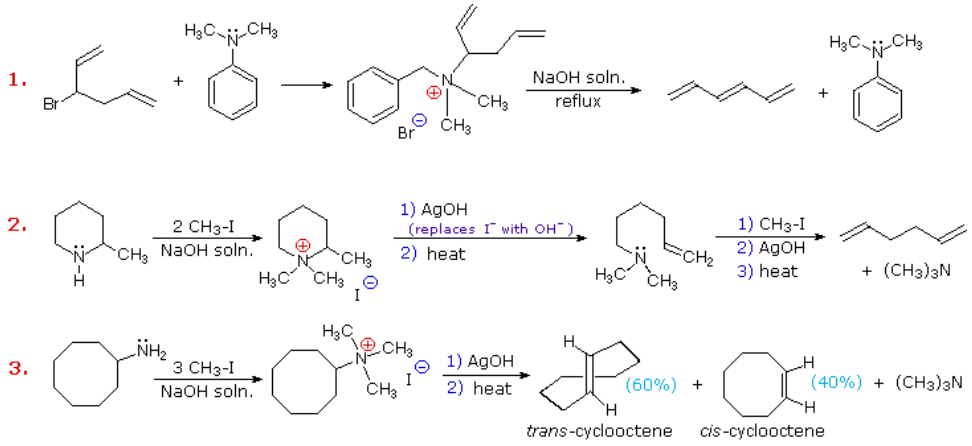


When predicting the products of an E2 elimination, the more substituted alkene is expected to be the preferred product based on Zaitsev's rule. The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**. To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state.

The reason for the difference in products in a Hofmann elimination is most likely due to steric hindrance of the base. The large size of of the quaternary ammonium group forces the base to remove a hydrogen from the least sterically hindered position. This correspondingly leads to the alkene with the least number of substituents to be preferred.



Examples



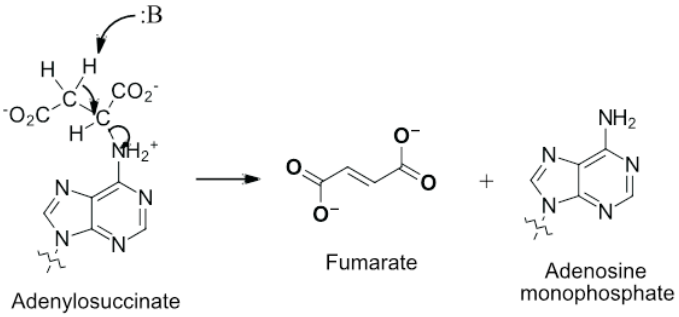
Example #1 is interesting in two respects. First, it generates a 4º-ammonium halide salt in a manner different from exhaustive methylation. Second, this salt is not converted to its hydroxide analog prior to elimination. A concentrated aqueous solution of the halide salt is simply dropped into a refluxing sodium hydroxide solution, and the volatile hydrocarbon product is isolated by distillation.

Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the

molecule, a second Hofmann elimination must be carried out. Indeed, if the nitrogen atom was a member of two rings (fused or spiro), then three repetitions of the Hofmann elimination would be required to remove the nitrogen from the remaining molecular framework.

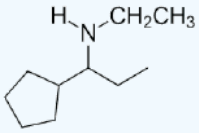
Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could also be formed by a syn-elimination. Cyclooctane is a conformationally complex structure. Several puckered conformations that avoid angle strain are possible, and one of the most stable of these is shown on the right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

Eliminations analogous to the Hofmann elimination are often seen in biological systems. In these cases, ammonium ions (protonated amines) are used instead of quaternary ammonium salts. An example is seen in the biosynthesis of nucleic acids where a biological base causes a Hofmann-like elimination of protonated adenylosuccinate to produce the alkene containing fumarate and adenosine monophosphate.



WORKED EXERCISE 24.7.1

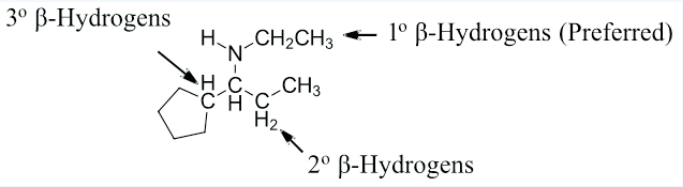
Predict the preferred product of a Hofmann elimination with the following molecule.



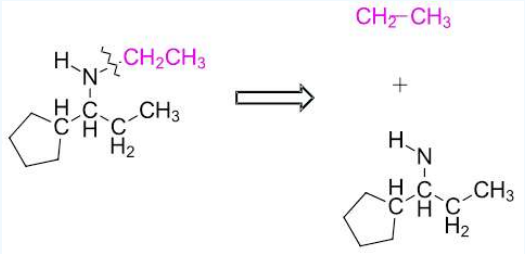
Answer

Predicting the product of a Hofmann elimination can be difficult so it is best done stepwise.

Step 1: Find the least sterically hindered beta hydrogens. Beta hydrogens are on the second carbon away from the nitrogen. The order of preferred hydrogens are $1^o > 2^o > 3^o$. If the molecule is presented as a line structure it is usually beneficial to convert to a condensed structure first.

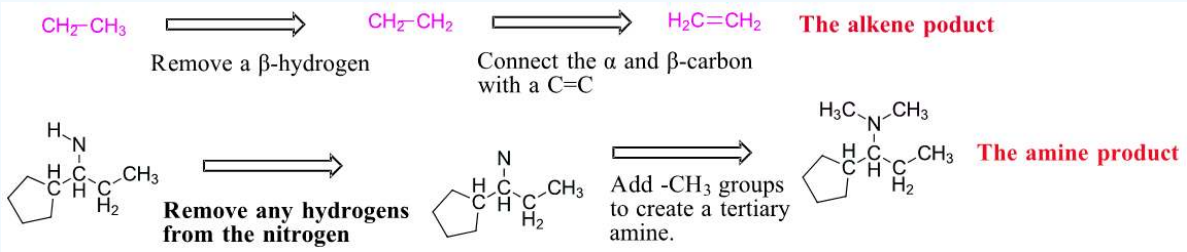


Step 2: Break the C-N bond of the alkyl group which contains the preferred hydrogens. This will form two fragments.



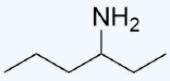
https://chem.libretexts.org/@go/page/36445

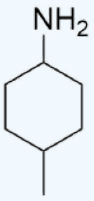
Step 3: Remove one of the original beta hydrogens in the alkyl fragment then draw a C=C between the alpha and beta carbon. This produces the alkene product of the Hofmann elimination. Sometimes the amine fragment of a Hofmann elimination is of interest. Remember that prior to elimination the amine is exhaustively alkylated with CH_3I. This means any hydrogens attached to amine will starting material will be removed and the amine product will have enough methyl ($-CH_3$) groups added to become a tertiary amine. In this case two methyl groups are added to the nitrogen. The end result are the two products of a Hofmann elimination.

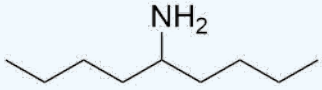


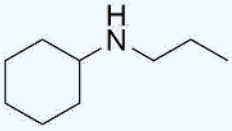
EXERCISE 24.7.1

Draw the product for a Hofmann elimination for each of the following molecules.

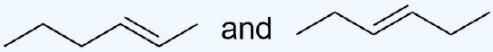
a. 

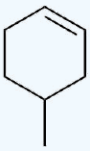
b. 

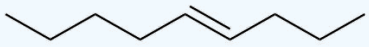
c. 

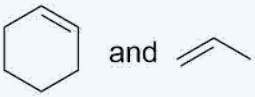
d. 

Answer

a. 

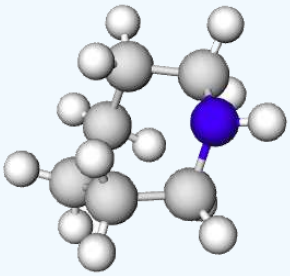
b. 

c. 

d. 

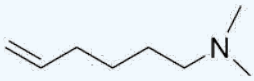
EXERCISE 24.7.2

Draw the product of a Hofmann elimination for the following molecule.



Azepane

Answer



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24.8: REACTIONS OF ARYLAMINES

OBJECTIVES

After completing this section, you should be able to

1. a. identify the product formed when a given arylamine is reacted with aqueous bromine.
   b. give an appropriate example to illustrate the high reactivity of arylamines in electrophilic aromatic substitution reactions.
   c. explain why arylamines cannot be used in Friedel-Crafts reactions.
2. a. show how the problems associated with carrying out electrophilic aromatic substitution reactions on arylamines can be circumvented by first converting the amine to an amide, and illustrate this process with an appropriate example.
   b. outline a possible synthetic route for the preparation of a given sulfa drug.
   c. identify the starting material, the necessary organic reagents, inorganic reagents, or both, and the intermediate compounds formed during the synthesis of a given sulfa drug.
   d. design a multi-step synthesis for a given compound in which it is necessary to protect the amino group by acetylation.
3. a. write a general equation to describe the formation of an arenediazonium salt.
   b. identify the product formed when a given arenediazonium salt is reacted with any of the following compounds: copper(I) chloride, copper(I) bromide, sodium iodide, copper(I) cyanide, hot aqueous acid, hypophosphorous acid.
   c. identify the arenediazonium salt, the inorganic reagents, or both, needed to produce a given compound by a diazonium replacement reaction.
4. a. illustrate, with appropriate examples, the importance to the synthetic chemist of the overall reaction sequence A nitration, B reduction, C diazotization, and D replacement.
   b. show how the removal of an amino (or nitro) group from an aromatic ring through the reaction of an arenediazonium salt with hypophosphorous acid (H_3PO_2) can sometimes be of use in organic synthesis.
5. a. write a general equation to represent a diazonium coupling reaction.
   b. write the detailed mechanism for the coupling reaction which takes place between arenediazonium salts and the electon-rich aromatic rings of phenols and arylamines.
   c. identify the product formed from the reaction of a given arenediazonium salt with a given arylamine or phenol.
   d. identify the arenediazonium salt and the arylamine or phenol needed to prepare a given azo compound.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

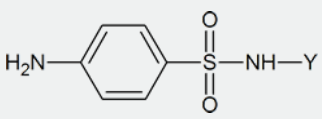
- arenediazonium salt
- azo compound
- Sandmeyer reaction
- sulfa drug

STUDY NOTES

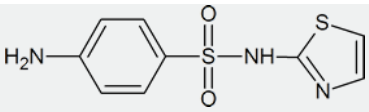
This section contains a considerable amount of new information. To absorb all of it, you should use the three subsections indicated in the reading: electrophilic aromatic substitution and overreaction of aniline (Objectives 1 and 2), the preparation of diazonium salts and the Sandmeyer reaction (Objectives 3 and 4), and diazonium coupling reactions (Objective 5).

The general process in which an aromatic amine is reacted with acetic anhydride, substituted, and then hydrolyzed is known as “protecting the amino group.”

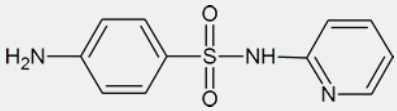
Sulfa drugs have the general formula



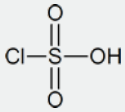
Typical examples are sulfathiazole



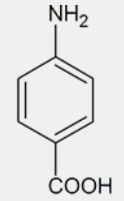
and sulfapyridine



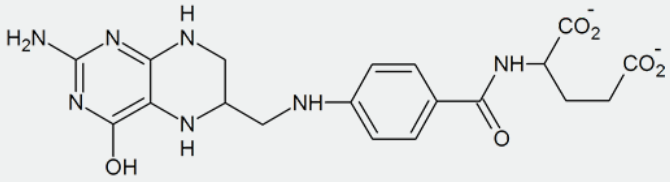
The reagent used to bring about the chlorosulfonation of acetanilide is chlorosulfuric acid



Sulfanilamide itself is toxic to humans, but derivatives of this compound, such as sulfathiazole, are less harmful to humans and are effective in killing many types of bacteria. The drugs work by “deceiving” the bacteria in the following way. To survive, many micro-organisms use *p*-aminobenzoic acid to synthesize folic acid, a coenzyme in a number of biochemical processes. These micro-organisms cannot distinguish between sulfa drugs and *p*-aminobenzoic acid; so, when the drug is administered, the bacteria use it to produce a compound which has a structure similar to that of folic acid, but which is unable to act as a coenzyme in essential biochemical processes. The result is that many of the bacteria’s amino acids and nucleotides cannot be made, and the bacteria die. Amino acids are discussed in Chapter 26; nucleotides are discussed in Section 28.1.

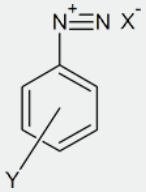


p-aminobenzoic acid



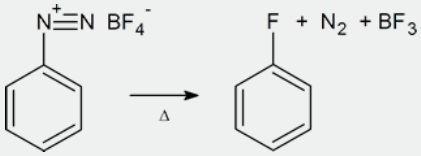
folic acid

An “arenediazonium salt” is formed by the reaction of an aromatic amine with nitrous acid at 0–5°C, and has the structure shown below.



Alkanediazonium salts are very unstable; therefore, arenediazonium salts are often simply referred to as diazonium salts.

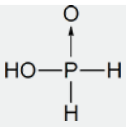
As is mentioned in the textbook, arenediazonium salts are very useful intermediates from which a wide variety of aromatic compounds can be prepared. You should be thoroughly familiar with the use of diazonium salts to prepare each of the classes of compounds. In addition, you should be aware that fluoroarenes can also be prepared from diazonium salts, as follows:



In this case the diazonium salt is prepared using fluoroboric acid, HBF_4, and sodium nitrite. The thermal decomposition of the salt, called the Schiemann reaction, can be quite hazardous.

Note that the IUPAC-preferred name for cuprous chloride is copper(I) chloride; similarly, cuprous cyanide is called copper(I) cyanide.

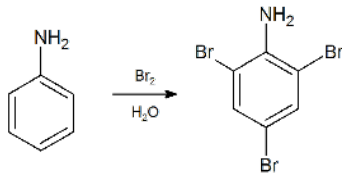
Hypophosphorous acid has the structure shown below:



The presence of the letters “azo” in a compound’s name usually implies that a nitrogen-nitrogen double bond is present in its structure. Azo compounds t in which two aryl groups are joined by a **–N=N–** linkage are usually very colorful.

OVERREACTION OF ANILINE

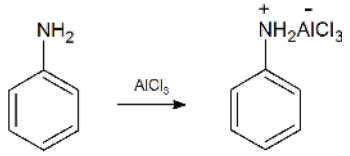
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable oxidative decomposition to tarry materials; aniline (aminobenzene) is largely destroyed. Monobromination of both phenol and aniline is difficult to control, with di- and tri-bromo products forming readily.



Because of their high nucleophilic reactivity, aniline and phenol undergo substitution reactions with iodine, a halogen that is normally unreactive with benzene derivatives. The mixed halogen iodine chloride (ICl) provides a more electrophilic iodine moiety, and is effective in iodinating aromatic rings having less powerful activating substituents.

$$C_6H_5{-}NH_2 + I_2 + NaHCO_3 \longrightarrow p\text{-}I{-}C_6H_4{-}NH_2 + NaI + CO_2 + H_2O$$

In addition to overreactivity, we have previously seen (Section 16.3) that Friedel-Crafts reactions employing $AlCl_3$ catalyst does not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



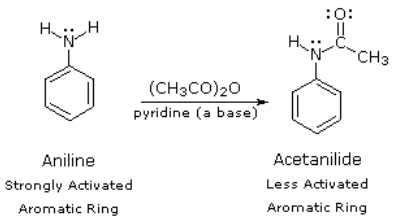
Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

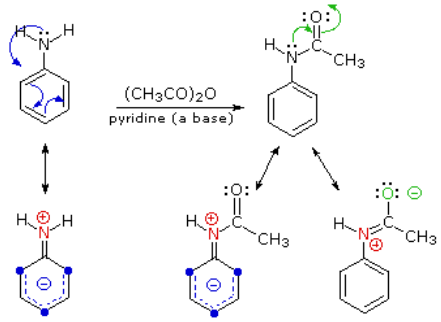
MODIFYING THE INFLUENCE OF STRONG ACTIVATING GROUPS

By acetylating the heteroatom substituent on aniline, its activating influence can be substantially attenuated. For example, acetylation of aniline gives acetanilide (first step in the following equation), which undergoes nitration at low temperature, yielding the para-nitro product in high yield. The modifying acetyl group can then be removed by acid-catalyzed hydrolysis (last step), to yield para-nitroaniline. Although the activating influence of the amino group has been reduced by this procedure, the acetyl derivative remains an ortho/para-directing and activating substituent.

$$C_6H_5{-}NH_2 + (CH_3CO)_2O \xrightarrow{\text{pyridine (a base)}} C_6H_5{-}NHCOCH_3 \xrightarrow{HNO_3\ ,\ 5\ ^oC} p\text{-}O_2N \quad (24.8.1)$$
$$-C_6H_4{-}NHCOCH_3 \xrightarrow{H_3O^+\ \text{and heat}} p\text{-}O_2N{-}C_6H_4{-}NH$$

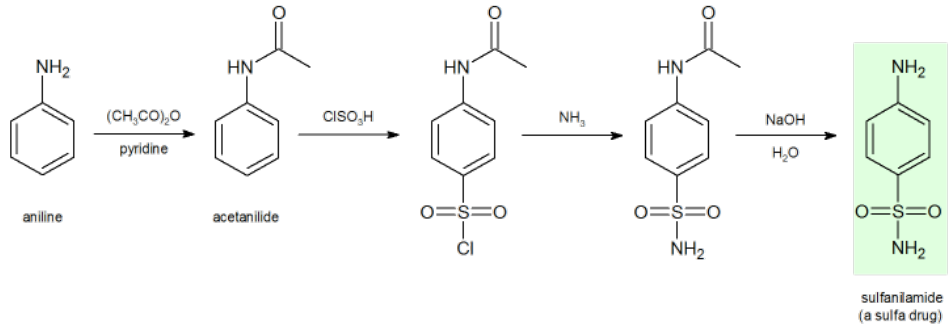
The following diagram illustrates how the acetyl group acts to attenuate the overall electron donating character of oxygen and nitrogen. The non-bonding valence electron pairs that are responsible for the high reactivity of these compounds (blue arrows) are diverted to the adjacent carbonyl group (green arrows). However, the overall influence of the modified substituent is still activating and ortho/para-directing.





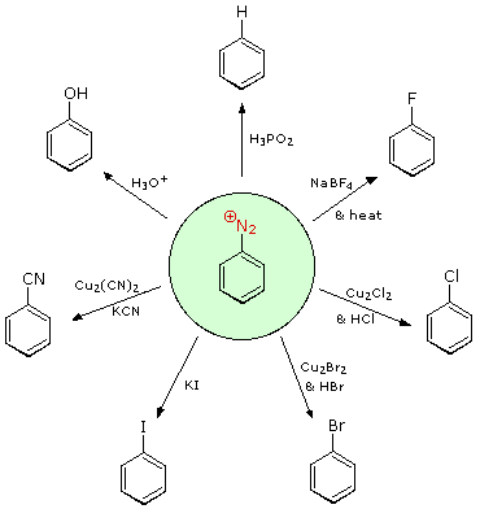
SULFA DRUG SYNTHESIS

Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group. The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution. The corresponding acetanilide undergoes chlorosulfonation. The resulting 4-acetamidobenzenesulfanyl chloride is treated with ammonia to replace the chlorine with an amino group and affords 4-acetamidobenzenesulfonamide. The subsequent hydrolysis of the sulfonamide produces the sulfanilamide.



DIAZONIUM SALTS: THE SANDMEYER REACTION

Aryl diazonium salts are important intermediates. They are prepared in cold (0 ° to 10 ºC) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored. Those substitution reactions that are catalyzed by cuprous salts are known as **Sandmeyer reactions**. Fluoride substitution occurs on treatment with $BF_4^{(-)}$, a reaction known as the **Schiemann reaction**. Stable diazonium tetrafluoroborate salts may be isolated, and on heating these lose nitrogen to give an arylfluoride product. The top reaction with hypophosphorus acid, H_3PO_2, is noteworthy because it achieves the reductive removal of an amino (or nitro) group. Unlike the nucleophilic substitution reactions, this reduction probably proceeds by a radical mechanism.



These aryl diazonium substitution reactions significantly expand the tactics available for the synthesis of polysubstituted benzene derivatives. Consider the following options:

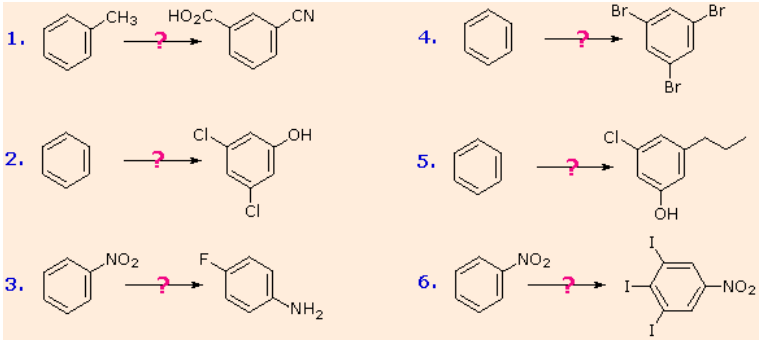
I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.

II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly activates an aromatic ring and directs electrophilic substitution to ortho & para locations.

III. The activating character of an amine substituent may be attenuated by formation of an amide derivative (reversible), or even changed to deactivating and meta-directing by formation of a quaternary-ammonium salt (irreversible).

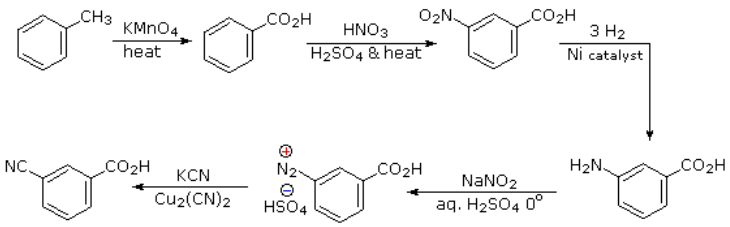
IV. Conversion of an aryl amine to a diazonium ion intermediate allows it to be replaced by a variety of different groups (including hydrogen), which may in turn be used in subsequent reactions.

The following examples illustrate some combined applications of these options to specific cases. You should try to conceive a plausible reaction sequence for each. Once you have done so, you may check suggested answers below.



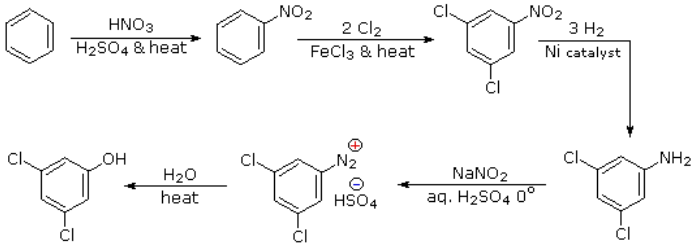
Answer 1:

It should be clear that the methyl substituent will eventually be oxidized to a carboxylic acid function. The timing is important, since a methyl substituent is ortho/para-directing and the carboxyl substituent is meta-directing. The cyano group will be introduced by a diazonium intermediate, so a nitration followed by reduction to an amine must precede this step.



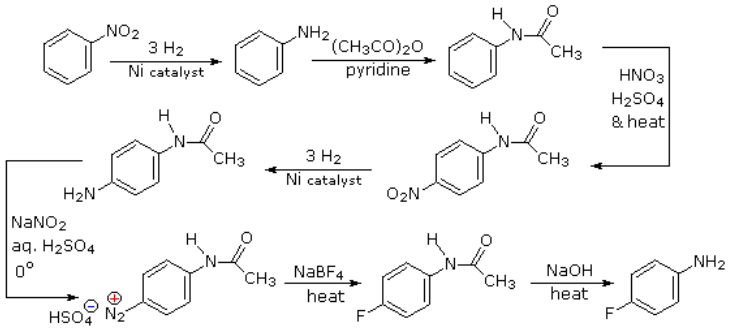
Answer 2:

The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



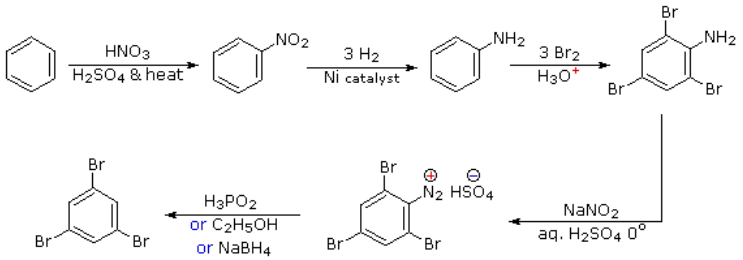
Answer 3:

Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must first reduce it to an ortho/para-directing amino group. Amino groups are powerful activating substituents, so we deactivate it by acetylation before nitration. The acetyl substituent also protects the initial amine function from reaction with nitrous acid later on. It is removed in the last step.



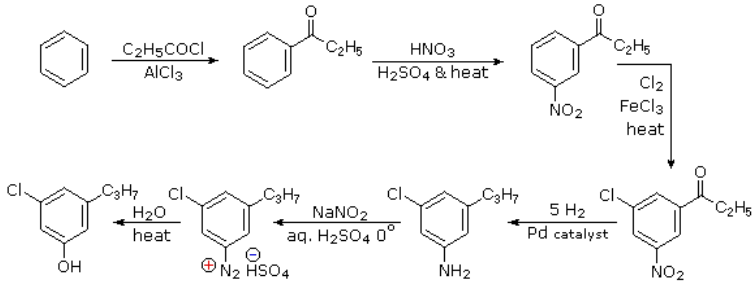
Answer 4:

Polybromination of benzene would lead to ortho/para substitution. In order to achieve the mutual meta-relationship of three bromines, it is necessary to introduce a powerful ortho/para-directing prior to bromination, and then remove it following the tribromination. An amino group is ideal for this purpose. Reductive removal of the diazonium group may be accomplished in several ways (three are shown).



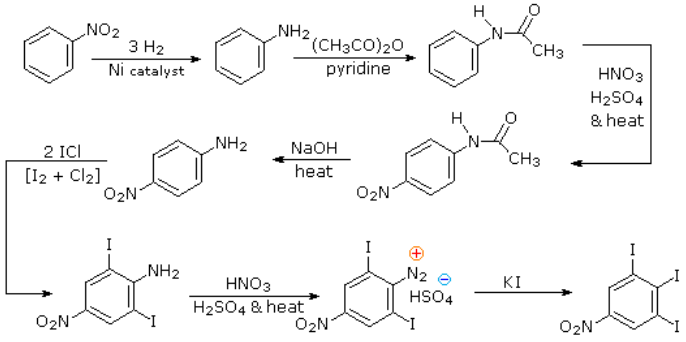
Answer 5:

The propyl substituent is best introduced by Friedel-Crafts acylation followed by reduction, and this cannot be carried out in the presence of a nitro substituent. Since an acyl substituent is a meta-director, it is logical to use this property to locate the nitro and chloro groups before reducing the carbonyl moiety. The same reduction method can be used to reduce both the nitro group (to an amine) and the carbonyl group to propyl. We have already seen the use of diazonium intermediates as precursors to phenols.



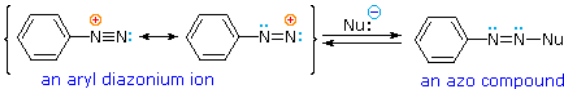
Answer 6:

Aromatic iodination can only be accomplished directly on highly activated benzene compounds, such as aniline, or indirectly by way of a diazonium intermediate. Once again, a deactivated amino group is the precursor of p-nitroaniline (prb.#3). This aniline derivative requires the more electrophilic iodine chloride (ICl) for ortho-iodination because of the presence of a deactivating nitro substituent. Finally, the third iodine is introduced by the diazonium ion procedure.



DIAZONIUM COUPLING REACTIONS

A resonance description of diazonium ions shows that the positive charge is delocalized over the two nitrogen atoms. It is not possible for nucleophiles to bond to the inner nitrogen, but bonding (or coupling) of negative nucleophiles to the terminal nitrogen gives neutral azo compounds. As shown in the following equation, this coupling to the terminal nitrogen should be relatively fast and reversible. The azo products may exist as E / Z stereoisomers. In practice it is found that the E-isomer predominates at equilibrium.



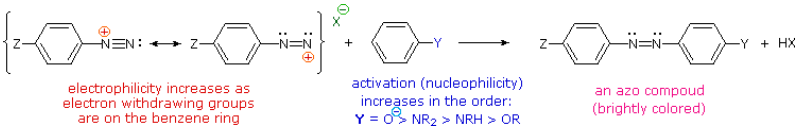
Unless these azo products are trapped or stabilized in some manner, reversal to the diazonium ion and slow nucleophilic substitution at carbon (with irreversible nitrogen loss) will be the ultimate course of reaction, as described in the previous section. For example, if phenyldiazonium bisufate is added rapidly to a cold solution of sodium hydroxide a relatively stable solution of sodium phenyldiazoate (the conjugate base of the initially formed diazoic acid) is obtained. Lowering the pH of this solution regenerates phenyldiazoic acid (pK_a ca. 7), which disassociates back to the diazonium ion and eventually undergoes substitution, generating phenol.

$C_6H_5N_2^{(+)}\ HSO_4^{(-)}$ + NaOH (cold solution)	⇌	$C_6H_5N_2$–OH + NaOH (cold)	⇌	$C_6H_5N_2$–$O^{(-)}\ Na^{(+)}$
phenyldiazonium bisulfate		phenyldiazoic acid		sodium phenyldiazoate

Aryl diazonium salts may be reduced to the corresponding hydrazines by mild reducing agents such as sodium bisulfite, stannous chloride or zinc dust. The bisulfite reduction may proceed by an initial sulfur-nitrogen coupling, as shown in the following equation.

$$Ar\text{-}N_2^{(+)}\ X^{(-)} \xrightarrow{NaHSO_3} Ar\text{-}N{=}N\text{-}SO_3H \xrightarrow{NaHSO_3} Ar\text{-}NH\text{-}NH\text{-}SO_3H \xrightarrow{H_2O} Ar\text{-}NH\text{-}NH_2 + H_2SO_4$$

The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles. The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes. Azobenzene (Y=Z=H) is light orange; however, the color of other azo compounds may range from red to deep blue depending on the nature of the aromatic rings and the substituents they carry. Azo compounds may exist as cis/trans isomer pairs, but most of the well-characterized and stable compounds are trans.



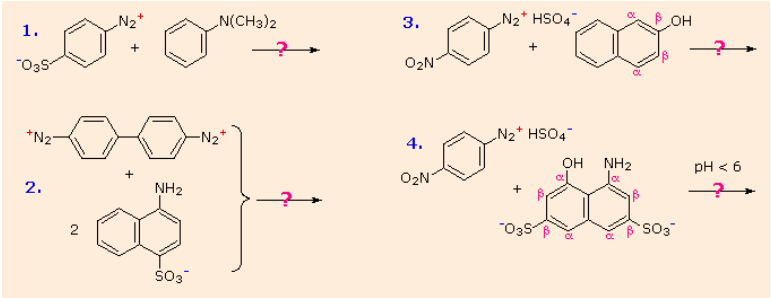
Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.

II. Coupling to an activated benzene ring occurs preferentially para to the activating group if that location is free. Otherwise ortho-coupling will occur.

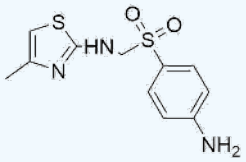
III. Naphthalene normally undergoes electrophilic substitution at an alpha-location more rapidly than at beta-sites; however, ortho-coupling is preferred. See the diagram for examples of α / β notation in naphthalenes.

You should try to conceive a plausible product structure for each of the following couplings.



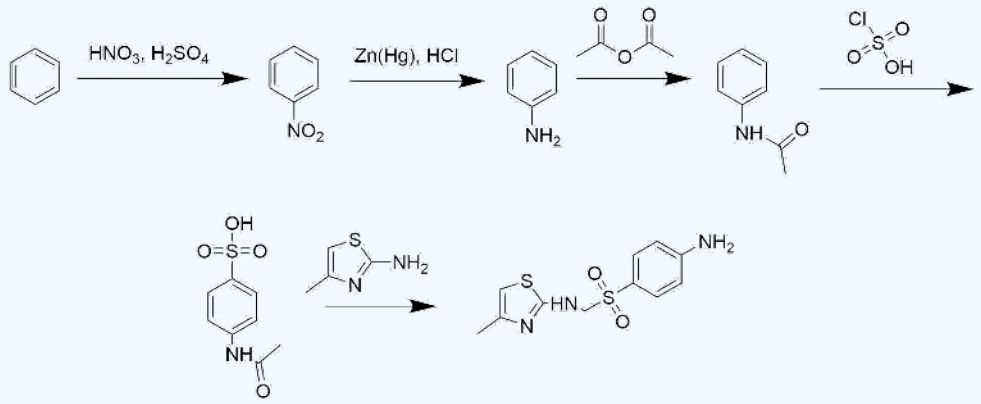
? EXERCISE 24.8.1

Propose a synthesis for the following compound via benzene and any amine you may require.



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Answer



EXERCISE 24.8.2

Proposes synthesis for each of the following compounds via benzene.

a. *N*,*N*-Diethylaniline
b. *p*-Bromoaniline
c. *m*-Bromoaniline
d. 2,4-Diethylaniline

Answer

a. 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. EtBr
b. 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. Br_2, $FeBr_3$; 5. H_2O, NaOH
c. 1. HNO_3, H_2SO_4; 2. Br_2, $FeBr_3$; 3. Zn(Hg), HCl
d. 1. HNO_3, H_2SO_4; 2. Zn(Hg), HCl; 3. $(CH_3CO)O_2$; 4. EtCl, $AlCl_3$; 5. H_2O, NaOH

EXERCISE 24.8.3

Propose a synthesis for each of the following molecules from benzene via the diazonium ion.

a. *p*-Chlorobenzoic acid
b. *m*-Chlorobenzoic acid
c. *m*-Dichlorobenzene
d. *p*-Ethylbenzoic acid
e. 1,2,4-Trichlorobenzene

Answer

a. 1. CH_3CH_2Cl, $AlCl_3$; 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuBr; 6. $KMnO_4$, H_2O
b. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$, H_3O^+; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
c. 1. HNO_3, H_2SO_4; 2. Cl_2, $FeCl_3$; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCl
d. 1. CH_3CH_2Cl, $AlCl_3$. 2. HNO_3, H_2SO_4; 3. $SnCl_2$; 4. $NaNO_2$, H_2SO_4; 5. CuCN; 6. H_3O^+
e. 1. HNO_3, H_2SO_4; 2. H_2/PtO_2; 3. $(CH_3CO)_2O$; 4. 2 Cl_2; 5. H_2O, NaOH; 6. $NaNO_2$, H_2SO_4; 7. CuCl

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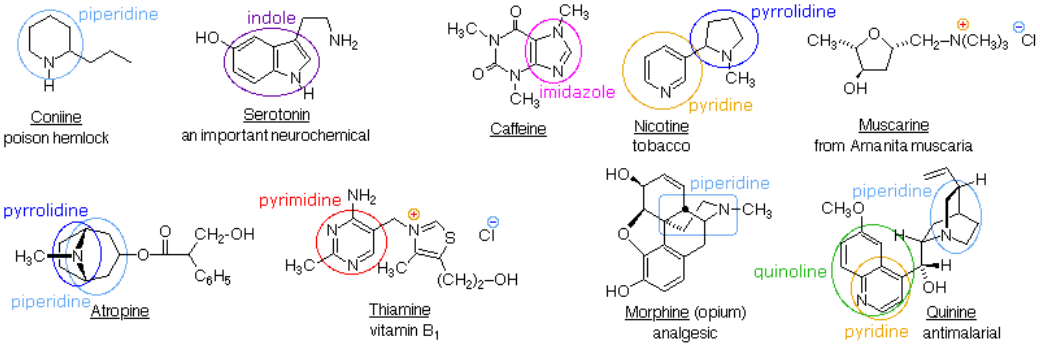
24.9: HETEROCYCLIC AMINES

OBJECTIVES

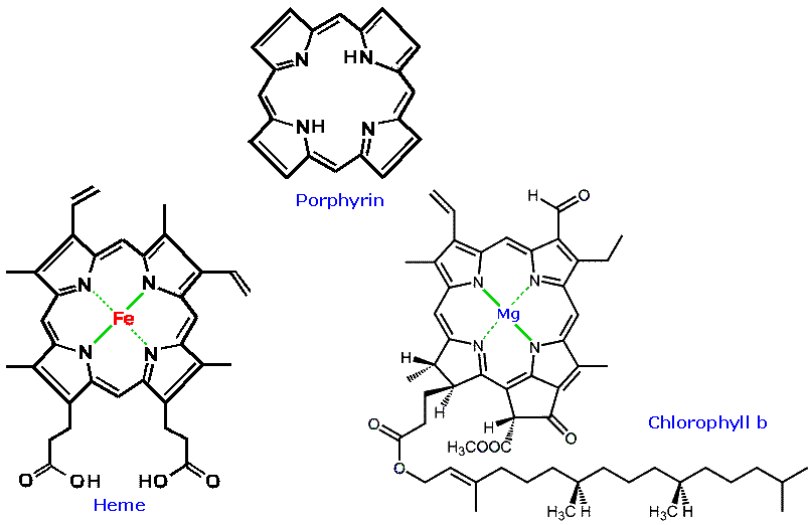
After completing this section, you should be able to

1. draw the structure of furan, pyrrole and imidazole.
2. use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
3. predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution, such as nitration, etc.
4. write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
5. describe the geometry of the pyridine molecule.
6. account for the difference in basicity between pyridine, pyrrole and other amines.
7. explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
8. identify the presence of a fused-ring heterocycle in a given structure.
9. make predictions about the chemical behaviour of the fused-ring heterocycle based on what you have learned about pyrrole, imidazole, pyridine and pyrimidine.

Heterocyclic structures containing nitrogen are found in many natural products. Examples of some nitrogen compounds, known as alkaloids because of their basic properties, were given in the amine chapter.



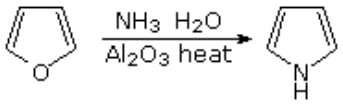
The porphyrin aromatic heterocycle contains multiple pyrrole ring strictures. The porphyrines, heme and chlorophyll b play vital parts in the metabolism of plants and animals.



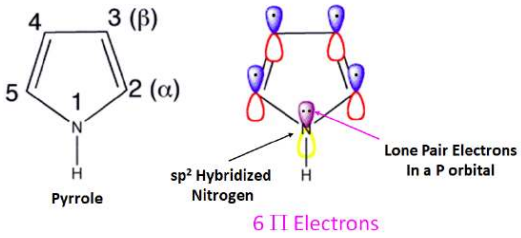
PYRROLE

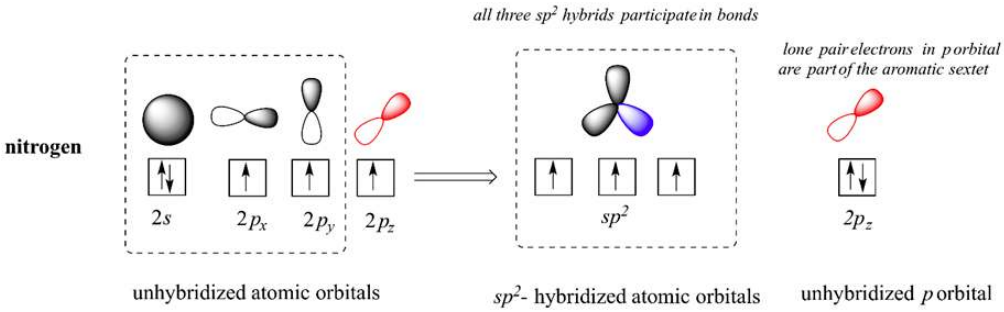
Pyrrole is obtained commercially by the reaction of furan with ammonia .

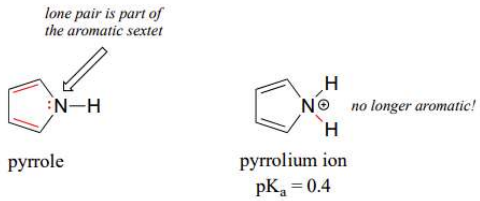
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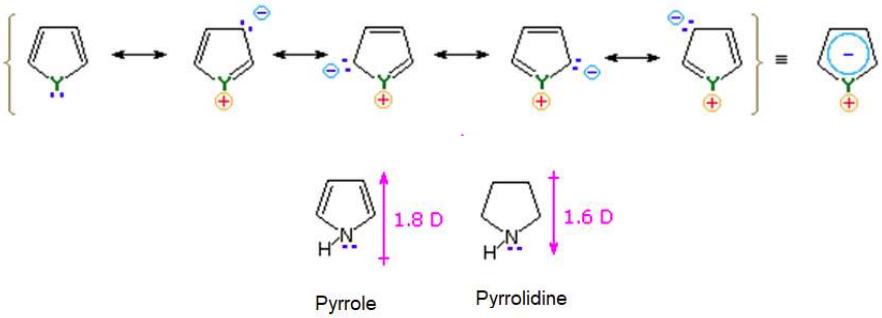
As discussed in Section 15-5, pyrrole has six pi electrons contributing to its aromaticity. Each carbon in pyrrole contributes one pi electron. The nitrogen in pyrrole contributes two pi electron by becoming sp^2 hybridized and placing its lone pair electrons into a p orbital. Because the nitrogen lone pair *is* part of the aromatic sextet, the electrons are very stable and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromatic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic. Pyrrole is a very weak base: the conjugate acid is a strong acid with a pK_a of 0.4.



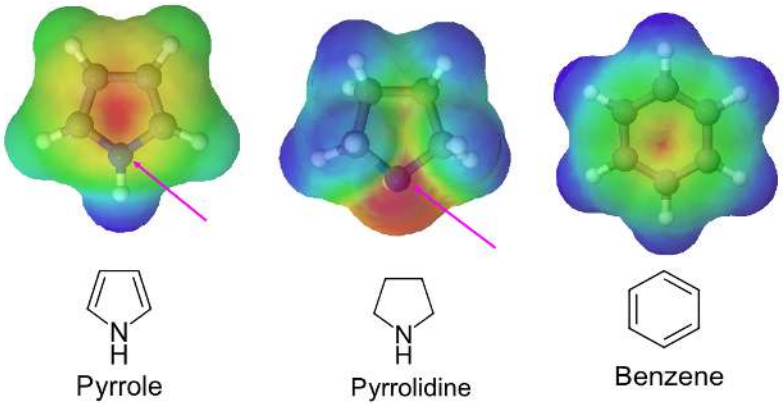




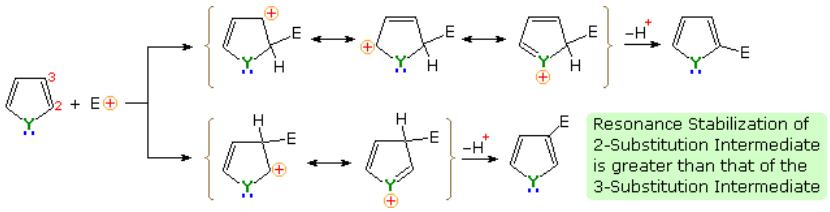
The involvement of the nitrogen lone pair electrons in pyrrole's aromatic conjugation creates charge separated structures not normally found for benzene. The combination of these resonance forms creates an overall separation of charge which increases the electron density around the ring carbons and decreases the electron density on the nitrogen. This effect has a number of ramifications. First is that pyrrole has a large dipole moment (1.8 D) pointing away from the ring nitrogen. This is in sharp contrast to the non-aromatic heterocycle pyrrolidine where the dipole moment (1.5 D) points towards the ring nitrogen.



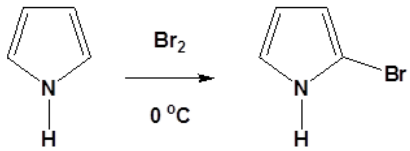
Due to the resonance forms, pyrrole has less electron density around it than the nitrogen in a typical alkyl amine. This agrees with fact that that pyrrole is a much weaker base than pyrrolidine. The electrostatic potential map of pyrrole (Shown Below) shows less electron density (shown as a red color) on the ring nitrogen when compared to its aliphatic equivalent, pyrrolidine. The map of pyrrole also shows that the resonance forms increase the electron density of pyrrole's ring carbons when compared to the ring carbons of benzene. The involvement of nitrogen's lone pair electrons in the aromaticity of pyrrole makes the ring activated towards electrophilic aromatic substitution.



Pyrrole can undergo many of the same electrophilic aromatic substitution reactions as benzene. Because of the activation of pyrrole's aromatic ring, many of these reactions are performed under a reduced temperature compared to a similar reaction with benzene. There is a clear preference for substitution at the 2-position (α) of the pyrrole ring. An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.

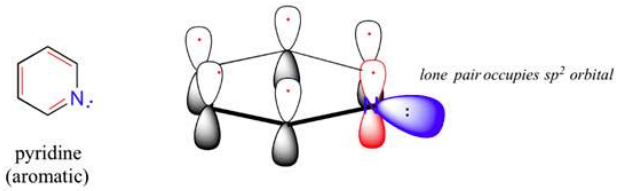


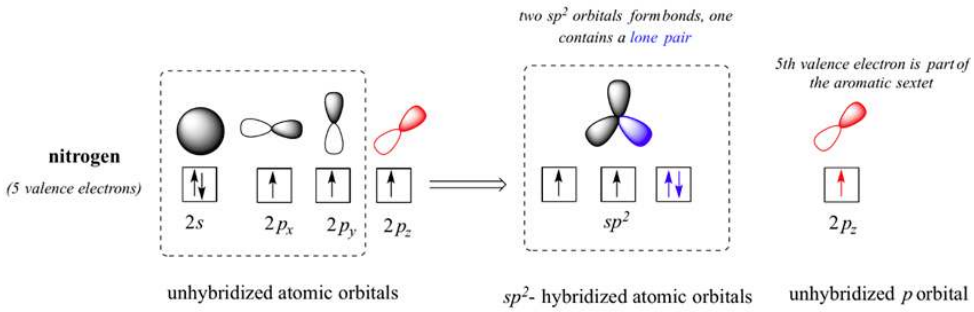
EXAMPLE



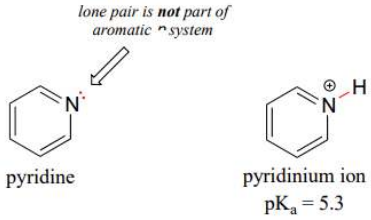
PYRIDINE

Pyridine is an example of a six-membered aromatic heterocycle. In the bonding picture for pyridine, the nitrogen is sp^2-hybridized, with two of the three sp^2 orbitals forming sigma overlaps with the sp^2 orbitals of neighboring carbon atoms, and the third nitrogen sp^2 orbital containing the lone pair. The unhybridized *p* orbital contains a single electron, which is part of the 6 pi-electron aromatic system delocalized around the ring.

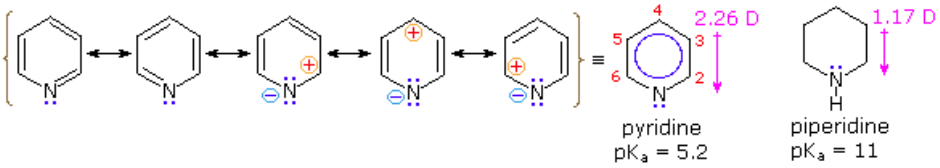




Pyridine's nitrogen lone pair occupies an sp^2-hybrid orbital, and *is not* part of the aromatic sextet. Thus, its electron pair is available for forming a bond to a proton, making pyridine's nitrogen atom (conjugate acid $pK_a = 5.25$) more basic than pyrrole's ($pK_a = 0.4$). However, pyridine is is less basic than a typical alkylamine ($pK_a \sim 10$-11). The difference is due to nitrogen hybridization. The lone pair electrons on a pyridine nitrogen occupy an sp^2 hybrid orbital, while the lone pair electrons on an amine nitrogen occupy an sp^3 hybrid orbital. sp^2 orbitals are composed of one part *s* and two parts *p* atomic orbitals, meaning that they have about 33% *s* character. sp^3 orbitals, conversely, are only 25% *s* character (one part *s*, three parts *p)* . An *s* atomic orbital holds electrons closer to the nucleus than a *p* orbital, thus *s* orbitals are more electronegative than *p* orbitals. Therefore, sp^2 hybrid orbitals, with their higher s-character, are more electronegative than sp^3 hybrid orbitals. Lone pair electrons in the more electronegative sp^2 hybrid orbitals of pyridine are held more tightly to the nitrogen nucleus, and are therefore less 'free' to break away and form a bond to a proton - in other words, they are less basic.

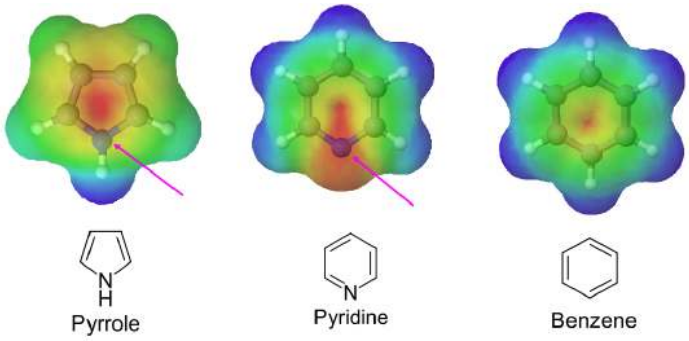


The lack of involvement of pyrrole's nitrogen lone pair electrons in the aromatic conjugation creates charge separated structures not normally found for benzene. The combination of the resonance forms creates an overall charge separation which increases the electron density around the ring's nitrogen and decreases the electron density on the ring carbons. This causes pyridine to have a larger dipole moment (2.26 D) than its non-aromatic equivalent piperidine where the dipole moment (1.17 D). In both cases the dipole moment points towards the ring nitrogen.



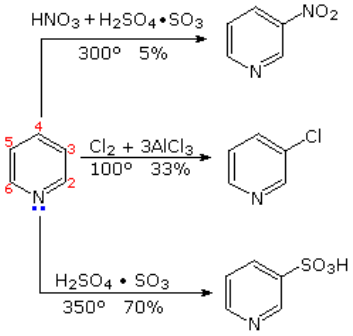
Due to the resonance forms, pyridine has more electron density around its nitrogen than in a typical alkyl amine. The electrostatic potential map of pyridine (Shown Below) shows more electron density (shown as a red color) on the ring nitrogen of pyridine when compared to pyrrole. The map of pyridine also shows that the resonance forms decrease the electron density of pyridine's ring carbons (Show as a blue/green color) when compared to those of benzene. The involvement of the nitrogen's lone pair electrons in the aromaticity of pyridine makes the ring deactivated towards electrophilic aromatic substitution.

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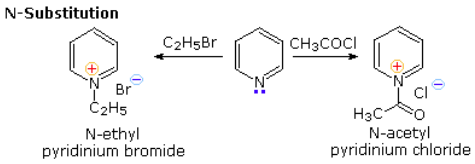
From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. When these reactions do occur then tend to produce the 3-substituted product. Three examples of the extreme conditions required for electrophilic substitution are shown below.

Example

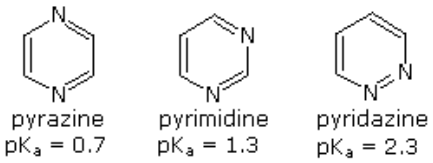


Friedel-Crafts reactions are not feasible because alkyl halides and acid halides prefer to react with pyridine nucleophilic ring nitrogen to provide a N-substituted product. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. Pyridine is a modest base (pK_a=5.2). Since the lone pair electrons on pyridine's nitrogen are not part of the aromatic sextet, the pyridinium species produced by N-substitution retains the aromaticity of pyridine.

Example

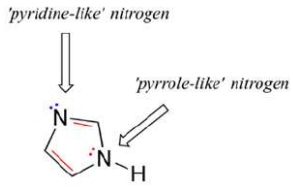


Other six-membered nitrogen contain aromatic heterocycles include pyrazine, pyrimidine, and pyridazine. The inductive effect of a second nitrogen makes all three of these heterocycles less basic than pyridine.

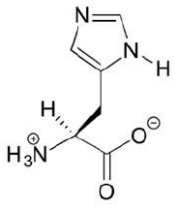


IMIDAZOLE

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring. The two nitrogens in imidazole are quite different. One nitrogen is pyrrole-like and donates its lone pair electrons, like pyrrole, to make imidazole aromatic. The other nitrogen is pyridine like and its lone pair electrons are contained is a sp^2 hybridized orbital. These lone pair electrons are readily available for bonding which imidazole (pK_a = 6.95) much more basic than pyrrole (pK_a = 0.4).



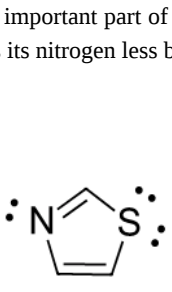
imidazole



histidine

THIAZOLE

Thiazole is a five-membered sulfur containing aromatic ring system which is found in biological systems, such as thiamine diphosphate. Thiamine diphosphate (ThDP, sometimes also abbreviated TPP or ThPP) is a coenzyme which, like PLP, acts as an electron sink to stabilize key carbanion intermediates. The most important part of the ThDP molecule from a catalytic standpoint is its thiazole ring. The presence of sulfur in thiazole's aromatic ring makes its nitrogen less basic (pK_a = 2.44) than imidazole.



Thiazole

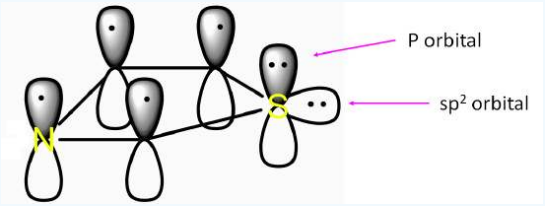


thiamine diphosphate (ThDP)

? EXERCISE 24.9.1

Describe how thiazole is aromatic. Use an orbital picture and include the lone pair electrons on sulfur. Assume the sulfur is sp^2 hybridized.

Answer



? EXERCISE 24.9.2

Would you expect a thiazole ring to be protonated at the physiological pH of 7.3 **(Section 24-5)**?

Answer

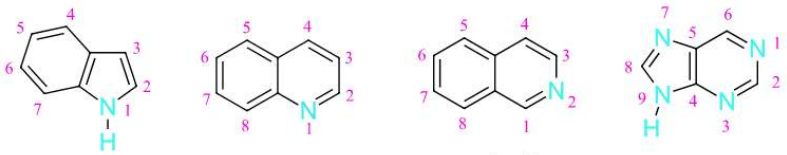
$7.3 = 2.44 + \log([RNH_2] / [RNH_3^+])$

$([RNH_2] / [RNH_3^+]) = 7.2 \times 10^4$

. . . so, $[RNH_2] >> [RNH_3^+]$ so thiazole would be almost completely unprotonated at pH = 7.3.

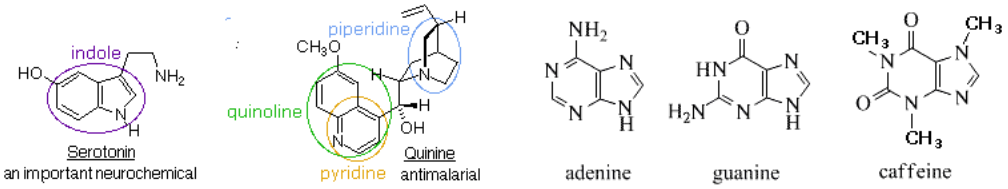
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POLYCYCLIC HETEROCYCLES



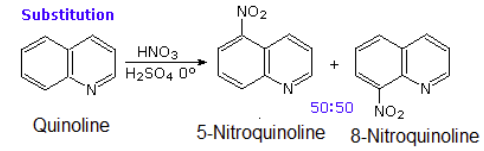
Indole (pK_a = -2) | Quinoline (pK_a = 4.9) | Isoquinoline (pK_a = 5.4) | Purine

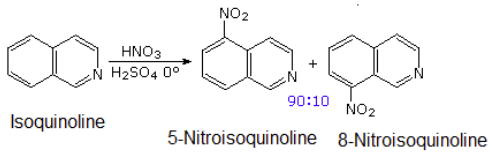
Indole, quinoline, isoquinoline, and purine are all polycyclic aromatic heterocycles commonly found in nature. Indole, quinoline, and isoquinoline all contain a hetrocyclic ring fused to benzene. Purine is made up to two heterocyclic rings, imidazole and pyrimidine, fused together. Quinoline is found in the antimalarial drug quinine. Indole is found in the neurotransmitter serotonin. The purine ring structure is found in adenine and guanine, two important parts of DNA and in the stimulant caffeine.



The pyridine-like nitrogen atom in quinoline and isoquinoline withdraws electrons making them both less reactive to electrophilic substitution than benzene. Likewise, quinoline (pK_a = 4.9) and isoquinoline (pK_a = 5.4) are less basic that a typical amine (pK_a ~10-11). Quinoline and isoquinoline can both undergo electrophilic aromatic substitution but substitution on the pyridine-like ring is avoided. Quinoline usually makes a roughly equal mixture of 5 and 8 substituted products. Isoquinoline favors making the 5 substituted product with a small amount of an 8 substituted side product.

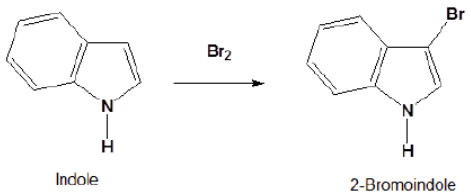
Example



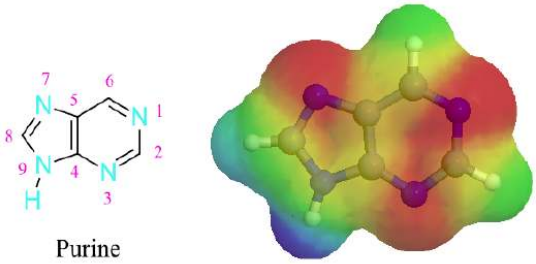


Indole has a ring nitrogen similar to to pyrrole. The lone pair electrons for this nitrogen are contained in a p orbital and are part of indole's 10 pi aromaticity. This makes indole relatively non-basic (pK_a = -2) and activated toward electrophilic substitution. Indole undergo electrophilic substitution more easily than benzene and substitution typically occurs at the 3 position on the pyrrole ring.

Example

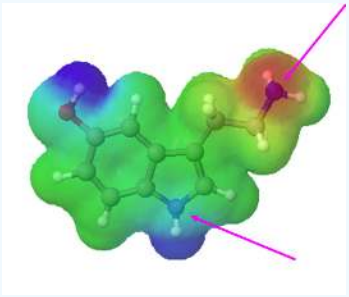


The purine ring system contain three pyridine-like nitrogens. This lone pair electrons of theses nitrogen are contained in sp^2 hybrid orbitals, making them not not part of purine's 10 pi aromaticity, allowing them to retain base-like characteristics. The lone pair electrons for the remaining, pyrrole-like, nitrogen are contained in a p orbital and are part of purine's 10 pi aromaticity. This makes the remaining nitrogen relatively non-basic.

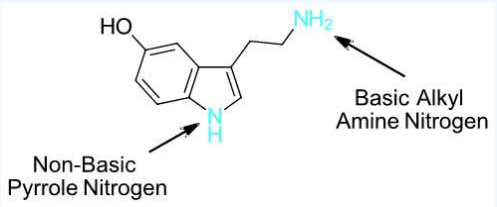


EXERCISE 24.9.1

Which nitrogen atom in the neurotransmitter serotonin is expected to be the most basic. Please explain your answer.



Answer

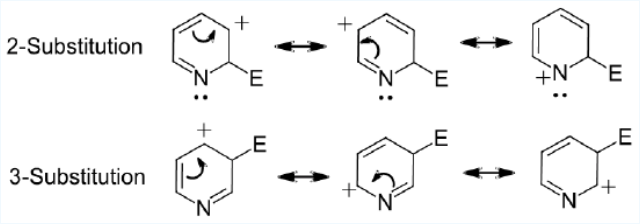


EXERCISE 24.9.2

Pyridine reacts with electrophiles to product a 3-substituted product rather than a 2-substituted product. Write a series of resonance forms for the cation intermediate formed during the reaction. Use these structures to explain the experimental result.

Answer

The resonance forms of 2-substitution places a positive charge on the ring nitrogen. The resonance forms of 3-substitution do not place a positive charge on the ring nitrogen. Having a positive charge on a nitrogen is less stable than on a carbon. Nitrogen is more electronegative than carbon making it less able to stabilize the positive charge. The 3-substituted product is preferred because it causes resonance forms which are more stable.



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24.10: SPECTROSCOPY OF AMINES

OBJECTIVES

After completing this section, you should be able to

1. identify the region of the infrared spectrum that shows absorptions resulting from the **N–H** bonds of primary and secondary amines.
2. describe a characteristic change that occurs in the infrared spectrum of an amine when a small amount of mineral acid is added to the sample.
3. use ^{1}H NMR spectra in determining the structure of an unknown amine.
4. use the “nitrogen rule” of mass spectrometry to determine whether a compound has an odd or even number of nitrogen atoms in its structure.
5. predict the prominent peaks in the mass spectrum of a given amine.
6. use the mass spectrum of an unknown amine in determining its structure.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- nitrogen rule

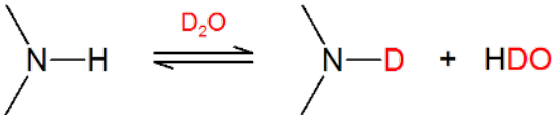
STUDY NOTES

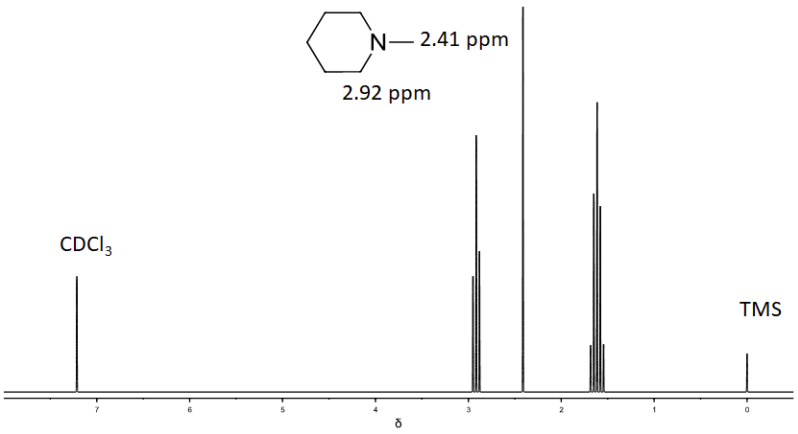
You should note the spectroscopic similarities between amines and alcohols: both have infrared absorptions in the 3300–3360 cm^{-1} region, and in both cases, the proton that is attached to the heteroatom gives rise to an often indistinct signal in the ^{1}H NMR spectrum.

^{1}H NMR OF AMINES

The hydrogens attached to an amine show up ~ 0.5-5.0 ppm. The location is dependent on the amount of hydrogen bonding and the sample's concentration. The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm. These hydrogens are deshielded by the electron-withdrawing effects of nitrogen and appear downfield in an NMR spectra compared to alkane hydrogens.

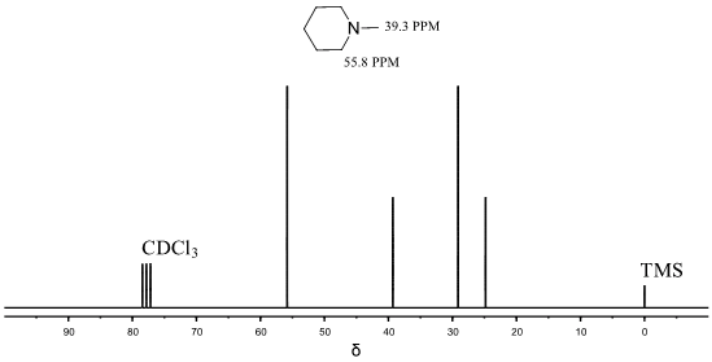
Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuterium, thus making these resonances "disappear." Addition of a few drops of D_2O causing a signal to vanish can help confirm the presence of -NH.





^{13}C NMR OF AMINES

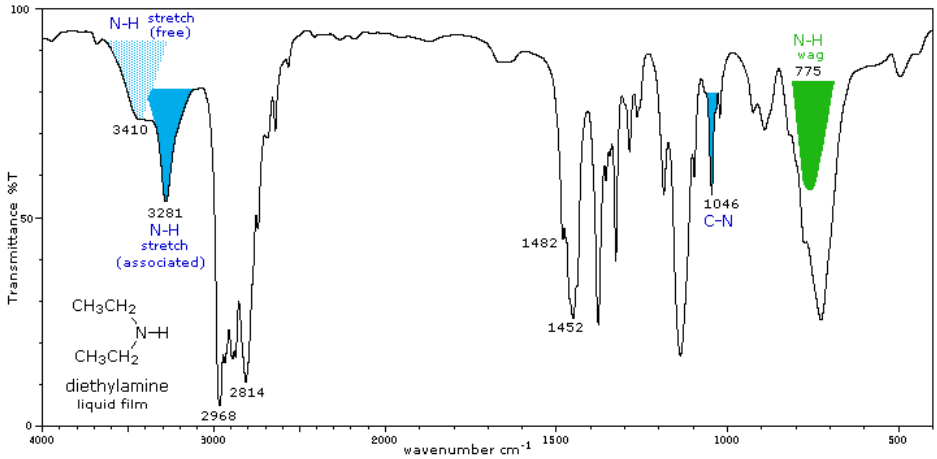
Carbons directly attached to the nitrogen appear in 10-65 ppm region of a ^{13}C NMR spectra. They are shifted slightly downfield compared to alkane carbons due to the electron-withdrawing effect of nitrogen again causing deshielding.

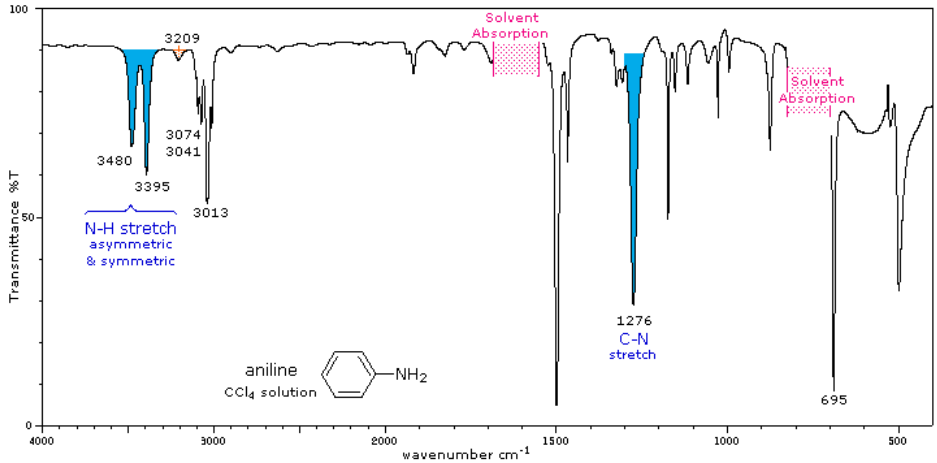


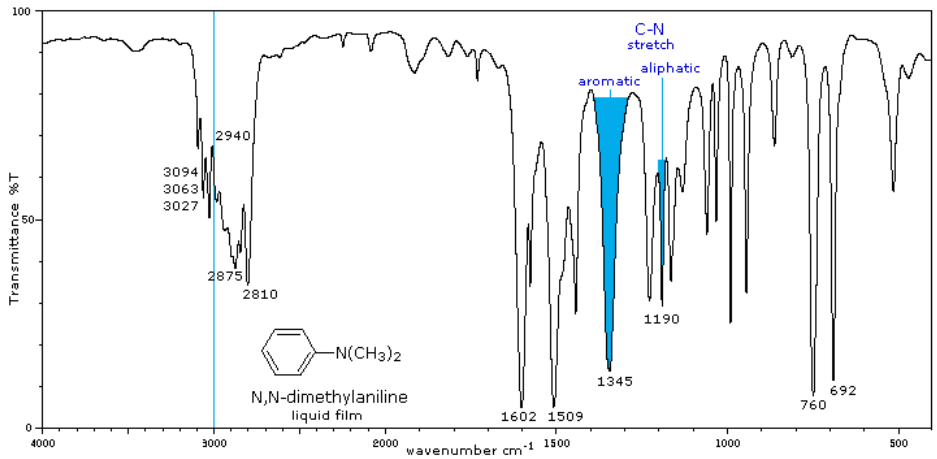
IR OF AMINES

The infrared spectra of several amines are shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

Amine Class	Stretching Vibrations	Bending Vibrations
Primary (1°)	The N-H stretching absorption is less sensitive to hydrogen bonding than are O-H absorptions. In the gas phase and in dilute CCl_4 solution free N-H absorption is observed in the 3400 to 3500 cm^{-1} region. Primary aliphatic amines display two well-defined peaks due to asymmetric (higher frequency) and symmetric N-H stretching, separated by 80 to 100 cm^{-1}. In aromatic amines these absorptions are usually 40 to 70 cm^{-1} higher in frequency. A smaller absorption near 3200 cm^{-1} (shaded orange in the spectra) is considered to be the result of interaction between an overtone of the 1600 cm^{-1} band with the symmetric N-H stretching band. C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.	Strong in-plane NH_2 scissoring absorptions at 1550 to 1650 cm^{-1}, and out-of-plane wagging at 650 to 900 cm^{-1} (usually broad) are characteristic of 1°-amines.
Secondary (2°)	Secondary amines exhibit only one absorption near 3420 cm^{-1}. Hydrogen bonding in concentrated liquids shifts these absorptions to lower frequencies by about 100 cm^{-1}. Again, this absorption appears at slightly higher frequency when the nitrogen atom is bonded to an aromatic ring. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1}(aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	A weak N-H bending absorption is sometimes visible at 1500 to 1600 cm^{-1}. A broad wagging absorption at 650 to 900 cm^{-1} may be discerned in liquid film samples.
Tertiary (3°)	No N-H absorptions. The C-N absorptions are found in the same range, 1200 to 1350 cm^{-1} (aromatic) and 1000 to 1250 cm^{-1} (aliphatic) as for 1°-amines.	Aside from the C-N stretch noted on the left, these compounds have spectra characteristic of their alkyl and aryl substituents.







UV/VIS SPECTRA OF AMINES

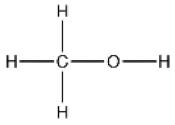
Alky Amines absorb in the region around 200 nm which make them of little value. In arylamines, the lone pair electron on the nitrogen interacts with pi electron system of the aromatic ring shifting the ring 's absorption to longer wavelengths. An example is benzene's lambda max of 256 nm while aniline's lambda max of 280 nm.

MASS SPECTRA OF AMINES

Nitrogen Rule

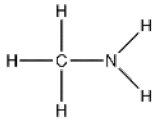
The nitrogen rule states that a molecule that has no or even number of nitrogen atoms has an even nominal mass, whereas a molecule that has an odd number of nitrogen atoms has an odd nominal mass.

Example



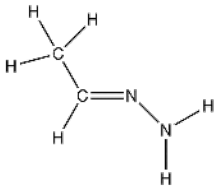
molecular formula = CH_4O
nominal mass = (1x12) + (4x1) + (1x16)
= 32

N atoms = 0
nominal mass = 32 (even #)



molecular formula = CH_5N
nominal mass = (1x12) + (5x1) + (1x14)
= 31

N atoms = 1 (odd #)
nominal mass = 31 (odd #)

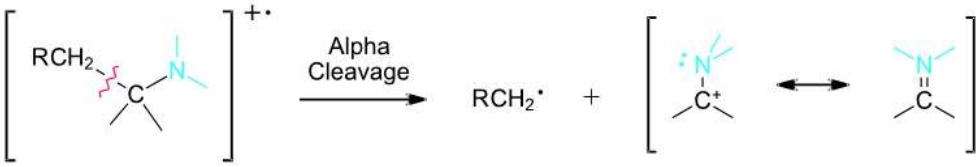


molecular formula = $C_2H_8N_2$
nominal mass = (2x12) + (6x1) + (2x14)
= 58

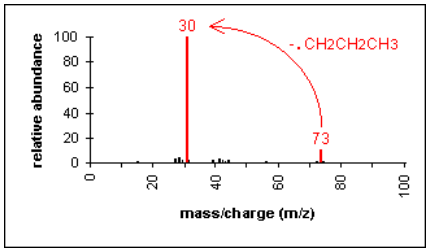
N atoms = 2 (even #)
nominal mass = 58 (even #)

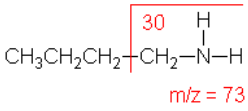
Fragmentation Patterns

The molecular ion peak is an odd number any time there is an odd number of nitrogen atoms in a molecule.. The mass spectra of amines is dominated by alpha-cleavage which produces an alkyl radical on a resonance stabilized nitrogen containing cation. Secondary and tertiary amines have the possibility of multiple alpha-cleavages.



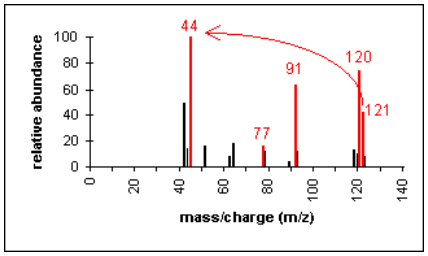
N-Butylamine ($C_4H_{11}N$) with MW = 73.13

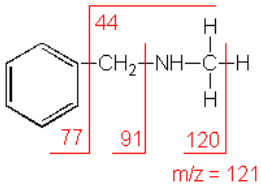




Another example is a secondary amine shown below. Again, the molecular ion peak is an odd number. The base peak (m/z = 44) is from the C-C cleavage adjacent to the C-N bond. Other important peaks come from the cleavage of the N-H bond (m/z = 120) and cleavage at the benzylic position (m/z = 91).

N-Methylbenzylamine ($C_8H_{11}N$) with MW = 121.18





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24.S: AMINES AND HETEROCYCLES (SUMMARY)

CONCEPTS & VOCABULARY

- Design a multi-step synthesis that involves the use of any of the reactions described in this unit.
- Solve road-map problems that require a knowledge of amine chemistry.
- Define, and use in context, the key terms introduced.

24.1 Naming Amines

- Amines are derivatives of ammonia in which one or more of the hydrogens has been replaced by an alkyl or aryl group.
- Several different nomenclature systems exist for naming amines, which is complicates this topic since there is no preferred option.
- The terms primary (1º), secondary (2º) & tertiary (3º) are used to classify amines by referring to the number of alkyl (or aryl) substituents bonded to the nitrogen atom.
- A nitrogen bonded to four alkyl groups will necessarily be positively charged, and is called a quaternary (4º)-ammonium cation.
- Amines are named following the IUPAC rules with -amino being added as a substitutent.
- Amines are named following the Chemical Abstract Service which the suffix -amine is attached to the root alkyl name.
- Amines are named with a common system where each alkyl substituent on nitrogen in alphabetical order, followed by the suffix -amine.

24.2 Structure and Properties of Amines

- Neutral amines have three bonds and one lone pair.
- The central nitrogen has sp^3 hybridization, which leads to trigonal pyramidal geometry with bond angles of 109.5º.
- Nitrogen does not lend to isolable stereisomers since it rapidly inverts its configuration (equilibrium arrows) by passing through a planar, sp^2-hybridized transition state, leading to a mixture of interconverting *R* and *S* configurations.
- Hydrogen bonding is the dominant factor for amines.
- Branching of amines (less bonds to Hydrogen) lowers the boiling point of amines.

24.3 Basicity of Amines

- When evaluating the basicity of a nitrogen-containing organic functional group, the central question we need to ask ourselves is: how reactive (and thus how basic) is the lone pair on the nitrogen?
- For amines, the more alkyl groups attached, the more basic the amine is due to the electron-donating effect of the alkyl group.
- The lone pair on the nitrogen atom in an amide is in resonance with the double bond making it a more stabilized lone pair and less basic.
- When a nitrogen atom is incorporated into a ring, the bascicity depends on where the lone pair resides.
- In a ring where the lone pair on the nitrogen atom resides in a hybrid orbital, then that lone pair is basic with the more basic equating with more s character in the hybrid orbital.
- In a ring where the lone pair on the nitrogen atom resides in a p orbital, then that lone pair is delocalized and less basic.
- In extraction, one can take advantage of amines and their basicity by forming the protonated salt ($RNH_2^+Cl^-$), which is soluble in water, in order to separate them.
- Amines are also acidic and the same factors that decreased the basicity of amines increase their acidity.
- Amines are often utilized as bases in reactions.

24.4 Basicity of Arylamines

- Nitrogen atoms as part of aromatic rings are less basic than methylamine.
- The basic lone pair on the nitrogen is to some extent tied up in – and stabilized by – the aromatic p system.
- This effect is accentuated by the addition of an electron-withdrawing groups.
- Imines are somewhat basic, which can be explained using orbital theory and the inductive effect: the sp^2 orbitals of an imine nitrogen are one part *s* and two parts *p*, meaning that they have about 67% *s* character.

24.5 Biological Amines and the Henderson-Hasselbalch Equation

- The chemistry of life occurs in a buffer that consists of a mixture of various phosphate and ammonium compounds.
- In an aqueous solution buffered at pH 7, carboxylic acid groups can be expected to be essentially 100% deprotonated and negatively charged (ie. in the carboxylate form), and amine groups essentially 100% protonated and positively charged (i.e., in the ammonium form).
- The imidizole group on the histidine side chain has a pK_a near 7, and thus exists in physiological solutions as mixture of both protonated and deprotonated forms.

24.6 Synthesis of Amines

- Secondary amines and their salts can be synthesized from primary amines and an alkyl halide.
- Tertiary amines and their salts can be synthesized from primary amines and an alkyl halide.
- Quaternary ammonium salts can be synthesized from primary amines and an alkyl halide.
- While a primary amine can by synthesized from ammonia and an alkyl halide, there are other better options.
- The reactions that provide a more pure primary amine in high yield occur in two steps.
  - First form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile.
  - Second, any extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.
- Another option to synthesize amines is to reduce nitro groups, which include catalytic hydrogenation, zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution.
- Reacting a nitrile with lithium aluminum hydride will yield a primary amine.
- Amides can be reduced to primary, secondary or tertiary amines using lithium aluminum hydride.
- Aldehydes and ketones can be converted to primary, secondary, or tertiary amines using reductive amination.
- Hofmann rearrangement is the reaction of a primary amide with a halogen in strongly basic conditions to give a primary amine as a product.
- The Curtius rearrangement converts an acid chloride to an amine by the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen in the acyl azide intermediate.

24.7 Reactions of Amines

- The direct alkylation of 1º or 2º-amines gives a more substituted product does not proceed cleanly.
- Acid chlorides can react with amines to form amides.
- Elimination reactions of 4º-ammonium salts are termed Hofmann eliminations, where the products are a tertiary amine and a alkene.
- The double bond Hofmann eliminations tends to give the less-substituted double bond isomer due to the Hofmann Rule.

24.8 Reactions of Arylamines

- Arylamines are very reactive towards electrophilic aromatic substitution substitutions.
- Aniline is a strong activating group and can overreact in electrophilic aromatic substitutions.
- Changing the functional group from an amine to an amide on an aromatic ring alters the reactivity in electrophilic aromatic substitutions for more control in the reaction.
- Sulfa drugs are an important group of synthetic antimicrobial agents (pharmaceuticals) that contain the sulfonamide group.
- The synthesis of sulfanilamide (a sulfa drug) illustrates how the reactivity of aniline can be modified to make possible an electrophilic aromatic substitution.
- Aryl diazonium salts are important intermediates, since the leaving group (N_2) is thermodynamically very stable, these reactions are energetically favored.
- Diazonium ions show that the positive charge is delocalized over the two nitrogen atoms while it is not possible for nucleophiles to bond to the inner nitrogen, negative nucleophiles can bond to the terminal nitrogen gives neutral azo compounds.
- The most important application of diazo coupling reactions is electrophilic aromatic substitution of activated benzene derivatives by diazonium electrophiles.
- The products of such reactions are highly colored aromatic azo compounds that find use as synthetic dyestuffs, commonly referred to as azo dyes.

24.9 Heterocyclic Amines

- Heterocyclic structures are found in many natural products an example of some nitrogen compounds, known as alkaloids because of their basic properties.
- Pyrrole is obtained commercially by the reaction of furan with ammonia.
- In a pyrrole ring, the nitrogen lone pair is part of the aromatic sextet, thus not very basic.
- Substitution preference is on the 2-position of pyrrole.
- Imidazole is another five-membered heterocyclic amine, which is part of the amino acid histidine.
- Thiazole is a five-membered ring system which is found in biological systems.
- When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context.
- In pyridine, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is not part of the aromatic sextet, therefore, its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.
- The aromatic stabilization energy of pyridine is 21 kcal/mole based on heat of combustion measurements.
- Polycyclic heterocyclic structures are found in many natural products like caffeine.
- Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products.
- The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA.

24.10 Spectroscopy of Amines

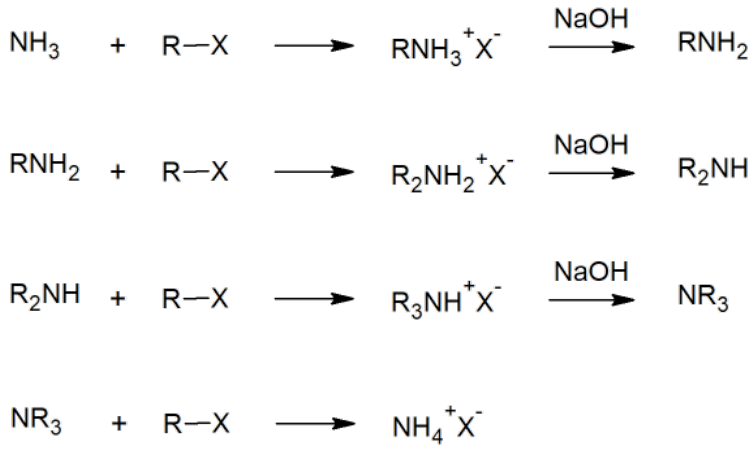
- The hydrogens attached to an amine show up ~ 0.5-5.0 ppm in ^{1}H NMR.
- The broad range is due to the fact that the location is dependent on the amount of hydrogen bonding and the sample's concentration.
- The hydrogens on carbons directly bonded to an amine typically appear ~2.3-3.0 ppm in ^{1}H NMR.
- IR for primary amines a free N-H absorption is observed in the 3400 to 3500 cm^{-1} region as two well-defined peaks.
- IR for amines the C-N stretching absorptions are found at 1200 to 1350 cm^{-1} for aromatic amines, and at 1000 to 1250 cm^{-1} for aliphatic amines.
- Secondary amines exhibit only one absorption near 3420 cm^{-1} in IR.
- For tertiary amines, there is not N-H stretch.

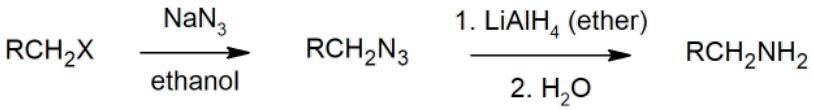
SKILLS TO MASTER

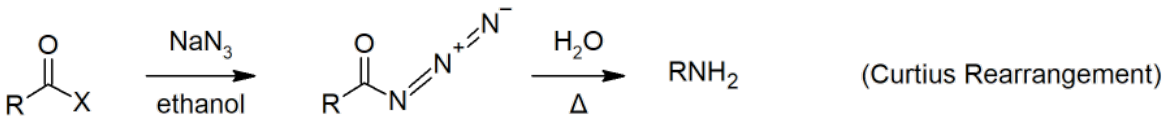
- Skill 24.1 Name amines using IUPAC rules.
- Skill 24.2 Draw the structure of amines from the IUPAC name.
- Skill 24.3 Describe the geometries and approximate bond angles of amines.
- Skill 24.4 Explain physical properties of amines.
- Skill 24.5 Explain why one amine is more basic than another.
- Skill 24.6 Explain how the basicity of an amine when the Nitrogen atom is incorporated in a ring depends on the bonding context.
- Skill 24.7 Describe how an amine can be extracted from a mixture that also contains neutral compounds illustrating the reactions which take place with appropriate equations.
- Skill 24.8 Explain why primary and secondary (but not tertiary) amines may be regarded as very weak acids.
- Skill 24.9 Use the concept of resonance to explain why arylamines are less basic than their aliphatic counterparts.
- Skill 24.10 Arrange a given series of arylamines in order of increasing or decreasing basicity.
- Skill 24.11 Explain using inductive and resonance effects arguments as to why a given arylamine is more or less basic than aniline.
- Skill 24.12 Identify the form that amine bases take within living cells.
- Skill 24.13 Use the Henderson-Hasselbalch equation to calculate the percentage of a base that is protonated in a solution, given the pK_a value of the associated ion and the pH of the solution.
- Skill 24.14 List general ways to synthesize amines.
- Skill 24.15 Draw mechanisms for preparing amines including:
  - reduction of nitriles, amides and nitro compounds.
  - reactions involving alkyl groups:
    1. S_N2 reactions of alkyl halides, ammonia and other amines.
    2. nucleophilic attack by an azide ion on an alkyl halide, followed by reduction of the azide so formed.
    3. alkylation of potassium phthalimide, followed by hydrolysis of the *N*-alkyl phthalimide so formed (i.e., the Gabriel synthesis).
  - reductive amination of aldehydes or ketones.
  - Hofmann or Curtius rearrangements.
- Skill 24.16 Write an equation to represent the reaction that takes place between ammonia, a primary or secondary amine, and an acid chloride.
- Skill 24.17 Identify the product formed when a given amine reacts with a given acid chloride.
- Skill 24.18 Draw the product for a Hoffman elimination.
- Skill 24.19 Propose a synthesis of arylamines using diazonium coupling reactions.
- Skill 24.20 Be able to draw the structure of furan, pyrrole and imidazole.
- Skill 24.21 Use the Hückel $2n + 4$ rule to explain the aromaticity of pyrrole.
- Skill 24.22 Be able to predict the product formed when pyrrole is subjected to an aromatic electrophilic substitution.
- Skill 24.23 Write the detailed mechanism for the electrophilic aromatic substitution of pyrrole to account for the fact that substitution takes place at C2 rather than C3.
- Skill 24.24 Explain the difference in basicity between pyridine, pyrrole and other amines.
- Skill 24.25 Explain why pyridine undergoes electrophilic substitution much less readily than does benzene.
- Skill 24.17 Use IR, NMR and MS in combination with the nitrogen rule to identify amines.

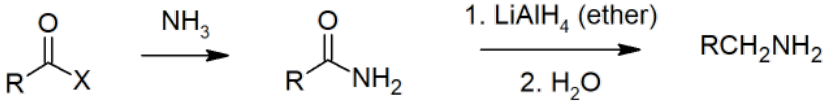
SUMMARY OF REACTIONS

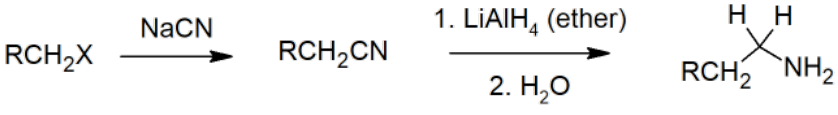
Amine Preparation

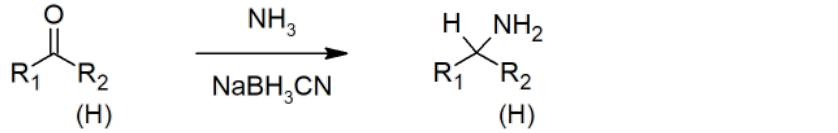




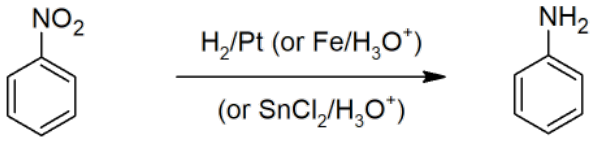


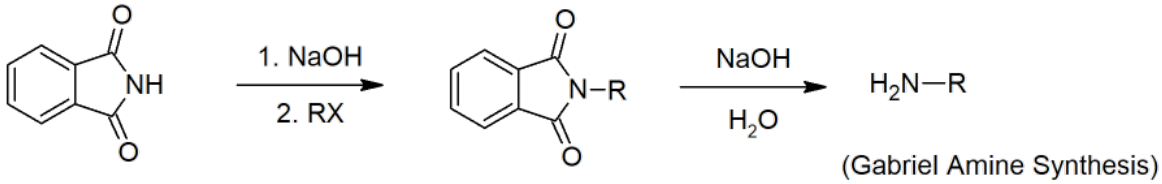






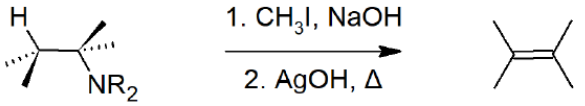
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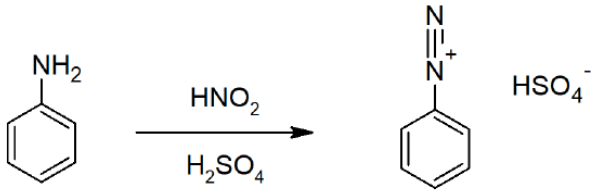


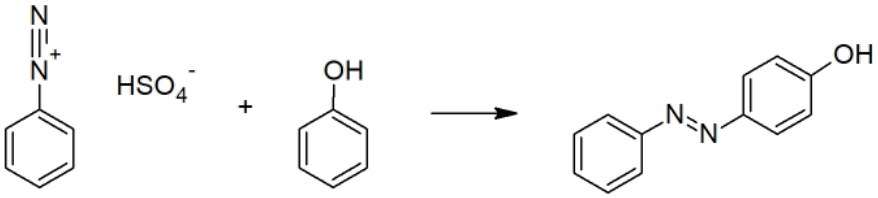


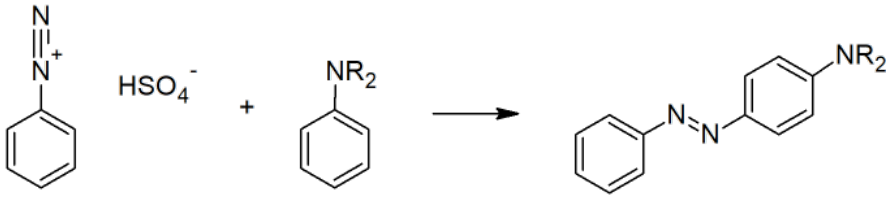


Amine Reactions

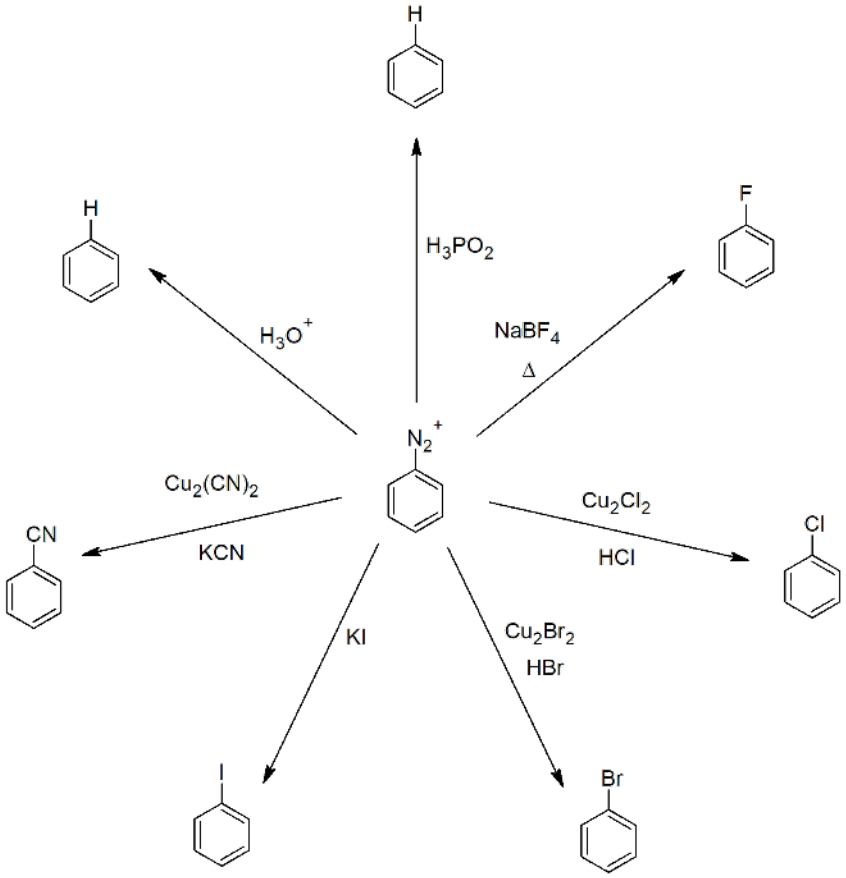








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CHAPTER OVERVIEW

25: BIOMOLECULES- CARBOHYDRATES

This chapter is designed to provide you with an overview of the biologically important group of compounds known as carbohydrates. Many of the compounds you will encounter while studying this chapter may appear to have very complex structures, but much of their chemistry can be readily understood in terms of the concepts and reactions discussed in earlier chapters of the course.

The chapter begins with an explanation of the classification schemes used to simplify the study of carbohydrates. We make extensive use of Fischer projection formulas throughout the chapter. We place considerable emphasis on gaining an appreciation of the configurations of carbohydrates, particularly of the aldoses. We describe the disadvantages of representing monosaccharides by open-chain structures, and at this point, introduce you to cyclic representations—called Haworth projections—of these substances. We describe the mutarotation of glucose, explaining it in terms of the existence of anomers. We then examine some reactions of monosaccharides, including the formation of ethers and esters, the formation of glycosides, and reduction and oxidation. We discuss the structures of some common disaccharides and polysaccharides, and conclude the chapter with a brief explanation of the role played by carbohydrates in cell recognition.

25.0: Introduction
25.1: Classification of Carbohydrates
25.2: Depicting Carbohydrate Stereochemistry - Fischer Projections
25.3: D, L Sugars
25.4: Configurations of Aldoses
25.5: Cyclic Structures of Monosaccharides - Anomers
25.6: Reactions of Monosaccharides
25.7: The Eight Essential Monosaccharides
25.8: Disaccharides
25.9: Polysaccharides and Their Synthesis
25.10: Other Important Carbohydrates
25.11: Cell-Surface Carbohydrates and Influenza Viruses
25.S: Biomolecules- Carbohydrates (Summary)

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25.0: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. identify carbohydrates (sugars) as being polyhydroxylated aldehydes and ketones.
2. describe, briefly, the process of photosynthesis, and identify the role played by carbohydrates as an energy source for living organisms.

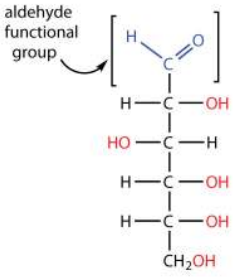
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- carbohydrate

INTRODUCTION

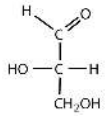
All carbohydrates consist of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes or ketones or are compounds that can be broken down to form such compounds. Examples of carbohydrates include starch, fiber, the sweet-tasting compounds called sugars, and structural materials such as cellulose. The term *carbohydrate* had its origin in a misinterpretation of the molecular formulas of many of these substances. For example, because its formula is $C_6H_{12}O_6$, glucose was once thought to be a "carbon hydrate" with the structure $C_6 \cdot 6H_2O$.



Because glucose has an aldehyde functional group and several –OH (hydroxyl) groups, it is described as a polyhydroxy aldehyde.

EXAMPLE 1

Which compounds would be classified as carbohydrates?

a. 

- 

- 

- 

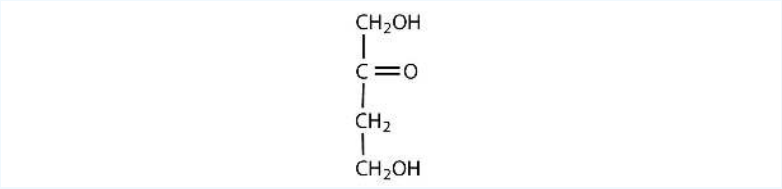
Solution

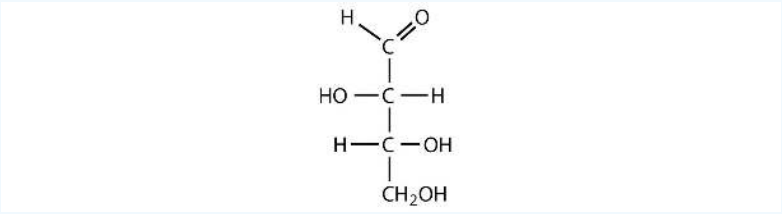
a. This is a carbohydrate because the molecule contains an aldehyde functional group with OH groups on the other two carbon atoms.
b. This is not a carbohydrate because the molecule does not contain an aldehyde or a ketone functional group.
c. This is a carbohydrate because the molecule contains a ketone functional group with OH groups on the other two carbon atoms.

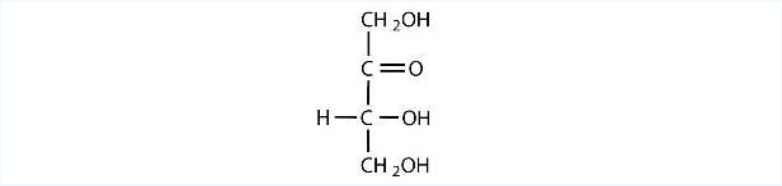
d. This is not a carbohydrate; although it has a ketone functional group, one of the other carbons atoms does not have an OH group attached.

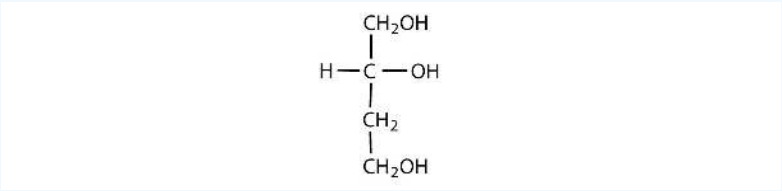
? EXERCISE 1

Which compounds would be classified as carbohydrates?

1. 

- 

- 

- 

Green plants are capable of synthesizing glucose ($C_6H_{12}O_6$) from carbon dioxide (CO_2) and water (H_2O) by using solar energy in the process known as photosynthesis:

$$6\,CO_2 + 6\,H_2O + 2870\,kJ \longrightarrow C_6H_{12}O_6 + 6\,O_2$$

(The 2870 kJ comes from solar energy.) Plants can use the glucose for energy or convert it to larger carbohydrates, such as starch or cellulose. Starch provides energy for later use, perhaps as nourishment for a plant's seeds, while cellulose is the structural material of plants. We can gather and eat the parts of a plant that store energy—seeds, roots, tubers, and fruits—and use some of that energy ourselves. Carbohydrates are also needed for the synthesis of nucleic acids and many proteins and lipids.

Animals, including humans, cannot synthesize carbohydrates from carbon dioxide and water and are therefore dependent on the plant kingdom to provide these vital compounds. We use carbohydrates not only for food (about 60%–65% by mass of the average diet) but also for clothing (cotton, linen, rayon), shelter (wood), fuel (wood), and paper (wood).

CONTRIBUTORS AND ATTRIBUTIONS

- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.1: CLASSIFICATION OF CARBOHYDRATES

OBJECTIVES

After completing this section, you should be able to

1. classify a specific carbohydrate as being a monosaccharide, disaccharide, trisaccharide, etc., given the structure of the carbohydrate or sufficient information about its structure.
2. classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

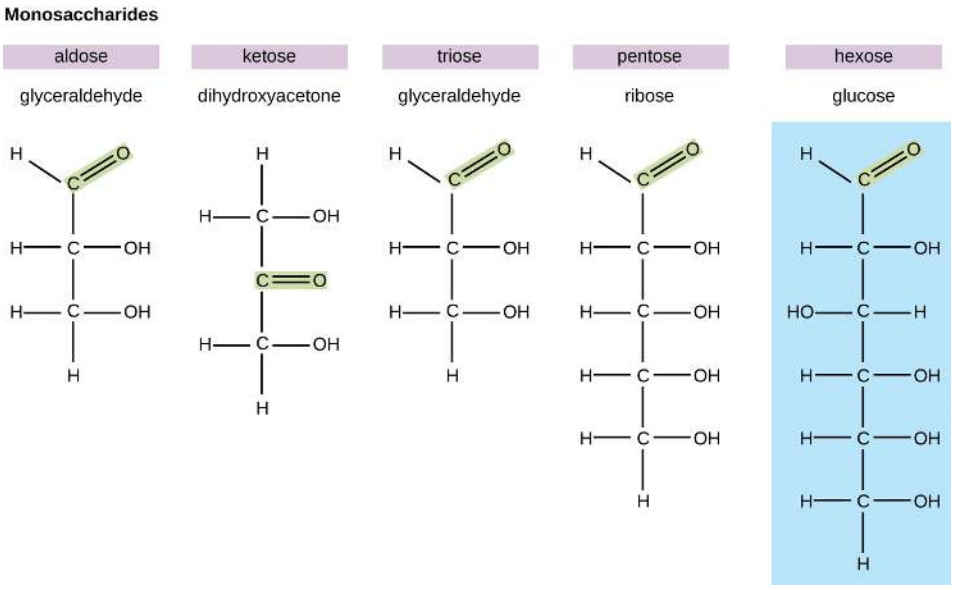
- aldose
- disaccharide
- ketose
- monosaccharide (simple sugar)
- polysaccharide

WHAT ARE CARBOHYDRATES?

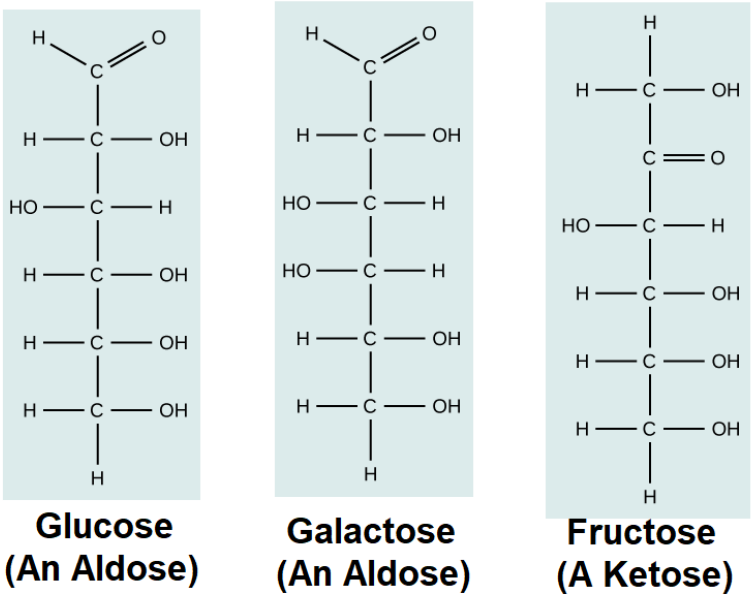
The most abundant biomolecules on earth are carbohydrates. From a chemical viewpoint, carbohydrates are primarily a combination of carbon and water, and many of them have the empirical formula $(CH_2O)_n$, where *n* is the number of repeated units. This view represents these molecules simply as "hydrated" carbon atom chains in which water molecules attach to each carbon atom, leading to the term "carbohydrates." Although all carbohydrates contain carbon, hydrogen, and oxygen, there are some that also contain nitrogen, phosphorus, and/or sulfur. Carbohydrates have myriad different functions. They are abundant in terrestrial ecosystems, many forms of which we use as food sources. These molecules are also vital parts of macromolecular structures that store and transmit genetic information (i.e., DNA and RNA). They are the basis of biological polymers that impart strength to various structural components of organisms (e.g., cellulose and chitin), and they are the primary source of energy storage in the form of starch and glycogen.

MONOSACCHARIDES

In biochemistry, carbohydrates are often called saccharides, from the Greek *sakcharon*, meaning sugar, although not all the saccharides are sweet. The simplest carbohydrates are called monosaccharides, or simple sugars. They are the building blocks (monomers) for the synthesis of polymers or complex carbohydrates, as will be discussed further in this section. Monosaccharides are classified based on the number of carbons in the molecule. General categories are identified using a prefix that indicates the number of carbons and the suffix *–ose*, which indicates a saccharide; for example, triose (three carbons), tetrose (four carbons), pentose (five carbons), and hexose (six carbons). The hexose D-glucose is the most abundant monosaccharide in nature. Other very common and abundant hexose monosaccharides are galactose, used to make the disaccharide milk sugar lactose, and the fruit sugar fructose.



A second comparison can be made when looking at glucose, galactose, and **fructose**. All three are hexoses; however, there is a major structural difference between glucose and galactose versus fructose: the carbon that contains the **carbonyl** (C=O). In glucose and galactose, the carbonyl group is on the C_1 carbon, forming an **aldehyde** group. In fructose, the carbonyl group is on the C_2 carbon, forming a **ketone** group. The former sugars are called **aldoses** based on the aldehyde group that is formed; the latter is designated as a **ketose** based on the ketone group. Again, this difference gives fructose different chemical and structural properties from those of the related aldoses, glucose, and galactose, even though fructose, glucose, and galactose all have the same chemical composition: $C_6H_{12}O_6$.



COMPLEX CARBOHYDRATES

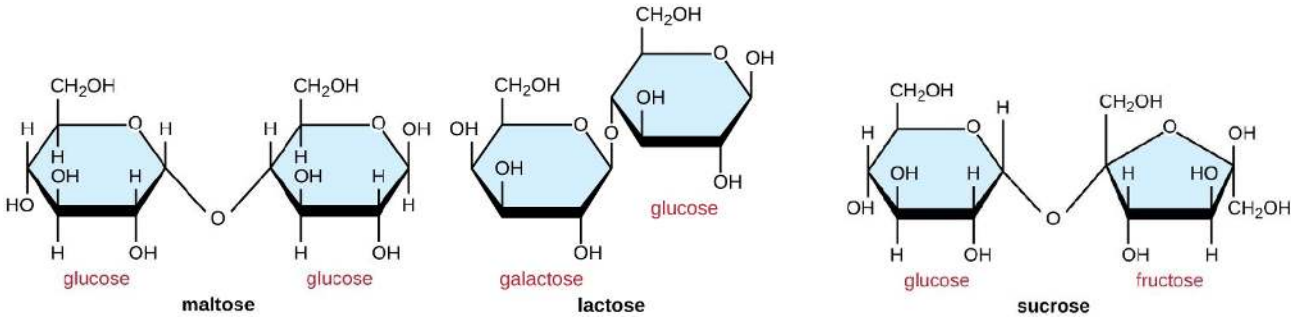
The simple sugars form the foundation of more complex carbohydrates. The cyclic forms of two sugars can be linked together by means of a condensation reaction to form a disaccharide. Multiple sugars can be linked to form polysaccharides.

DISACCHARIDES

Two monosaccharide molecules may chemically bond to form a disaccharide. The name given to the covalent bond between the two monosaccharides is a glycosidic bond. Glycosidic bonds form between hydroxyl groups of the **two saccharide molecules**, an example of the dehydration synthesis described later in this chapter.

$$\text{monosaccharide-OH} + \text{HO-monosaccharide} \rightarrow \underbrace{\text{monosaccharide-O-monosaccharide}}_{\text{disaccharide}}$$

Common disaccharides are the grain sugar maltose, made of two glucose molecules; the milk sugar lactose, made of one galactose and one glucose molecule; and the table sugar sucrose, made of one glucose and one fructose molecule.

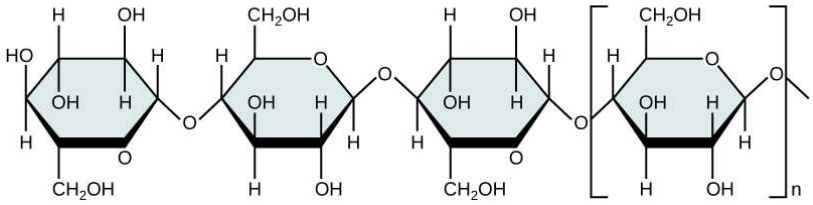


POLYSACCHARIDES

Polysaccharides, also called glycans, are large polymers composed of hundreds of monosaccharide monomers. Unlike mono- and disaccharides, polysaccharides are not sweet and, in general, they are not soluble in water. Like disaccharides, the monomeric units of polysaccharides are linked together by glycosidic bonds.

Polysaccharides are very diverse in their structure. Three of the most biologically important polysaccharides—starch, glycogen, and cellulose—are all composed of repetitive glucose units, although they differ in their structure. **Cellulose** consists of a linear chain of glucose molecules and is a common structural component of cell walls in plants and other organisms. **Glycogen** and **starch** are branched polymers; glycogen is the primary energy-storage molecule in animals and bacteria, whereas plants primarily store energy in starch. The orientation of the glycosidic linkages in these three polymers is different as well and, as a consequence, linear and branched macromolecules have different properties.

Cellulose structure



SUMMARY

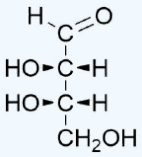
Complexity	**Simple Carbohydrates** monosaccharides	**Complex Carbohydrates** disaccharides, oligosaccharides & polysaccharides

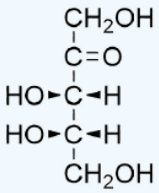
Size	**Tetrose** C_4 sugars	**Pentose** C_5 sugars	**Hexose** C_6 sugars	**Heptose** C_7 sugars	etc.

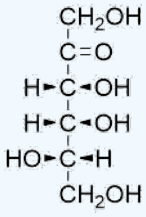
C=O Function	**Aldose** sugars having an aldehyde function or an acetal equivalent. **Ketose** sugars having a ketone function or an acetal equivalent.

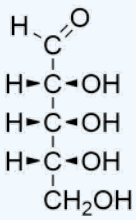
? EXERCISE 25.1.1

Classify each of the following sugars.

a. 

b. 

c. 

d. 

Answer

a. Aldoterose
b. Ketopentose
c. Ketohexose
d. Aldopentose

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25.2: DEPICTING CARBOHYDRATE STEREOCHEMISTRY - FISCHER PROJECTIONS

OBJECTIVES

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge and dash structure or a molecular model.
2. draw the wedge and dash structure of a monosaccharide, given its Fischer projection or a molecular model.
3. construct a molecular model of a monosaccharide, given its Fischer projection or wedge and dash structure.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

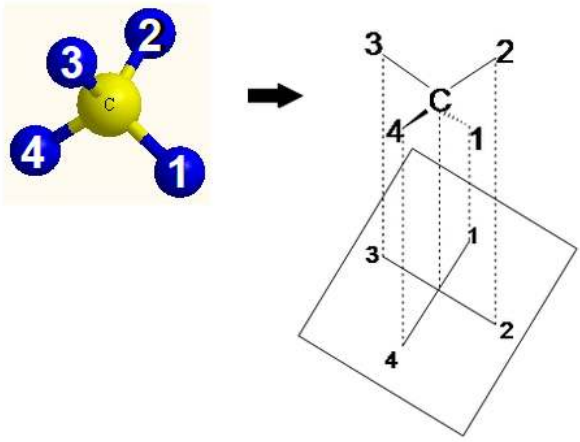
- Fischer projection

STUDY NOTES

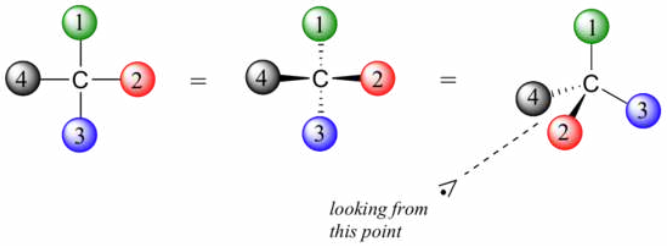
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

DRAWING REPRESENTATIONS OF 3D STRUCTURES

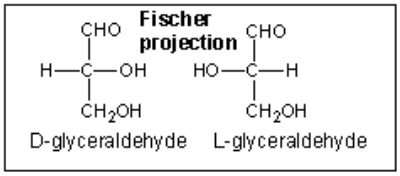
The problem of drawing three-dimensional configurations on a two-dimensional surface, such as a piece of paper, has been a long-standing concern of chemists. The wedge and dash notations we have been using are effective, but can be troublesome when applied to compounds having many chiral centers. As part of his Nobel Prize-winning research on carbohydrates, the great German chemist Emil Fischer, devised a simple notation that is still widely used. Fischer Projections allow us to represent 3D molecular structures in a 2D environment without changing their properties and/or structural integrity.

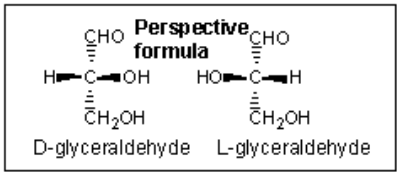


Fisher projections show sugars in their open chain form. In a Fischer projection, the carbon atoms of a sugar molecule are connected vertically by solid lines, while carbon-oxygen and carbon-hydrogen bonds are shown horizontally. Stereochemical information is conveyed by a simple rule: vertical bonds point into the plane of the page, while horizontal bonds point out of the page.

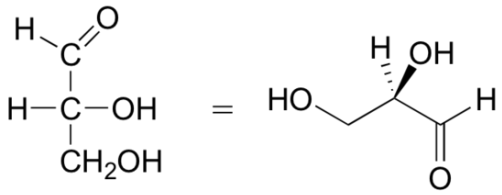


Sugars can be drawn in the straight chain form as either Fisher projections or perspective structural formulas. When drawing Fischer projections, the aldehyde group is written at the top, and the H and OH groups that are attached to each chiral carbon are written to the right or left. The arrangement of the atoms distinguishes one stereoisomer from the other.



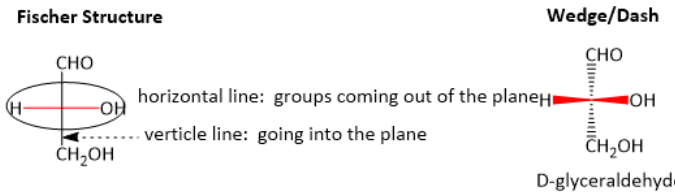


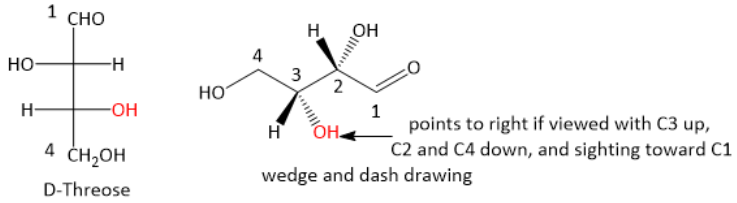
Below are two different representations of (R)-glyceraldehyde, the smallest sugar molecule (also called D-glyceraldehyde in the stereochemical nomenclature used for sugars):



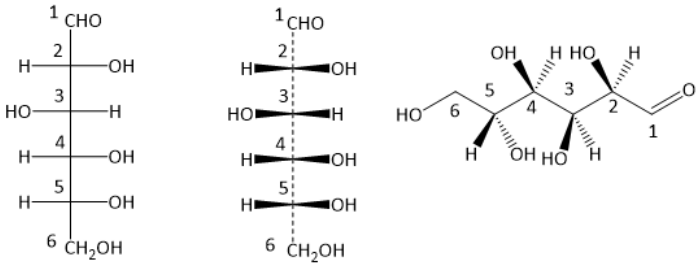
(R)-glyceraldehyde
(D-glyceraldehyde)

In the Fisher projection, the vertical bonds point down into the plane of the paper. That's easy to visualize for 3C molecules. but more complicated for bigger molecules. For those draw a wedge and dash line drawing of the molecule. When determining the orientation of the hydroxides on each C, orient the wedge and dash drawing in your mind so that the C atoms adjacent to the one of interest are pointing down. Sighting towards the carbonyl C, if the OH is pointing to the right in the Fisher project, it should be pointing to the right in the wedge and dash drawing, as shown below for D-erthyrose and D-glucose.



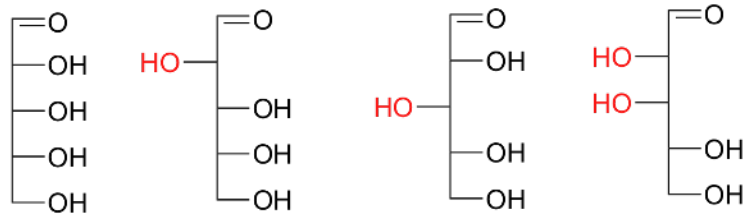


Below are three representations of the open chain form of D-glucose: in the conventional Fischer projection, a wedge/dash version of a Fischer projection, and finally in the 'zigzag' style that is preferred by many organic chemists.



D-Glucose

Fischer projections are useful when looking at many different diastereomeric sugar structures, because the eye can quickly pick out stereochemical differences according to whether a hydroxyl group is on the left or right side of the structure.



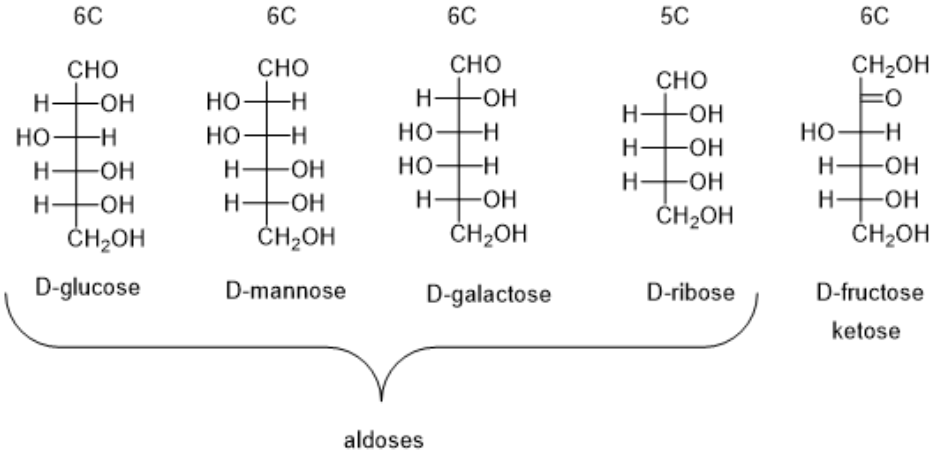
The usefulness of this notation to Fischer, in his carbohydrate studies, is evident in the following diagram. There are eight stereoisomers of 2,3,4,5-tetrahydroxypentanal, a group of compounds referred to as the aldopentoses (aldo- since the oxidized carbon is an aldehyde and -pentose since the molecules contain 5 carbons). Since there are three chiral centers in this constitution, we should expect a maximum of 2^3 stereoisomers. These eight stereoisomers consist of four sets of enantiomers. If the configuration at C-4 is kept constant (*R* in the examples shown here), the four stereoisomers that result will be **diastereomers**.

Four Diastereomeric $C_5H_{10}O_5$ Aldopentoses



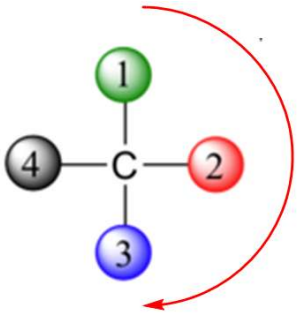
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

The Fisher structures of the most common monosaccharides (other than glyceraldehyde and dihydroxyacetone), which you will encounter most frequently are shown below.



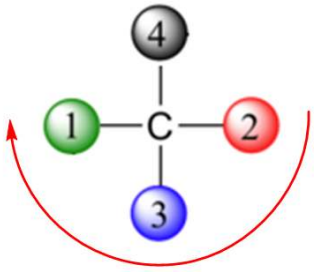
DETERMINING R AND S IN FISCHER PROJECTIONS

Determining whether a chiral carbon is R or S may seem difficult when using Fischer projections, but it is actually quite simple. If the lowest priority group (often a hydrogen) is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents. If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer (you are in looking at the configuration from the wrong side), so you simply reverse it.



Lowest Priority is on a horizontal bond so answer is reversed

Substiuents 1-3 are clockwise so the carbon is S

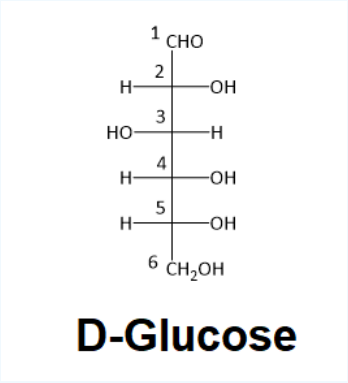


Lowest Priority is on a vertical bond so answer is correct

Substiuents 1-3 are clockwise so the carbon is R

Worked Example 25.2.1

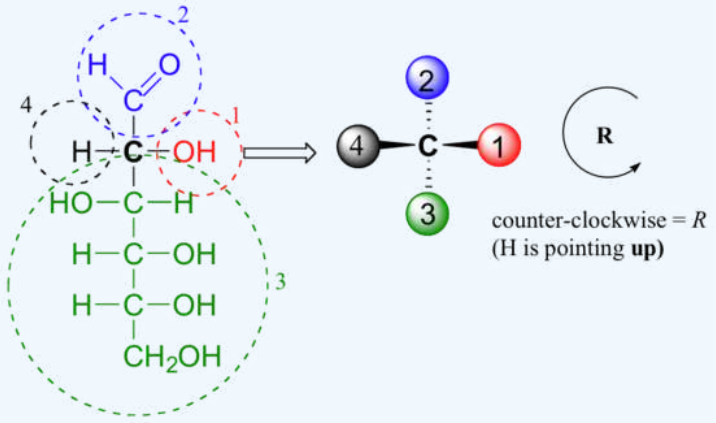
Determine if carbon #2 in D-glucose is R or S.



https://chem.libretexts.org/@go/page/36454

Answer

When deciding whether a stereocenter in a Fischer projection is *R* or *S*, realize that the hydrogen, in a horizontal bond. Therefore, the orientation of the three remaining substituents is reversed to create the correct answer or a counterclockwise circle means *R*, and a clockwise circle means *S*. For carbon #2 in D-Glucose substituent 1, 2, and 3 form a counterclockwise circle so the carbon is R.



HOW TO MAKE FISCHER PROJECTIONS

To make a Fischer Projection, it is easier to show through examples than through words. Lets start with the first example, turning a 3D structure of ethane into a 2D Fischer Projection.

EXERCISE 25.2.1

Start by mentally converting a 3D structure into a Dashed-Wedged Line Structure. Remember, the atoms that are pointed toward the viewer would be designated with a wedged lines and the ones pointed away from the viewer are designated with dashed lines.

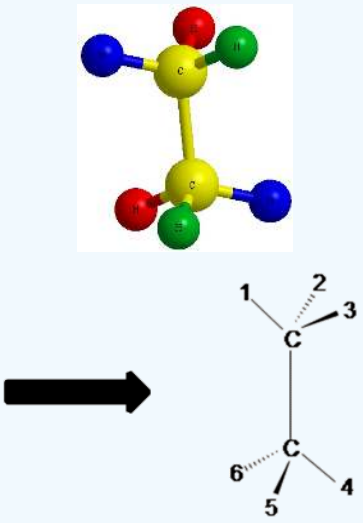


Figure B

Notice the red balls (atoms) in Figure A above are pointed away from the screen. These atoms will be designated with dashed lines like those in Figure B by number 2 and 6. The green balls (atoms) are pointed toward the screen. These atoms will be designated with wedged lines like those in Figure B by number 3 and 5. The blue atoms are in the plane of the screen so they are designated with straight lines.

Now that we have our Dashed- Wedged Line Structure, we can convert it to a Fischer Projection. However, before we can convert this Dashed-Wedged Line Structure into a Fischer Projection, we must first convert it to a “flat” Dashed-Wedged Line Structure. Then from there we can draw our Fischer Projection. Lets start with a more simpler example. Instead of using the ethane shown in Figure A and B, we will start with a methane. The reason being is that it allows us to only focus on one central carbon, which make things a little bit easier.

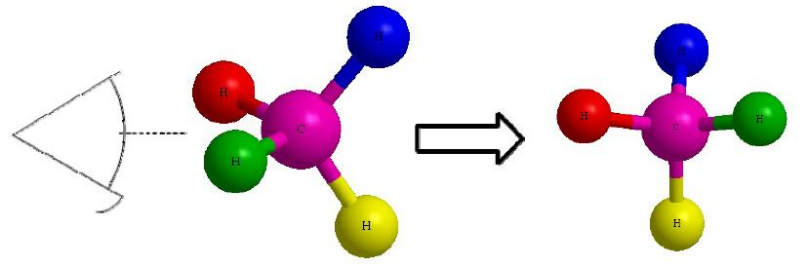
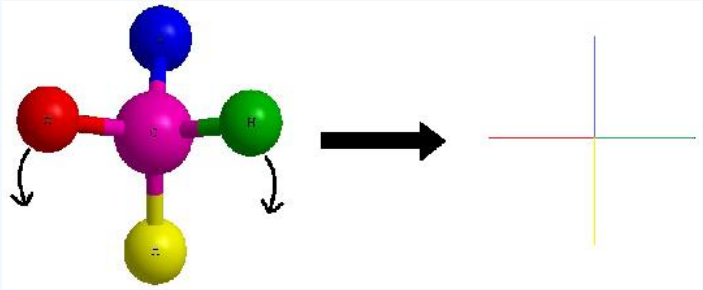


Figure D

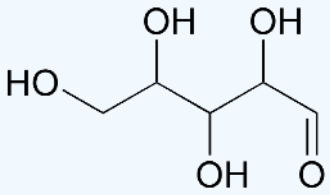
Lets start with this 3D image and work our way to a dashed-wedged image. Start by imagining yourself looking directly at the central carbon from the left side as shown in Figure C. It should look something like Figure D. Now take this Figure D and flatten it out on the surface of the paper and you should get an image of a cross.



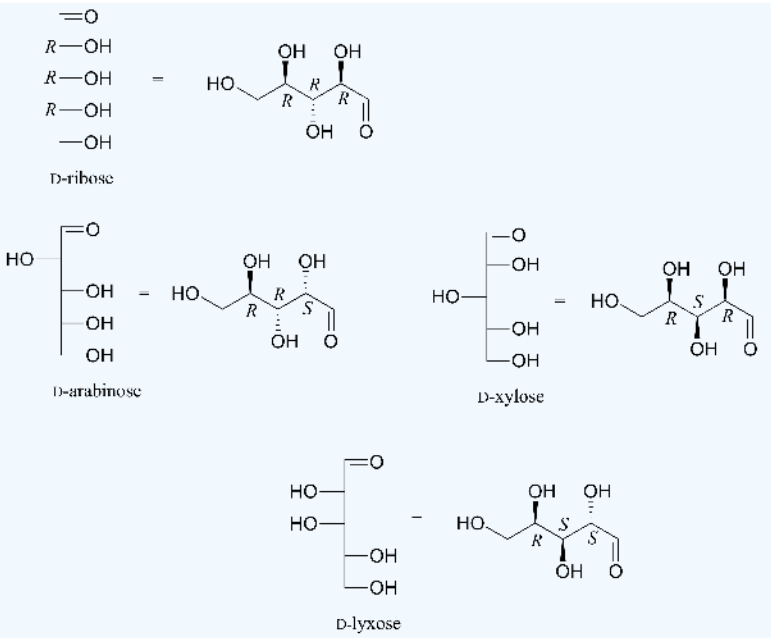
As a reminder, the horizontal line represents atoms that are coming out of the paper and the vertical line represents atoms that are going into the paper. The cross image to the right of the arrow is a Fischer projection.

? EXERCISE 25.2.1

Draw 'zigzag' structures (using the solid/dash wedge convention to show stereochemistry) for the four sugars in the figure below. Label all stereocenters *R* or *S*.



Answer



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25.3: D, L SUGARS

OBJECTIVES

After completing this section, you should be able to

1. identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
2. identify the limitations of the D, L system of nomenclature for carbohydrates.
3. assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
4. draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
5. construct a molecular model of a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

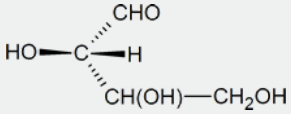
- D sugar
- L sugar

STUDY NOTES

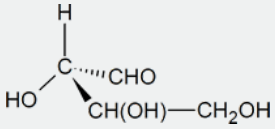
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

How would you set about the task of deciding whether each chiral carbon has an *R* or an *S* configuration? True, you could use molecular models, but suppose that a model set had not been available—what would you have done then?

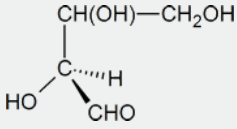
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the page. Thus, the configuration around carbon atom 2 in structure a can be represented as follows:



In your mind, you should be able to imagine how this molecule would look if it was rotated so that the bonds that are shown as coming out of the page are now in the plane of the page. [One possible way of doing this is to try and imagine how the molecule would look if it was viewed from a point at the bottom of the page.] What you should see in your mind is a representation similar to the one drawn below.



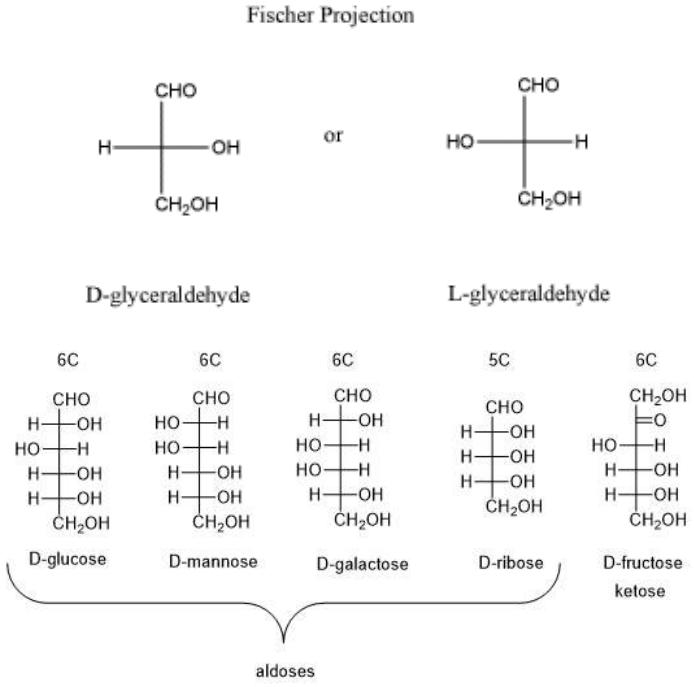
To determine whether the configuration about the central carbon atom is *R* or *S*, we must rotate the molecule so that the group with the lowest priority (H), is directed away from the viewer. This effect can be achieved by keeping the hydroxyl group in its present position and moving each of the other three groups one position clockwise.



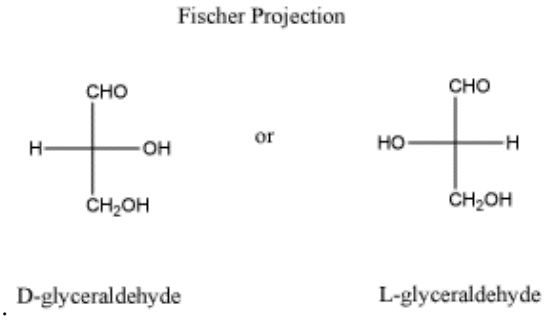
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

D AND L LABELING OF MONOSACCHARIDE STEREOCHEMISTRY

Glyceraldehyde, the simplest possible aldose, is made up of three carbons and only one these is chiral. Glyceraldehyde has two stereoisomers, an R/S pair of enantiomers. Before the R,S system for designating chiral configuration was adopted by organic chemists (R)-glyceraldehyde was called D-glyceraldehyde (Latin for right: dexter) and (S)-glyceraldehdye was called L-glyceraldehyde (Latin for left:laevus). D- and L-glyceraldehyde were then used to provide reference points for designating and drawing all other monosaccharides. Sugars whose Fischer projections have the same configuration at the chiral carbon furthest from the carbonyl group as D-glyceraldehyde are designated as **D sugars**; those with the same configuration as L-glyceraldehyde are designated as **L sugars**. D and L designations of sugars are based on the position of the hydroxyl on the chiral carbon farthest from the carbonyl group in the Fischer projection of the molecule. All D-sugars have the –OH on the right side and L-sugars have the –OH on the left side.



D-sugars predominate in nature, though L-forms of some sugars, such as fucose, do exist. The D and L designation is a bit more complicated than it would appear on the surface. The confusion about D and L arises because the L sugars of a given name (glucose, for example) are mirror images of the D sugars of the same name. This concept is most easily seen with glyceraldehyde. In the same way D- and L- glyceraldehyde represent two enantiomers, the D- and L- forms larger monosaccharides are enantiomers of one another. The figure below shows the structure of D- and L- glucose. Notice that D-glucose is not converted into L-glucose simply by flipping the configuration of the fifth carbon in the molecule. Rather all of the arrangement around all of the chiral centers (horizontal lines) in the Fischer project of D-glucose need to be opposite to make L-glucose.



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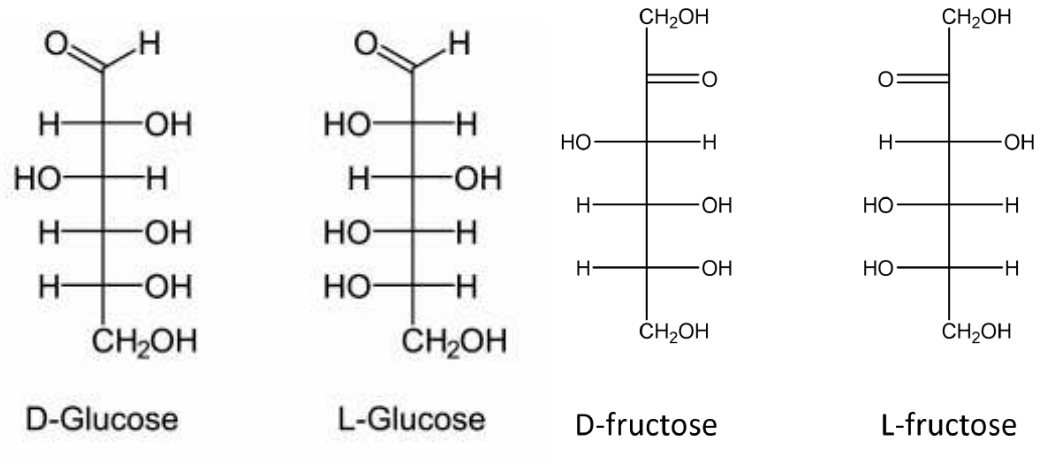


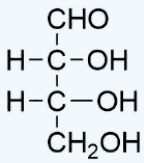
Figure 6. Fischer projections of enantiomers of glucose (left) and fructose (right).

It is important to recognize that the sign of a compound's specific rotation of plane polarized light (+)/(−) does not correlate with its configuration (D or L). The D/L labeling does not indicate which enantiomer is (+)/(−). Rather, it says that the compound's stereochemistry is related to that of the D or L enantiomer of glyceraldehyde. It is a simple matter to measure an optical rotation with a polarimeter. Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

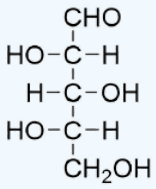
? EXERCISE 25.3.1

In the following Fischer projections, assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

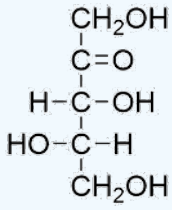
a)



b)



c)



Answer

a) From top to bottom, 2R, 3R, and it is a D sugar.

b) From top to bottom, 2S, 3R, 4S, and it is an L sugar.

c) From to to bottom, 3R, 4S, and it is an L sugar.

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25.4: CONFIGURATIONS OF ALDOSES

OBJECTIVES

After completing this section, you should be able to

1. draw the structures of all possible aldotetroses, aldopentoses, and aldohexoses, without necessarily being able to assign names to the individual compounds.
2. draw the Fischer projection of D-glyceraldehyde, D-ribose and D-glucose from memory.

The four chiral centers in glucose indicate there may be as many as sixteen (2^4) stereoisomers having this constitution. These would exist as eight diastereomeric pairs of enantiomers, and the initial challenge was to determine which of the eight corresponded to glucose. This challenge was accepted and met in 1891 by the German chemist Emil Fischer. His successful negotiation of the stereochemical maze presented by the aldohexoses was a logical tour de force, and it is fitting that he received the 1902 Nobel Prize for chemistry for this accomplishment. At the time Fischer undertook the glucose project it was not possible to establish the **absolute configuration** of an enantiomer. Consequently, Fischer made an arbitrary choice for (D)-glucose and established a network of related aldose configurations that he called the **D**-family. The mirror images of these configurations were then designated the **L**-family of aldoses. To illustrate using present day knowledge, Fischer projection formulas and names for the D-aldose family (three to six-carbon atoms) are shown below, with the asymmetric carbon atoms (chiral centers) colored red.

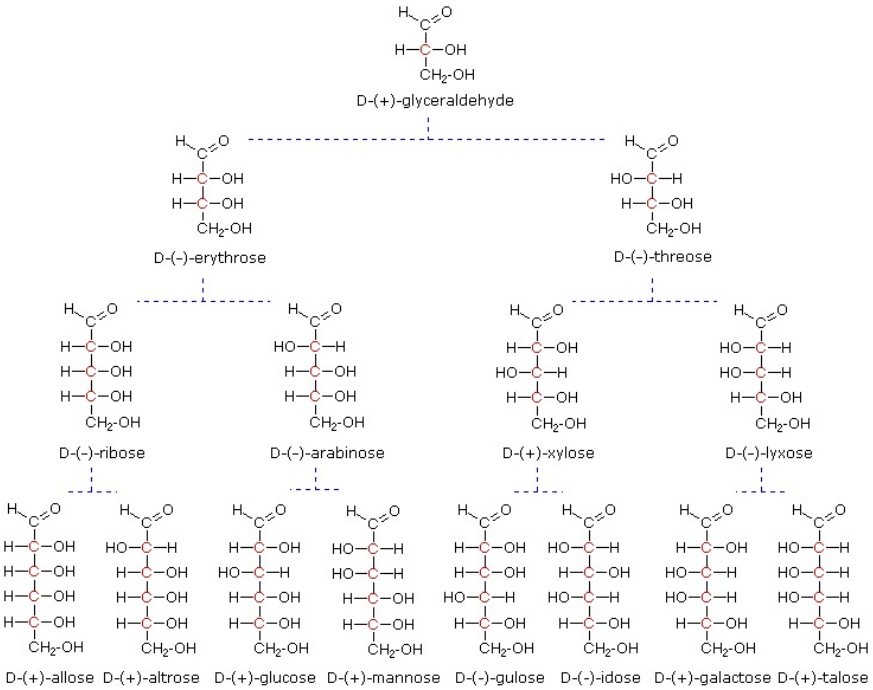
Aldotrioses: 3 carbon sugars with one chiral center. Aldotrioses have two (2^1) possible stereoisomers. A pair of enantiomers called D-gylceraldehyde and L-glyceraldehyde.

Aldotetroses: 4 carbon sugars with two chiral centers. Aldotetroses have four (2^2) possible stereoisomers. Two pairs of D/L enantiomers called erythrose and threose.

Aldopentoses: 5 carbon sugars with three chiral centers. Aldopentoses have eight (2^3) possible stereoisomers. Four pairs of D/L enantiomers called ribose, arabinose, xylose, and lyxose.

Aldohexoses: 6 carbon sugars with four chiral centers. Aldohexoses have sixteen (2^4) possible stereoisomers. five pairs of D/L enantiomers called allose, altrose, glucose, mannose, gulose, idose, galactose, and talose.

Below are the Fischer projects 3-6 carbon aldoses. Starting with the three carbon aldose D-glyceraldehyde, each additional carbon adds a new chiral center and doubles the number of possible stereoisomers of the D-aldoses. Remember that only D-aldoses are represented below. Each D-aldose has an L-aldose enantiomer which is not shown. The L-aldose versions can be draw by inverting all of the chiral centers in the D-aldose's Fischer projection as discussed in the previous section.



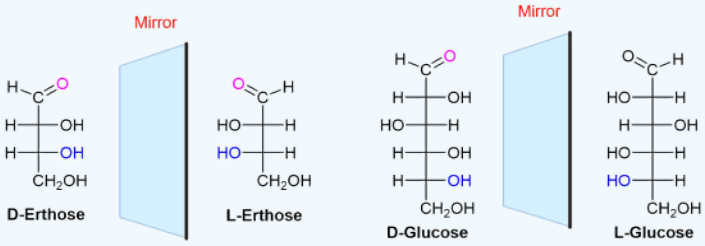
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WORKED EXAMPLE 25.4.1

Draw the Fisher projection of L-erythrose and L-Glucose

Solution

Use the Fischer projection provided above and reverse all of the chiral centers to provide the L-sugar. Note that in both cases the D sugars have the OH going to the right on the chiral center furthest away from the carbonyl. The L-sugars have the OH going to the left.



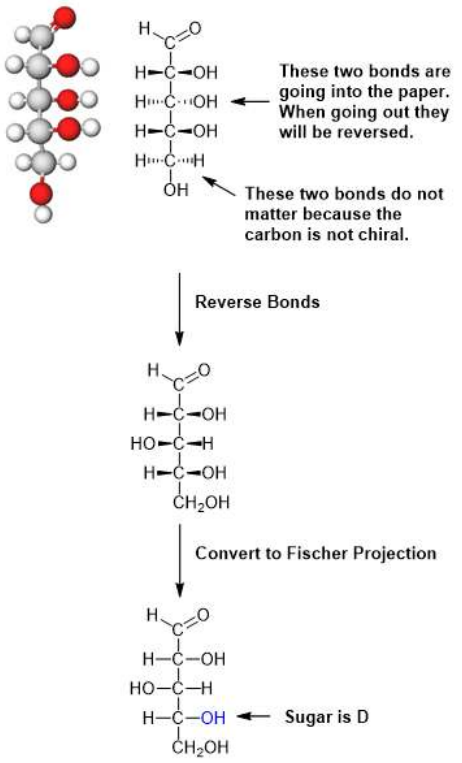
WORKED EXAMPLE 25.4.2

Please draw the Fischer projection fo the following aldopentose and determine if the sugars is D or L.

GLmol

Solution

First, rotate the model so that the carbonyl is at the top. This is requirement of a Fischer projection. Next rotate the model so that the H and OH of the chiral carbon just below the carbonyl are facing towards you. In this orientation, a dash/wedge model will have every other set of bonds going into the plane of the page. This is not the correct orientation of a Fischer project so they must be modified. The H and OH bonds need to be coming out of the plane of the page in a Fisher projects. When converting bonds from going into the page to going out of the page the orientation of the H and OH are reversed. Remember that the last -CH_2OH of a sugar is achiral so the orientation does not need to be shown. Once the bonds are oriented correctly the wedge bonds can be converted to those of a Fischer projection.



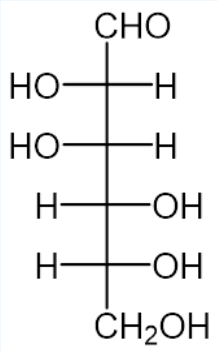
EXERCISE 25.4.1

For the following model of a sugar, please draw its Fischer projection and name it.

GLmol

Answer

D-Mannose



EXERCISE 25.4.2

How many heptose stereoisomers would there expected to be? How many would be D-Sugars?

Answer

There would be $2^5 = 32$ heptose stereoisomers. Half of these would be D-sugars or 16.

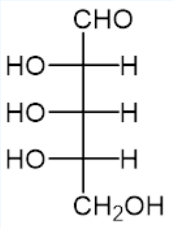
EXERCISE 25.4.3

Draw the Fischer projection of the following sugars.

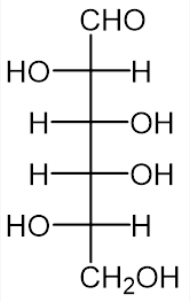
a. L-Ribose
b. L-Galactose
c. L-Talose

Answer

a)

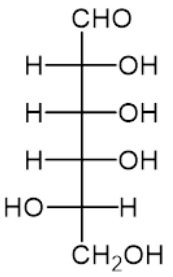


b)



c)

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25.5: CYCLIC STRUCTURES OF MONOSACCHARIDES - ANOMERS

OBJECTIVES

After completing this section, you should be able to

1. determine whether a given monosaccharide will exist as a pyranose or furanose.
2. draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
3. draw the Fischer projection of a monosaccharide, given its cyclic pyranose form.
4. draw, from memory, the cyclic pyranose form of D-glucose.
5. determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
6. describe the phenomenon known as mutarotation.
7. explain, through the use of chemical equations, exactly what happens at the molecular level during the mutarotation process.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

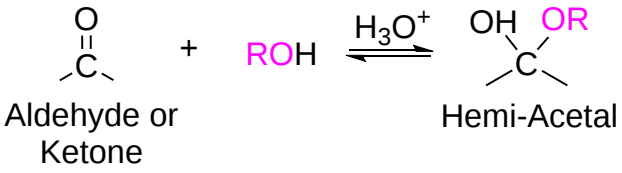
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

STUDY NOTES

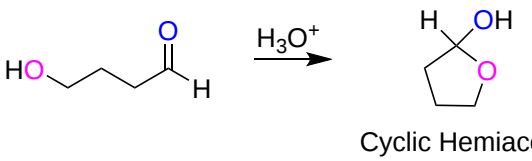
If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

CYCLIC MONOSACCHARIDES

In Section 19-10 it was discussed that the reaction of one equivalent of an alcohol, in the presence of an acid catalyst, adds reversibly to aldehydes and ketones to form a hydroxy ether called a **hemiacetal** (R_2COHOR') (h*emi*, Greek, half).



Molecules which have both an alcohol and a carbonyl can undergo an intramolecular version of the same reaction forming a cyclic hemiacetal.



Because sugars often contain alcohol and carbonyl functional groups, intramolecular hemiacetal formation is common in carbohydrate chemistry. Five and six-membered rings are favored over other ring sizes because of their low angle and eclipsing strain. Cyclic structures of this kind are termed furanose (five-membered) or pyranose (six-membered), reflecting the ring size relationship to the common heterocyclic compounds furan and pyran shown below.

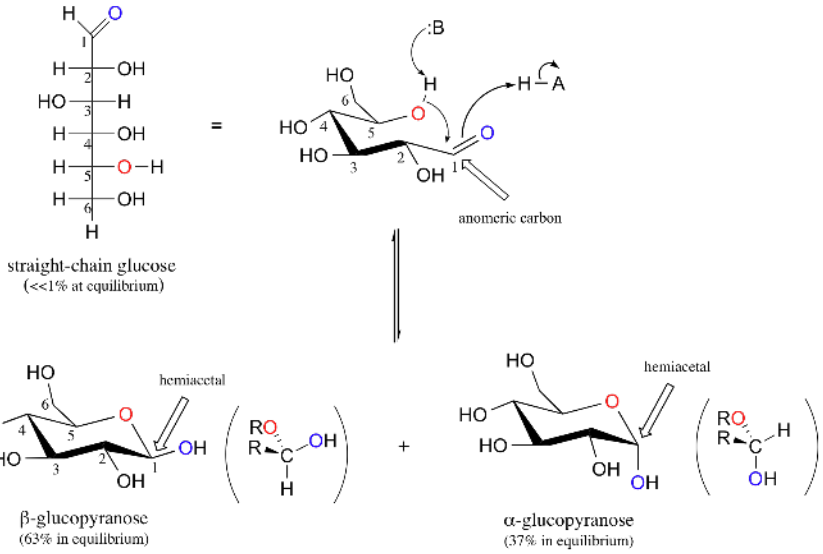


Furan (5-membered ring) and pyran (6-membered ring) structures

Unlike most of the biochemical reactions you will see in this text, sugar cyclization reactions are not catalyzed by enzymes: they occur spontaneously and reversibly in aqueous solution. Sugars are often shown in their open-chain form, however, in aqueous solution, glucose, fructose, and other sugars of five or six carbons rapidly interconvert between straight-chain and cyclic forms. For most five- and six-carbon sugars, the cyclic forms predominate in equilibrium since they are more stable. The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.

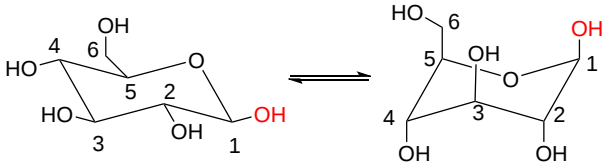
Aldohexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. At equilibrium less than 1% of glucose is in an open chain form with the rest being almost exclusively in its cyclic pyranose form. The pyranose ring is formed by attack of the hydroxyl on carbon 5 of glucose to the aldehyde carbon (carbon #1, also called the anomeric carbon in carbohydrate terminology). The cyclic form of glucose is called glucopyranose. Notice that for glucose and other aldohexoses the hydroxyl that forms the cyclic hemiacetal is also the one that determines the D/L designation of a sugar.

Pyranose rings are often drawn in a chair conformation like cyclohexane rings (**Section 4-6)** with substituents being either an axial or equatorial position. Pyranose rings are even capable of undergoing a ring flip to change between chair conformations. By convention the ring oxygen is placed to the right and to the rear of the structure (top right of the drawing). Groups which go to the right in a Fischer projection will be orientend 'down' of the pyranose ring while groups to the left are oriented 'up' in the chair structure. Also, the terminal -CH_2OH group is oriented up on the pyranose ring for D-sugars and down for L-Sugars.



When D-glucose cyclizes it forms a 37/63 mixture of the alpha and beta anomer respectively. The beta anomer is preferred because β-D-glucopyranose is the only aldohexose which can be drawn with all its bulky substituents (-OH and -CH_2OH) in equatorial positions, making it the most stable of the eight D-aldohexoses, which probably accounts for its widespread prevalence in nature.

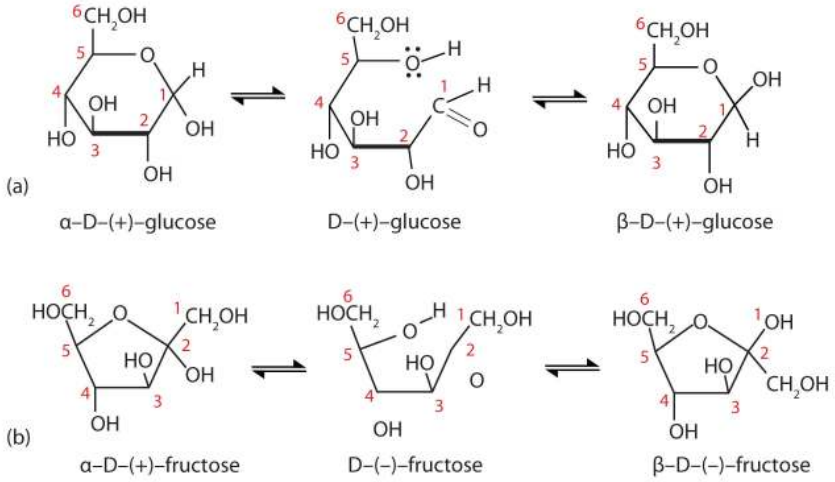
Conformational Isomers



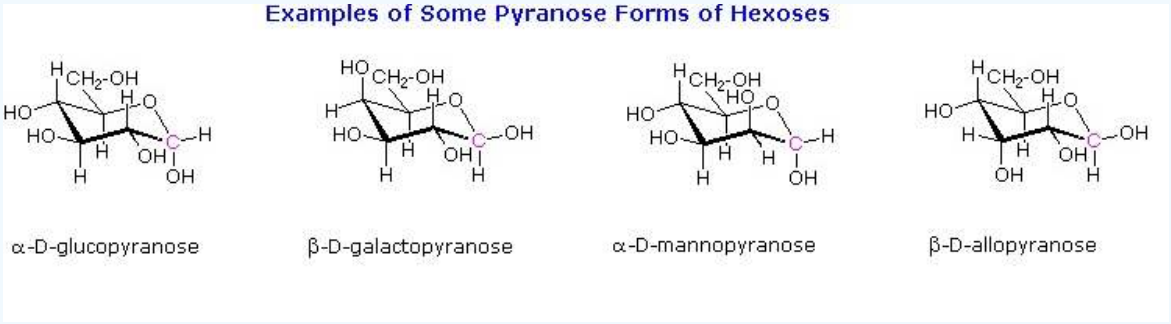
b-D-glucopyranose

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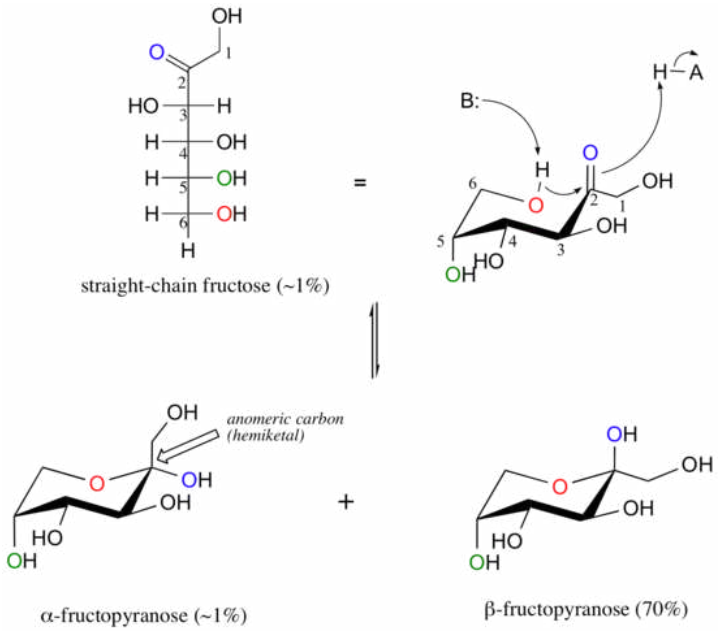
It is possible to obtain a sample of crystalline glucose in which all the molecules have the α structure or all have the β structure. The α form melts at 146°C and has a specific rotation of +112°, while the β form melts at 150°C and has a specific rotation of +18.7°. When the sample is dissolved in water, however, a mixture is soon produced containing both anomers as well as the straight-chain form, in dynamic equilibrium. You can start with a pure crystalline sample of glucose consisting entirely of either anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then re-close to form either the α or the β anomer. The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation (Latin *mutare*, meaning "to change"). At equilibrium, the mixture consists of about 36% α-D-glucose, 64% β-D-glucose, and less than 0.02% of the open-chain aldehyde form. The observed rotation of this solution is +52.7°.



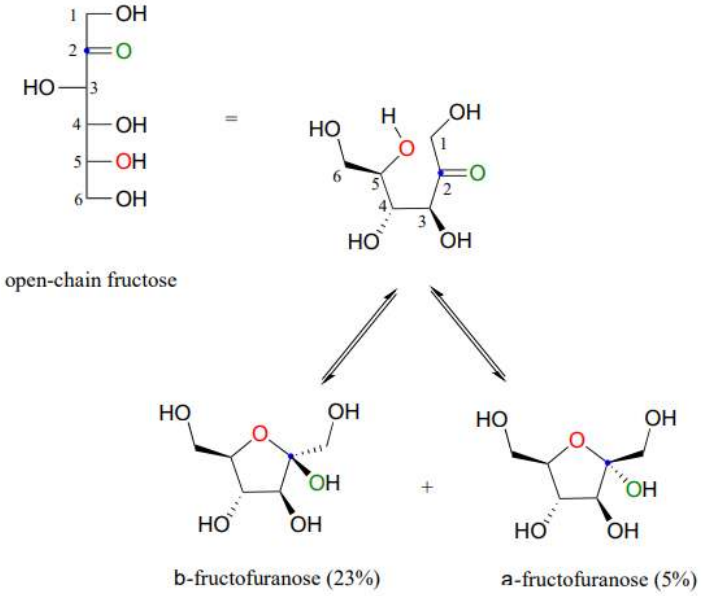
? EXAMPLE 25.5.1



Fructose in aqueous solution forms a six-membered cyclic hemiketal called fructopyranose when the hydroxyl oxygen on carbon #6 attacks the ketone carbon (carbon #2, the anomeric carbon in fructose).



In this case, the β anomer is heavily favored in equilibrium by a ratio of 70:1, because in the minor α anomer the bulkier -CH_2OH group occupies an axial position. Notice in the above figure that the percentages of α and β anomers present at equilibrium do not add up to 100%. Fructose also exists in solution as a five-membered cyclic hemiketal, referred to in carbohydrate nomenclature as fructofuranose. In the formation of fructofuranose from open-chain fructose, the hydroxyl group on the fifth carbon attacks the ketone.



In aqueous solution, then, fructose exists as an equilibrium mixture of 70% β-fructopyranose, 23% β-fructofuranose, and smaller percentages of the open chain and cyclic α-anomers. The β-pyranose form of fructose is one of the sweetest compounds known, and is the main component of high-fructose corn syrup. The β-furanose form is much less sweet.

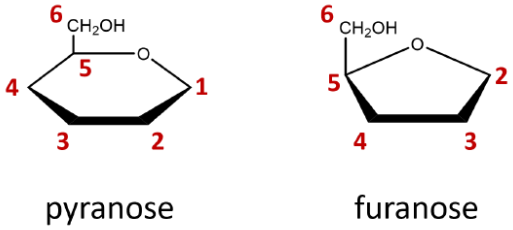
Although we have been looking at specific examples for glucose and fructose, other five- and six-carbon monosaccharides also exist in solution as equilibrium mixtures of open chains and cyclic hemiacetals and hemiketals. Shorter monosaccharides are unlikely to undergo analogous ring-forming reactions, however, due to the inherent instability of three and four-membered rings.

DRAWING CYCLIC STRUCTURES OF MONOSACCHARIDES

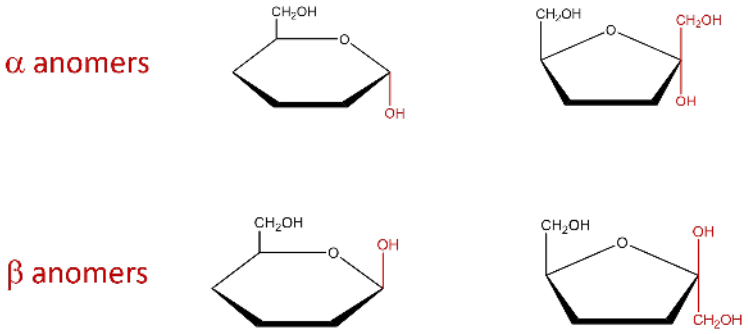
The cyclic forms of sugars are commonly depicted as **Haworth projections**. This convention, first suggested by the English chemist Walter N. Haworth, shows molecules drawn as planar rings with darkened edges representing the side facing toward the viewer. The structure is simplified to show only the functional groups attached to the carbon atoms. Any group written to the *right* in a Fischer projection appears *below (bottom face)* the plane of the ring in a Haworth projection, and any group written to the *left* in a Fischer projection appears *above* (top face) the plane in a Haworth projection.

Figure: Conversion of the Fischer projection of D-glucose to the Haworth projection of ß-D-glucose.

1. When converting a Fischer projection (line) to a Haworth projection, you must first identify the type of monosaccharide involved. If the carbohydrate represents an aldohexose, the **pyranose** ring is typically used. A pyranose is a cyclic structure that contains five carbon atoms and an oxygen. If the carbohydrate represents a ketohexose, the **furanose** ring is typically used. The furanose ring contains four carbon atoms and an oxygen.

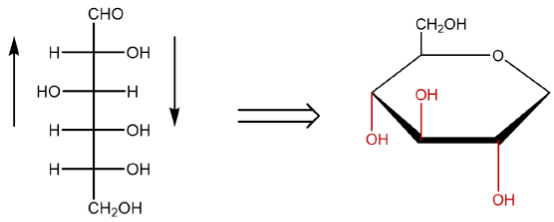


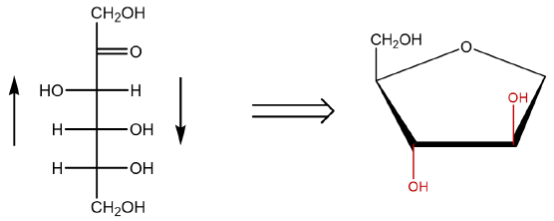
2. Indicate the arrangement of the hydroxyl group attached to the anomeric carbon to identify the sugar as an alpha or beta anomer. The α and β anomers are determined with respect to carbon 6. If the molecule represents a D-sugar, carbon 6 will be above the plane of the ring (top face) and form an L-sugar, carbon 6 will be below the plane of the ring (ring). The α anomer occurs when the OH on the anomeric carbon is trans to carbon 6 and the β anomer occurs when the OH on the anomeric carbon is cis to carbon 6. If the cyclic structure contains a furanose, since carbon 1 is not included within the ring, that carbon group would be arranged in the opposite direction of the OH group.



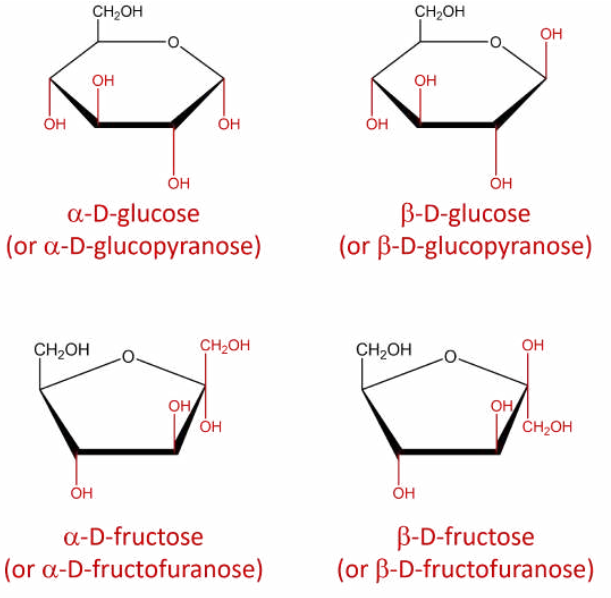
3. The remaining chiral centers (carbons 2, 3 and 4 of the pyranose or carbons 3 and 4 of the furanose) are arranged based on the directions of the hydroxyl from the Fischer projection structures. Groups to the left of the Fischer projection would point up (top face), while groups to the right would point down (bottom face).

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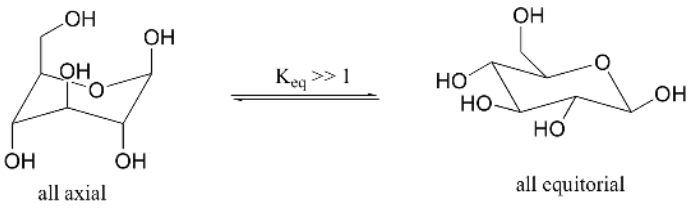


Since the Fischer Projection of any given carbohydrate is always the same, the Haworth Projection is essentially always the same. The only differences between the Haworth Projection of the alpha or beta form of a single carbohydrate, is how the OH (and carbon 1 if furanose ring) is arranged around the anomeric carbon to determine whether the molecule is alpha or beta.

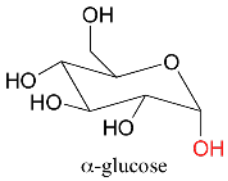


STABILITY OF CHAIR CONFORMATION IN PYRANOSE SUGARS

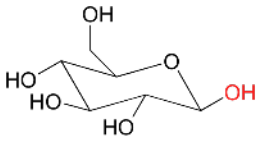
Previously, we have seen the six ring atoms of cyclic glucose drawn in two dimensions. A more accurate depiction shows that the molecule adopts, as expected, a chair conformation.



The conformation in which all substituents are equatorial is lower in energy. The two isomeric forms are referred to by the Greek letters alpha (α) and beta (β).



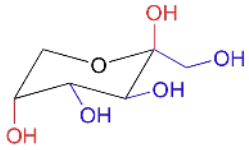
α-glucose



β-glucose

We have not learned about stereoisomerism quite yet, but you can still recognize that the bonding configuration on one carbon is different. On the alpha isomer, one of the hydroxyl groups is axial – this isomer is not able to adopt a chair conformation in which all non-hydrogen substituents are equatorial. The lower energy conformation is the one in which four of the five substituents are equatorial, but the presence of the one axial hydroxyl group means that the alpha isomer is, overall, less stable than the beta isomer.

The most abundant form of fructose in aqueous solution is also a six-membered ring.



fructose
(major form)

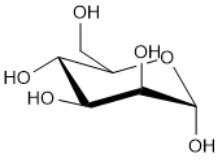
The lower energy chair conformation is the one with three of the five substituents (including the bulky $–CH_2OH$ group) in the equatorial position.

EXERCISE 25.5.1

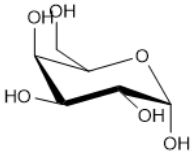
Draw the following in their most stable chair conformation: α-D-galactopyranose and α-D-mannopyranose. Which is expected to be the more stable?

Answer

Because the both have two axial OH's their chair conformations should be roughly the same stability.



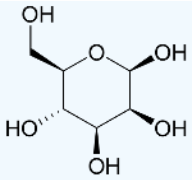
a-D-Mannose



a-D-Galactose

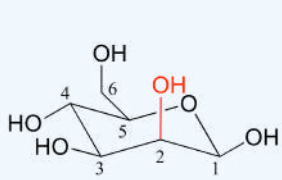
EXERCISE 25.5.2

Draw the two chair conformations of the sugar called mannose, being sure to clearly show each non-hydrogen substituent as axial or equatorial. Predict which conformation is likely to be more stable, and explain why.

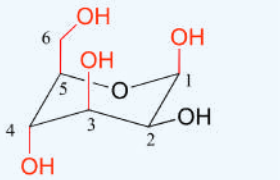


mannose

Answer



major chair form of mannose
(only one substituent axial)

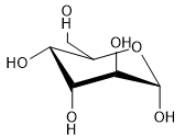


minor chair form of mannose
(four substituents axial)

EXERCISE 25.5.3

Draw the cyclic structure of α-D-altrose.

Answer

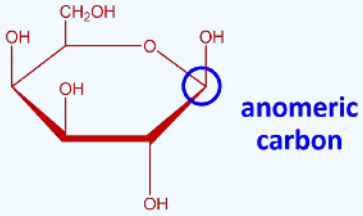


a-D-Altrose

EXERCISE 25.5.4

Draw the cyclic structure for β-D-galactose. Identify the anomeric carbon.

Answer

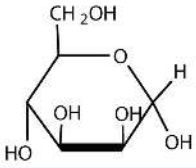


To identify the structure, we should first start with the Fischer projection of D-galactose. Since it is an aldohexose, we will start with the pyranose ring. The beta anomer was requested, so the OH on the anomeric carbon (C1) is cis to C6. Since C6 is top face (pointing up), the OH will be top face. Carbons 2, 3, and 4 are then arranged based on the Fischer projection arrangement at those carbons (C2 right, C3 left, and C4 left).

EXERCISE 25.5.5

Given that the aldohexose D-mannose differs from D-glucose only in the configuration at the second carbon atom, draw the cyclic structure for α-D-mannose.

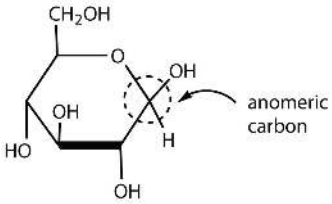
Answer



EXERCISE 25.5.6

Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.

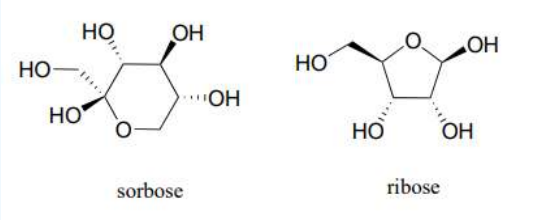
Answer



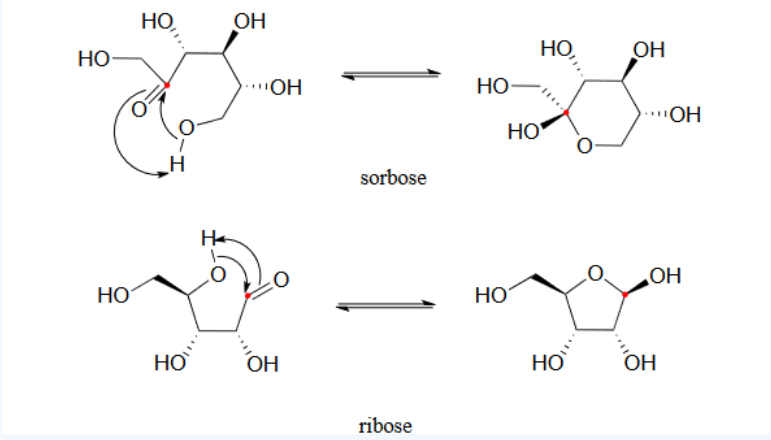
EXERCISE 25.5.7

a) Identify the anomeric carbon of each of the sugars shown below, and specify whether the structure shown is a hemiacetal or hemiketal.

b) Draw mechanisms for cyclization of the open-chain forms to the cyclic forms shown.



Answer

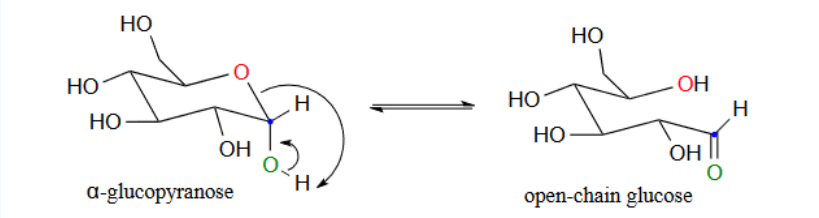


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EXERCISE 25.5.8

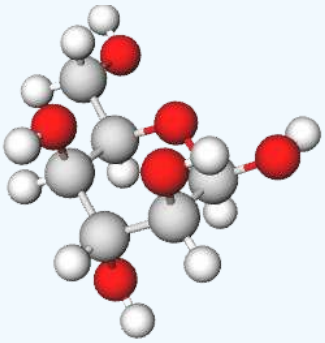
Draw a mechanism for the conversion of α-glucopyranose to open-chain glucose.

Answer



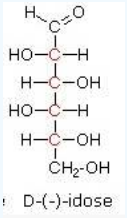
EXERCISE 25.5.9

Identify the following monosaccharide, write its full name, and draw its open-chain form as a Fischer projection.



Answer

β-D-idopyranose.



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25.6: REACTIONS OF MONOSACCHARIDES

OBJECTIVES

After completing this section, you should be able to

1. a. write equations to illustrate that the hydroxyl groups of carbohydrates can react to form esters and ethers.
   b. identify the product formed when a given monosaccharide is reacted with acetic anhydride or with silver oxide and an alkyl halide.
   c. identify the reagents required to convert a given monosaccharide to its ester or ether.
2. a. write an equation to show how a monosaccharide can be converted to a glycoside using an alcohol and an acid catalyst.
   b. identify the product formed when a given monosaccharide is treated with an alcohol and an acid catalyst.
   c. write a detailed mechanism for the formation of a glycoside by the reaction of the cyclic form of a monosaccharide with an alcohol and an acid catalyst.
3. identify the ester formed by phosphorylation in biologically important compounds.
4. a. identify the product formed when a given monosaccharide is reduced with sodium borohydride.
   b. identify the monosaccharide which should be reduced in order to form a given polyalcohol (alditol).
5. a. explain that a sugar with an aldehyde or hemiacetal can be oxidized to the corresponding carboxylic acid (also known as aldonic acid). **Note:** The sugar is able to reduce an oxidizing agent, and is thus called a reducing sugar. Tests for reducing sugars include the use of Tollens' reagent, Fehling's reagent and Benedict's reagent.
   b. explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
   c. identify warm HNO_3 as the reagent needed to form dicarboxylic acid (an aldaric acid).
6. a. describe the chain-lengthening effect of the Kiliani-Fischer synthesis.
   b. predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
   c. identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
7. a. describe the chain-shortening effect of the Wohl degradation.
   b. predict the product that would be produced by the Wohl degradation of a given aldose.
   c. identify the aldose or aldoses that would yield a given product following Wohl degradation.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- aldaric acid
- aldonic acid
- alditol
- aldonic acid
- glycoside
- Kiliani-Fischer synthesis
- neighbouring group effect
- reducing sugar
- Wohl degradation

STUDY NOTES

While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

The formation of esters and ethers is quite straightforward and should not require further clarification.

Note that glycosides are in fact acetals, and that glycoside formation is therefore analogous to acetal formation. To refresh your memory about the chemistry of acetals, quickly review Section 19.10

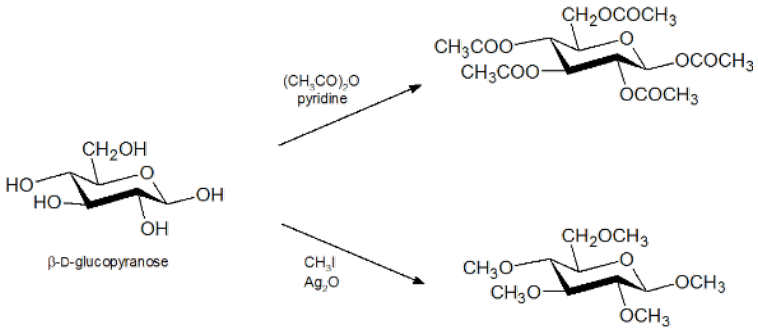
Monosaccharides contain both alcohol and carbonyl functional groups. This allows monosaccharides to undergo many of the reactions typical for these functional groups. In particular, alcohols can be converted to esters, converted to ethers, converted to acetals, or oxidized. Carbonyls can be reacted with nucleophiles, be reduced to form alcohols, or be oxidized to form carboxylic acids.

ESTER AND ETHER FORMATION

The hydroxyl groups of monosaccharides are often converted to ether or ester groups to increase solubility in organic solvents. Also, the conversion allows the sugar to be easily purified and crystallized.

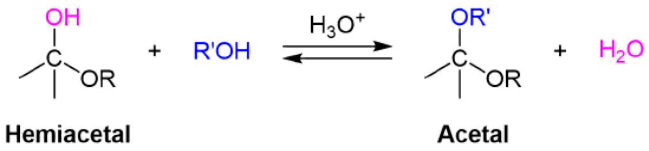
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5) in the presence of a base. During these reactions all of the -OH groups are converted to esters. The monosaccharide, D-glucopyranose can be coverted to the pentacetate through reaction with acetic anhydride.

Treatment of carbohydrates with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the formation of ethers. The strongly basic conditions typically used for the Williamson ether synthesis can degrade some sugar molecules. Instead, milder bases or silver oxide (Ag_2O) are used to provide ethers in high yields. The monosaccharide, D-glucopyranose can be converted to the pentamethyl ether through reaction with iodomethane and silver oxide.

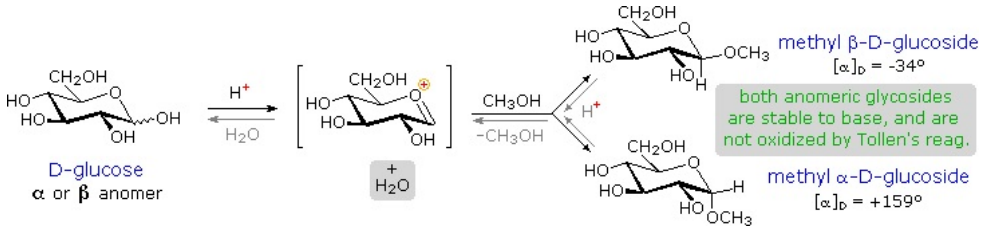


GLYCOSIDE FORMATION

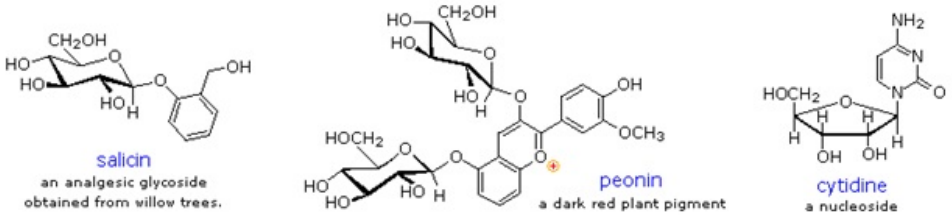
Reacting a hemiacetal with an alcohol and an acid catalyst produces an acetal in which the anomeric hydroxide has been replaced by an ether group.



Monosaccharide acetal derivatives, called glycosides, are formed when a hemiacetal reacts with an alcohol in the presence of an acid catalyst. During the reaction the -OH group from the anomeric carbon is replaced by a -OR group from the alcohol. A mixture of alpha and beta products are formed regardless of the conformation of the reactant. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. This reaction is illustrated below for D-glucopyranose and methanol which forms a mixture of alpha and beta methyl-glucopyranosides. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The acetal product is stable to base and alkaline oxidants such as Tollen's reagent. They are not in equilibrium with the open-chain form and thus do not undergo mutarotation. Since this acid-catalyzed reaction is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.



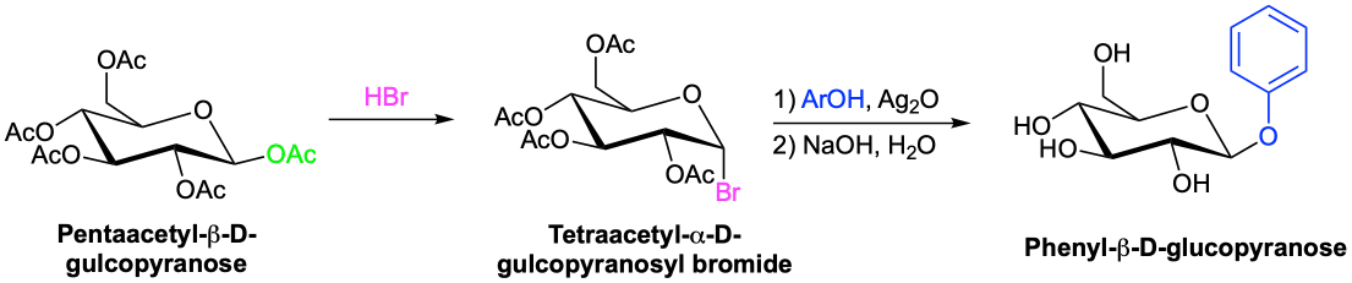
Two examples of naturally occurring glycosides and one example of an amino derivative are displayed below.



- Salicin, one of the oldest herbal remedies known, was the model for the synthetic analgesic aspirin.
- A large class of hydroxylated, aromatic oxonium cations called anthocyanins provide the red, purple and blue colors of many flowers, fruits and some vegetables. Peonin is one example of this class of natural pigments, which exhibit a pronounced pH color dependence. The oxonium moiety is only stable in acidic environments, and the color changes or disappears when base is added. The complex changes that occur when wine is fermented and stored are in part associated with glycosides of anthocyanins.
- Amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

KOENIGS–KNORR REACTION

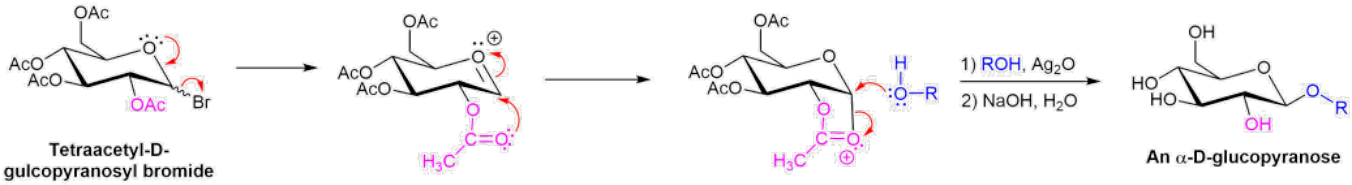
The presence of multiple -OH groups on a sugar molecular makes the synthesis of glycosides particularly difficult. One of the oldest glycosylation reactions, called the **Koenigs–Knorr reaction**, is effective for preparing the beta-glycosides of glucose. The pathway starts with the reaction of glucose pentaacetate with HBr to form a pyranosyl bromide. Addition of silver oxide allows for the nucleophilic addition of the chosen alcohol. Hydrolysis of the remaning acetal groups forms the beta-glucopyranoside.



Although the final step of the reaction appears to show the inversion characteristic of an S_N2 reaction, the same product forms if either the alpha or beta anomers of the glucopyranosyl bromide is used. This provides evidence that stereochemical control is lost at some point during the mechanism of the reaction.

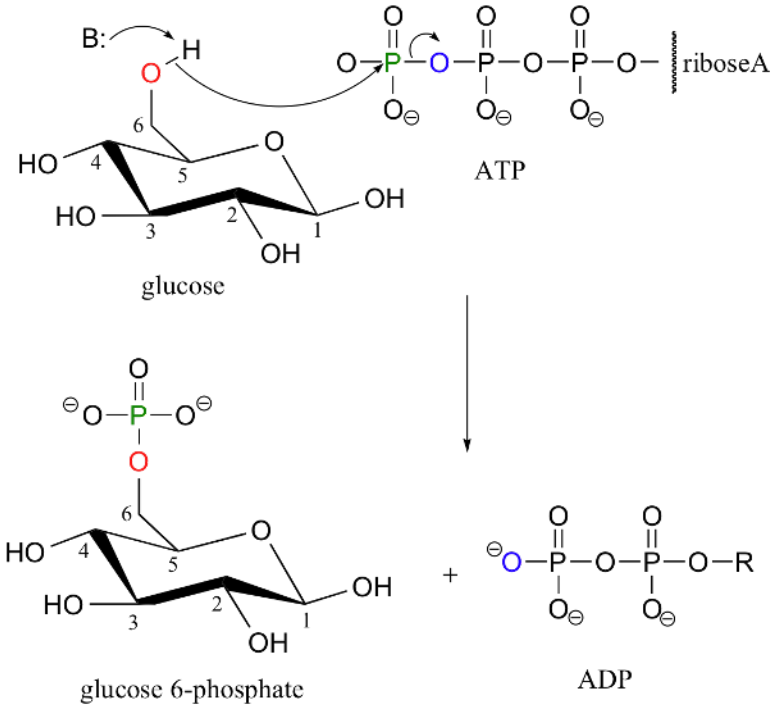
KOENIGS–KNORR REACTION MECHANISM

The mechanism starts with the S_N1 like removal of the bromine leaving group which is promoted by the formation of an oxonium ion intermediate. Either anomer of the glucopyranosyl bromide will produce the same oxonium intermediate. Lone pair electrons from the carbonyl oxygen of an adjacent acetate group adds to the oxonium ion in an internal ring-forming reaction. Because the adjacent acetate was on the bottom of the glucose ring the newly form C-O bond is also on the bottom. During this step a new oxonium ion is formed. The alcohol then displaces the oxonium ion as a leaving groups during an S_N2 reaction. The inversion of configuration of the S_N2 reaction produces a beta-glycoside. Participation of an adjacent acetate group in the mechanism of the Koenigs–Knorr reaction is called a **neighboring-group effect**.



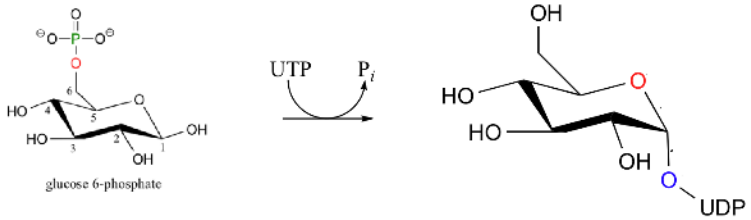
BIOLOGICAL ESTER FORMATION: PHOSPHORYLATION

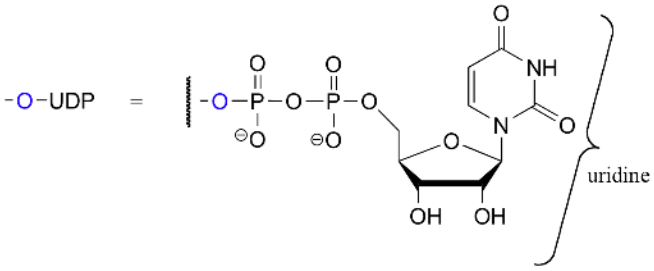
Recall that almost all biomolecules are charged species, which 1) keeps them water soluble, and 2) prevents them from diffusing across lipid bilayer membranes. Although many biomolecules are ionized by virtue of negatively charged carboxylate and positively charged amino groups, the most common ionic group in biologically important organic compounds is phosphate - thus the phosphorylation of alcohol groups is a critical metabolic step. In alcohol phosphorylations, ATP is almost always the phosphate donor, and the mechanism is very consistent: the alcohol oxygen acts as a nucleophile, attacking the gamma-phosphorus of ATP and expelling ADP.



Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Called glycoconjugates these sugar bonded molecules are often found in biological membranes, to which they are anchored through covalent bonds. These compounds are crucial to determine to how different cell types recognized one another which will be discussed further in **Section 25.11**.

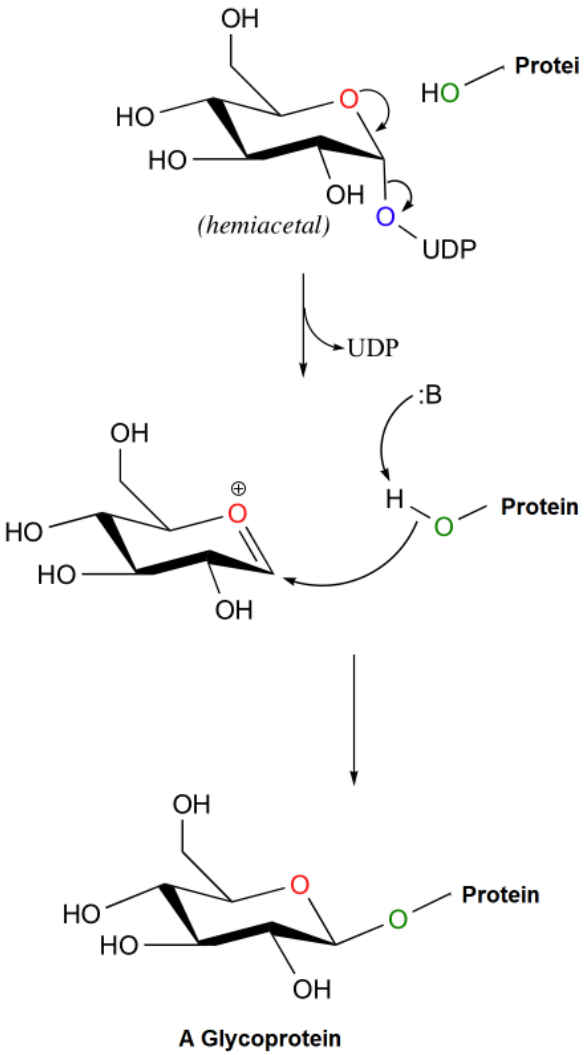
Glycoconjugate formation begins with the formation of a phosphorylated sugar such as glucose-6-phosphate which is then reacted with uridine triphosphate (UTP), to give a glycosyl uridine diphosphate. The phosphorylation makes the anomeric -OH of the sugar a better leaving group. During nucleophilic substitutions reaction with a protein or a lipid to form a glycoconjugate the anomeric -OH does not leave as a water molecule, but rather as part of a uridine nucleotide diphosphate group.





To form a glycoprotein the anomeric carbon of a glucopyranose-UDP derivative is attacked from above by an -OH of $-NH_2$ group from a protein. The UDP leaving group is displaced, and inversion of stereochemistry results at the anomeric carbon.

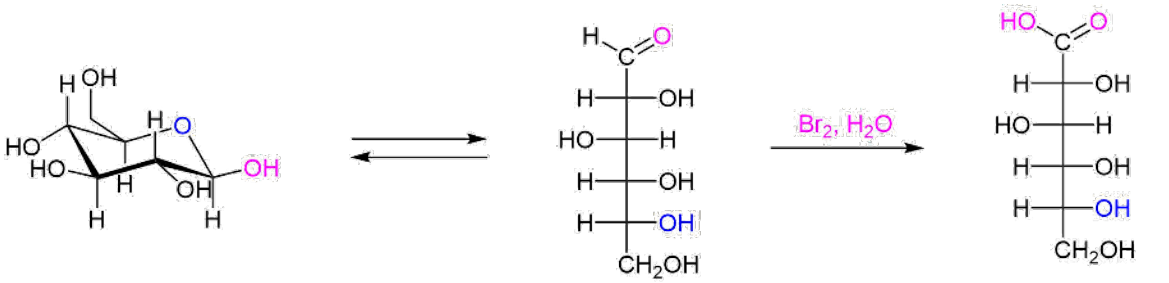
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A Glycoprotein

OXIDATION OF MONOSACCHARIDES

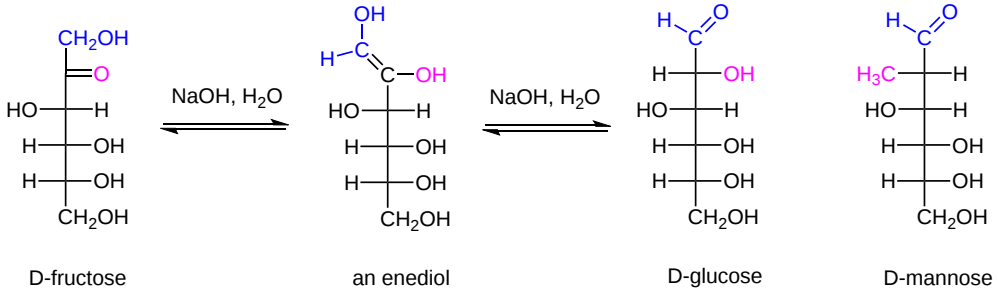
When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an **aldonic acid**. Because of the 2º hydroxyl functions that are also present in these compounds, a mild oxidizing agent such as aqueous Br_2 can be used for this conversion. The oxidation occurs by reaction of the open-chain form of the sugar. Because of the equilibrium between the open and ring form of the sugar, eventually the entire sample will undergo the reaction.



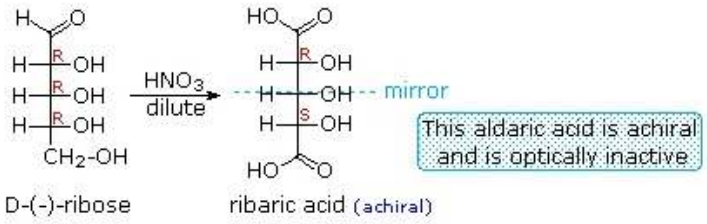
Historically sugars have been classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'** (Ag^+ in NH_3) or **Benedict's** (Cu^{2+} and sodium citrate) reagents. If a sugar is oxidized by these reagents it is called a reducing sugar, since the oxidant ($Ag^{(+)}$ or $Cu^{(+2)}$) is

reduced in the reaction, as evidenced by formation of a silver mirror or precipitation of cuprous oxide. The Tollens' test is commonly used to detect aldehyde functions; and because of the facile interconversion of ketoses and aldoses under the basic conditions of this test, ketoses such as fructose also react and are classified as reducing sugars.

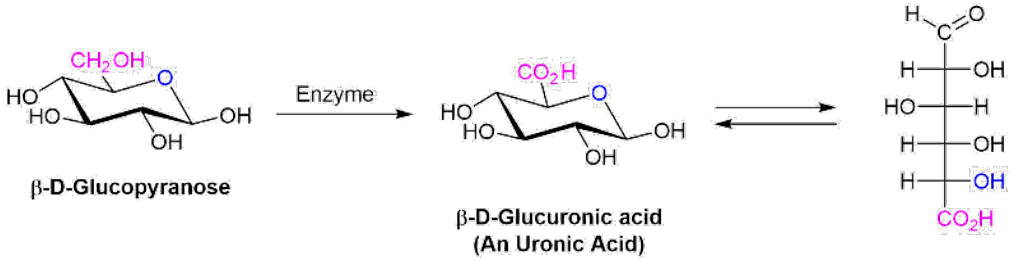
Becuase aldoses contain an aldehyde group they are reducing sugars and will be oxidized by Tollen's and Benedict's reagent. Some ketoses are also reducing sugars. Despite not having an aldehyde groups, fructose is capable of isomerizing to glucose and mannose by keto-enol tautomerism under basic conditions. Once formed, these aldoses are capable of being oxidized by Tollens reagent.



Aldoses can be oxidized to a dicarboxylic acid by dilute nitric acid. Nitric acid is a strong enough oxidizing agent to cause both the aldehyde carbonyl and the -CH_2OH group to be oxidized to carboxylic acids. If both ends of an aldose chain are oxidized to carboxylic acids, the product is called an aldaric acid. By converting an aldose to its corresponding aldaric acid derivative, the ends of the chain become identical. Such an operation will disclose any latent symmetry in the remaining molecule and possibly form an achiral meso compound. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown below.



If the -CH_2OH group of an aldose is oxidized to a carboxylic acid while the aldehyde carbonyl is not affected, the monocarboxylic acid product is called a uronic acid. This selective oxidation is difficult to accomplish and can only be done enzymatically.

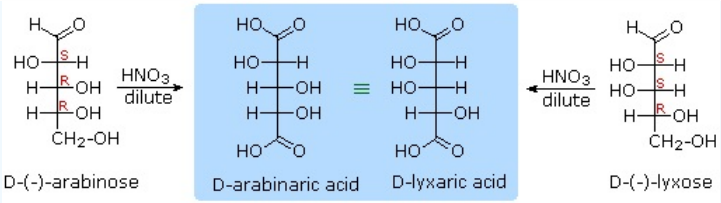


? EXERCISE 25.6.1

D-arabinose and D-lyxose produce the same chiral aldaric acid product when oxidized with dilute HNO_3. Please explain.

Answer

1) Remember, a Fischer projection formula may be rotated by 180° in the plane of projection without changing its configuration.



EXERCISE 25.6.2

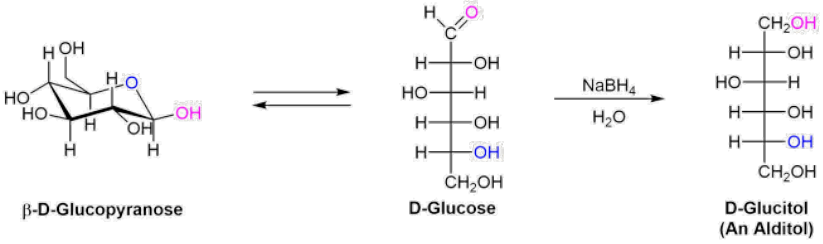
Which two D-aldohexoses are oxidized to produce an optically inactive (meso) aldaric acid?

Answer

D-Allose and D-galactose.

REDUCTION OF MONOSACCARIDES

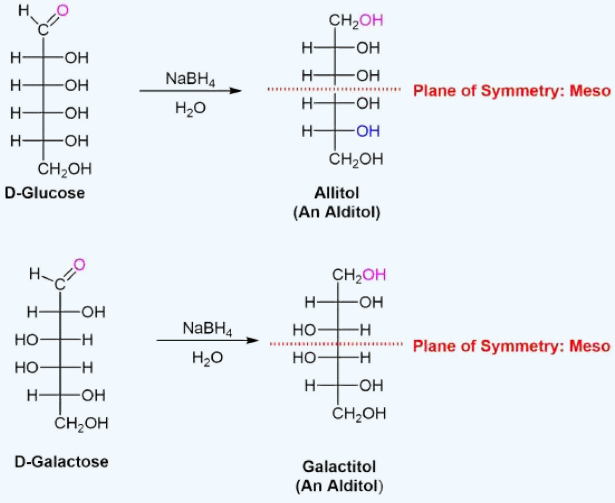
Treatment of an aldose or ketose with sodium borohydride reduces it to a polyalcohol called an alditol. The reduction occurs by reaction of the open-chain form. Although only a small amount of the open-chain form is present at any given time, that small amount is reduced, more is produced by opening of the pyranose form, that additional amount is reduced, and so on, until the entire sample has undergone reaction. The reaction products can be formally named by removing the **-ose** ending from the open-chain sugar and replacing it with **-itol**. Note! The alditol products have identical end groups, $HOCH_2(CHOH)_nCH_2OH$ which means that forming an achiral meso compound is possible.



EXERCISE 25.6.3

Allitol and galactitol from the reduction of allose and galactose are achiral. Explain why this occurs.

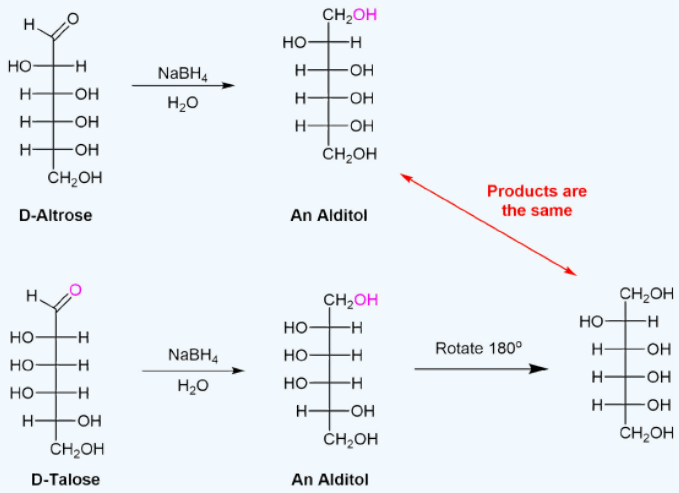
Answer



EXERCISE 25.6.4

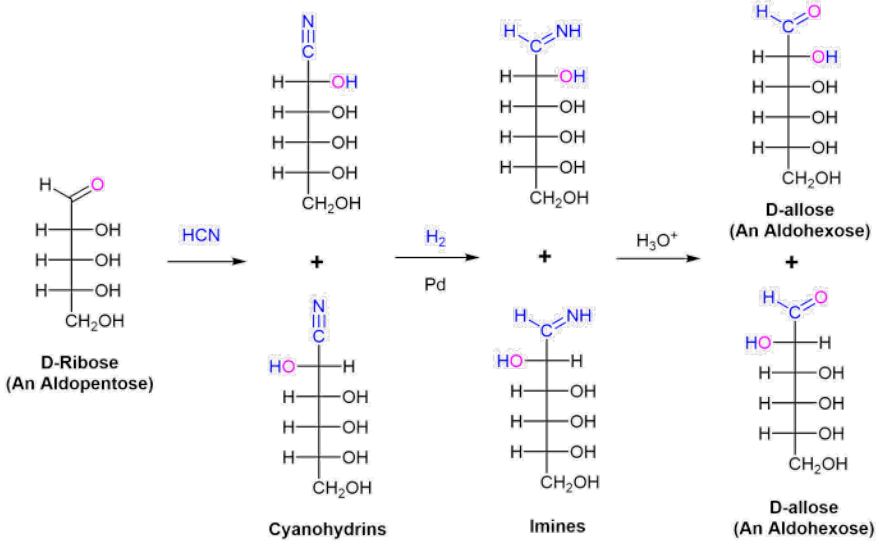
Altrose and talose are reduced to the same chiral alditol. Explain why this occurs.

Answer



CHAIN LENGTHENING: THE KILIANI–FISCHER SYNTHESIS

The Kiliani–Fischer synthesis lengthens the carbon chain of an aldose by one carbon atom. In doing this two new sugar epimers are created. The synthesis starts by reacting an aldose with HCN. Nucleophilic addition adds the cyanide nucleophile to the electrophilic carbon of the aldose aldehyde forming a cyanohydrin intermediate. The cyanide nucleophile adds a carbon. Stereochemical control is lost, so a racemic mixture of two cyanohydrins differing in the stereochemistry at C2 is formed. The nitrile group of the cyanohydrin is reduced to an imine intermediate by hydrogenation over a palladium catalyst. Finally, the imine is hydrolyzed to an aldehyde to create two new aldoses with an additional carbon. For example performing the Kiliani–Fischer synthesis on D-ribose produces a mixture of D-allose and D-altrose.



EXERCISE 25.6.5

What products would you expect from Kiliani–Fischer reaction of D-xylose?

Answer

D-Gluose and D-idose

? EXERCISE 25.6.6

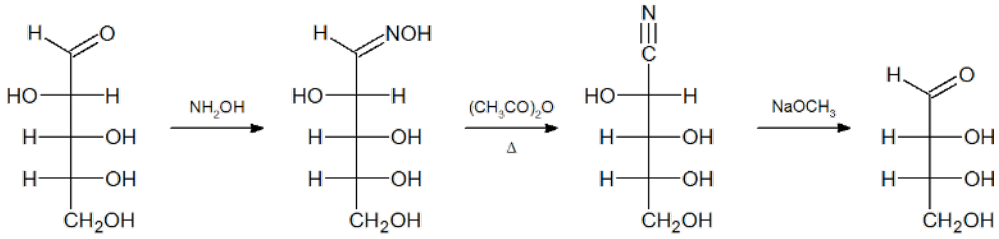
What aldopentose would be expected to produce a mixture of D-xylose and D-lyxose from an Kiliani–Fischer synthesis?

Answer

D-Threose

CHAIN SHORTENING: THE WOHL DEGRADATION

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This is commonly accomplished the **Wohl degradation**, which is virtually the reverse of the Kiliani–Fischer synthesis. The aldose aldehyde is converted to an oxime (Section 19-8) by treatment with hydroylamine (NH_2OH). Dehydration of the oxime with acetic anhydride forms a cyanohydrin. Under basic conditions, the cyanohydrine loses HCN to reform an aldehyde carbonyl. The following equation illustrates the application of this procedure to the aldopentose, D-arabinose to form the aldotetrose, D-erythrose.



? EXERCISE 25.6.7

Two of the four D- aldopentoses yield D-erythrose on Wohl degradation. What are their structures?

Answer

D-Ribose and D-arabinose

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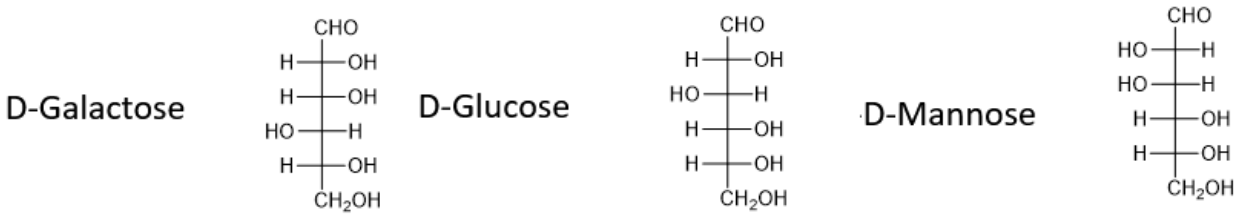
25.7: THE EIGHT ESSENTIAL MONOSACCHARIDES

OBJECTIVES

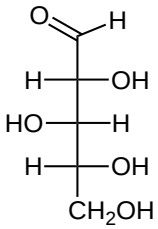
1. identify and draw the eight essential monosaccharides

Eight monosaccharides are required for the proper functioning of human beings. Although they are typically supplied through a healthy diet, they can be biosynthesized if required. The eight monosaccharides are L-fucose, D-galactose, N-acetyl-D-glucosamine, N-acetyl-D-galactosamine, D-glucose, D-mannose, N-acetyl-D-neuraminic acid, and D-xylose.

D-Galactose, D-Glucose, and D-Mannose are commonly found aldohexoses:

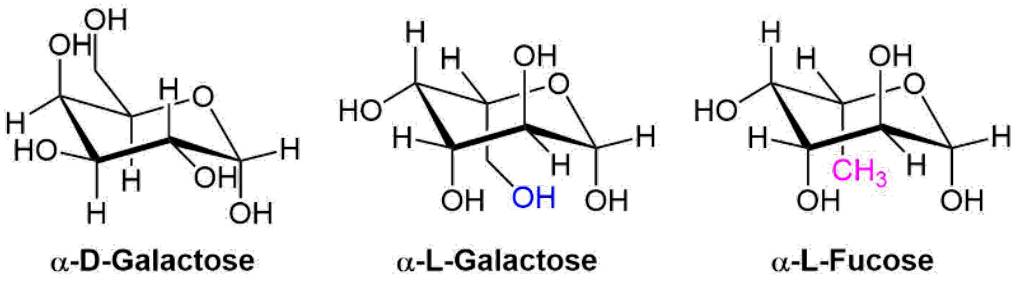


D-Xylose is a common aldopentose.

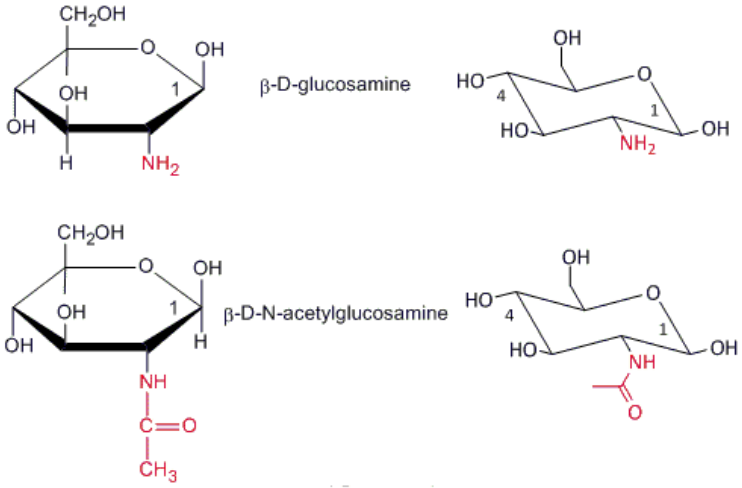


D-Xylose

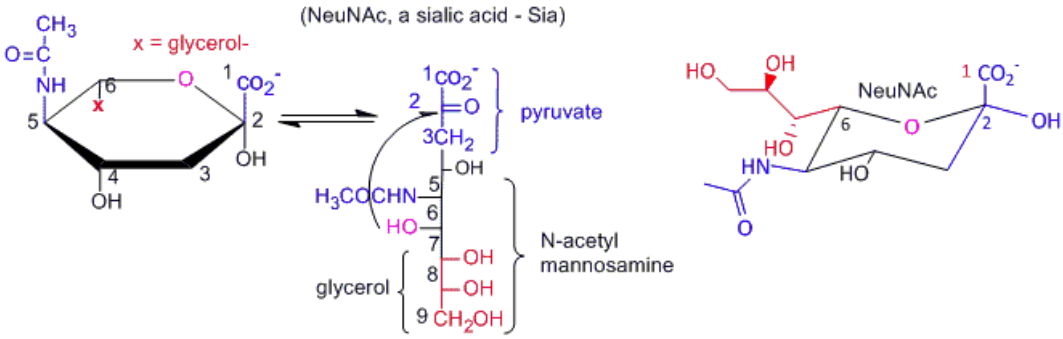
L-Fucose is a deoxy sugar. Fucose is is the monosaccaride L-galactose with the -OH group on C6 replaced with an -H.



N-acetylgalactosamine and N-acetylglucosamine are derivatives where the corresponding amino sugars have been converted to amides by N-acylation. Amino sugars have had their -OH groups at C2 replaced by an $-NH_2$.

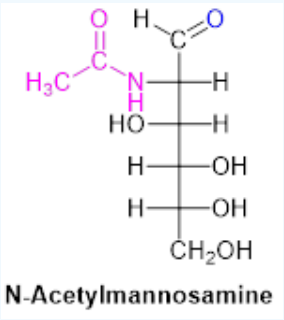


N-Acetylneuraminic acid is nine carbon sugar created by an aldol reaction between N-acetymannosamine and pyruvate. N-acetylneuaminic acid forms a pyranose ring by a intramolecular hemiacetal formation between the -OH on C6 and the ketone functional group in the pyruvate moiety.



EXERCISE 25.7.1

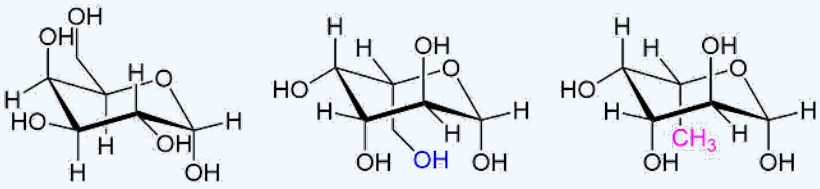
1) Please show the mechanism of the aldol reaction between *N*-acetylmannosamine and pyruvate to form neuraminic acid.



Answer

1)

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25.8: DISACCHARIDES

OBJECTIVES

After completing this section, you should be able to

1. identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
2. identify the two monosaccharide units in a given disaccharide.
3. identify the type of glycoside link (e.g., 1,4′-*β*) present in a given disaccharide structure.
4. draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.

   Note: If *α*- or *β*-D-glucose were one of the monosaccharide units, its structure would not be provided.
5. identify the structural feature that determines whether or not a given disaccharide behaves as a reducing sugar and undergoes mutarotation, and write equations to illustrate these phenomena.
6. identify the products formed from the hydrolysis of a given disaccharide.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- 1,4′ link
- disaccharide (see Section 25.1)
- invert sugar

STUDY NOTES

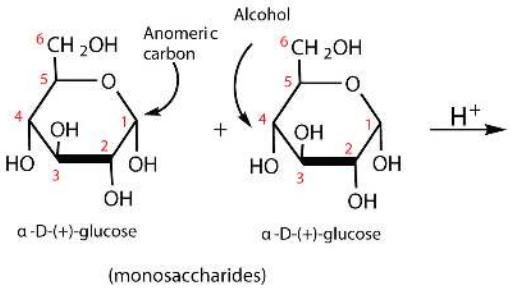
Notice that most of the disaccharides discussed in this section contain one unit of D-glucose. You are not expected to remember the detailed structures of maltose, lactose and sucrose. Similarly, we do not expect you to remember the systematic names of these substances.

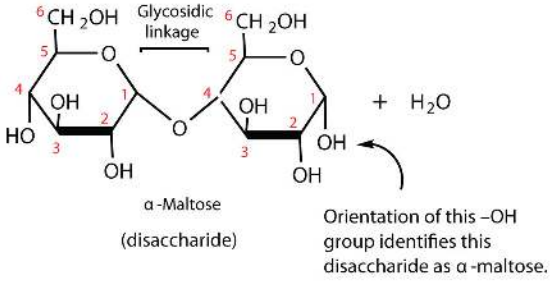
Previously, you learned that monosaccharides can form cyclic structures by the reaction of the carbonyl group with an OH group. These cyclic molecules can in turn react with another alcohol to form a glycoside. When the alcohol component of a glycoside is provided by a hydroxyl function on another monosaccharide, the compound is called a disaccharide. Disaccharides ($C_{12}H_{22}O_{11}$) are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage. This linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide. The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them. There are three common disaccharides: maltose, lactose, and sucrose. All three are white crystalline solids at room temperature and are soluble in water.

MALTOSE

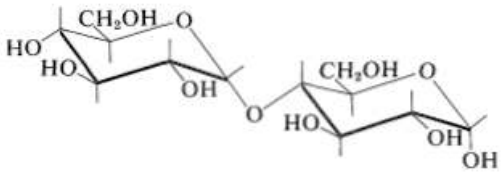
Maltose occurs to a limited extent in sprouting grain. It is formed most often by the partial hydrolysis of starch and glycogen. In the manufacture of beer, maltose is liberated by the action of malt (germinating barley) on starch; for this reason, it is often referred to as *malt sugar*. Maltose is about 30% as sweet as sucrose. The human body is unable to metabolize maltose or any other disaccharide directly from the diet because the molecules are too large to pass through the cell membranes of the intestinal wall. Therefore, an ingested disaccharide must first be broken down by hydrolysis into its two constituent monosaccharide units. In the body, such hydrolysis reactions are catalyzed by enzymes such as *maltase*. The same reactions can be carried out in the laboratory with dilute acid as a catalyst, although in that case the rate is much slower, and high temperatures are required. Whether it occurs in the body or a glass beaker, the hydrolysis of maltose produces two molecules of D-glucose

The glucopyranose units in maltose are joined in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucopyranose molecule to the fourth carbon atom of the second glucopyranose molecule (an α-1,4-glycosidic linkage). The bond from the anomeric carbon of the first monosaccharide unit is directed downward, which is why this is known as an α-glycosidic linkage. The OH group on the anomeric carbon of the second glucopyranose can be in either the α or the β position.



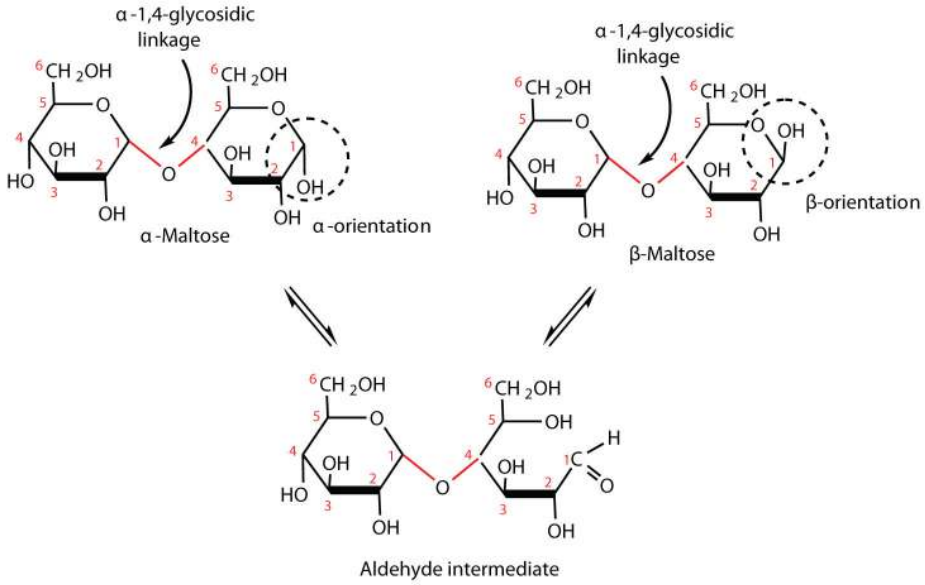


Cellobiose is a disaccharide made up of two D-glucopyranose molecules linked with a β-1,4-glycosidic linkage. Like maltose, the OH group on the anomeric carbon of the second glucopyranose of cellobiose can be in either the α or the β position. Although the difference between maltose and cellobiose seems small they have vastly different biological properties. Maltose can be digested by humans whereas cellobiose cannot.



maltose, **25**

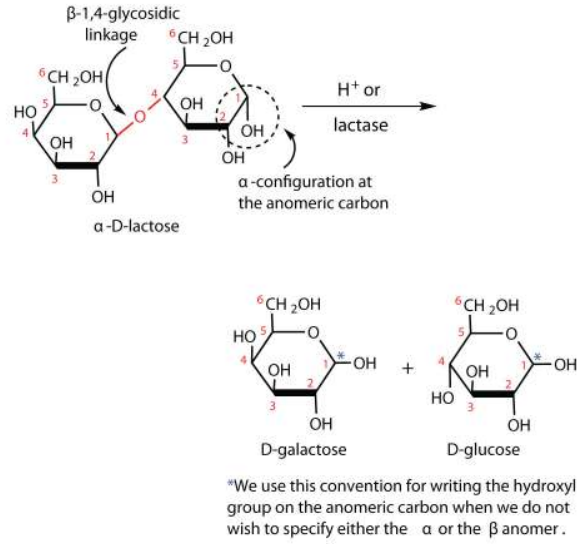
Maltose is a reducing sugar. Thus, its two D-glucopyranose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. Although one anomeric carbon in maltose and cellobiose is used to form the 1,4-glycosidic linkage, the anomeric carbons on the second glucopyranose remain a hemiacetal. Like an individual monosaccharide, the second glucopyranose subunit undergoes mutarotation and thus is in equilibrium with its aldehyde and both anomer forms. For this reason, maltose and cellobiose contain a mixture of α and β anomers of the second glucopyranose.



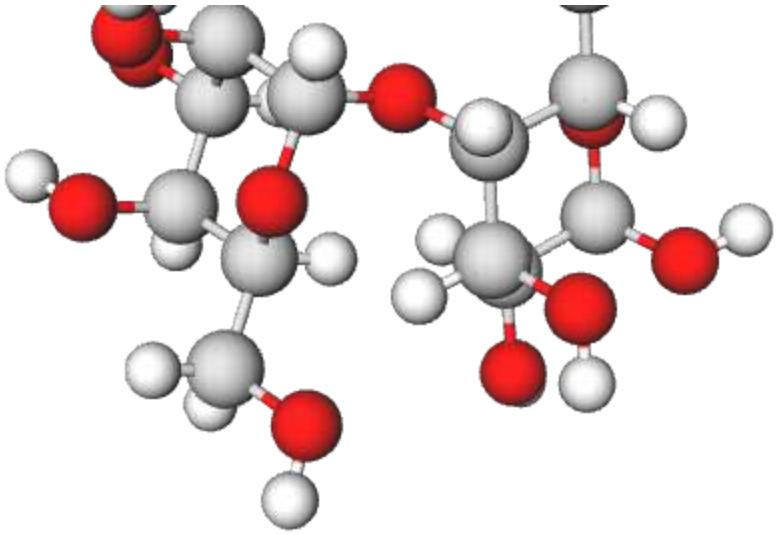
LACTOSE

Lactose is known as *milk sugar* because it occurs in the milk of humans, cows, and other mammals. In fact, the natural synthesis of lactose occurs only in mammary tissue, whereas most other carbohydrates are plant products. Human milk contains about 7.5% lactose, and cow's milk contains about 4.5%. This sugar is one of the lowest ranking in terms of sweetness, being about one-sixth as sweet as sucrose. Lactose is produced commercially from whey, a by-product in the manufacture of cheese. It is important as an infant food and in the production of penicillin.

Lactose is a disaccharide composed of one molecule of D-galactopyranose and one molecule of D-glucopyranose joined by a β-1,4-glycosidic bond between the 1 of D-galactopyranose and the C4 of glucose. Lactose is a reducing sugar and undergoes mutarotation to exhibit both anomers of the D-glucopyranose subunit. The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic action of the enzyme *lactase*.



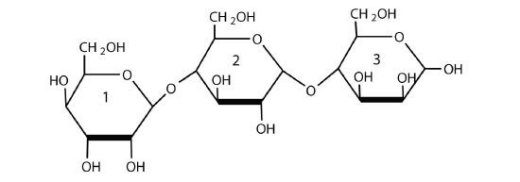




Many adults and some children suffer from a deficiency of lactase. These individuals are said to be lactose intolerant because they cannot digest the lactose found in milk. A more serious problem is the genetic disease galactosemia, which results from the absence of an enzyme needed to convert galactose to glucose. Certain bacteria can metabolize lactose, forming lactic acid as one of the products. This reaction is responsible for the "souring" of milk.

EXAMPLE 1

For this trisaccharide, indicate whether each glycosidic linkage is α or β.



Solution

The glycosidic linkage between sugars 1 and 2 is β because the bond is directed up from the anomeric carbon. The glycosidic linkage between sugars 2 and 3 is α because the bond is directed down from the anomeric carbon.

TO YOUR HEALTH: LACTOSE INTOLERANCE AND GALACTOSEMIA

Lactose makes up about 40% of an infant's diet during the first year of life. Infants and small children have one form of the enzyme lactase in their small intestines and can digest the sugar easily; however, adults usually have a less active form of the enzyme, and about 70% of the world's adult population has some deficiency in its production. As a result, many adults experience a reduction in the ability to hydrolyze lactose to galactose and glucose in their small intestine. For some people the inability to synthesize sufficient enzyme increases with age. Up to 20% of the US population suffers some degree of lactose intolerance.

In people with lactose intolerance, some of the unhydrolyzed lactose passes into the colon, where it tends to draw water from the interstitial fluid into the intestinal lumen by osmosis. At the same time, intestinal bacteria may act on the lactose to produce organic acids and gases. The buildup of water and bacterial decay products leads to abdominal distention, cramps, and diarrhea, which are symptoms of the condition.

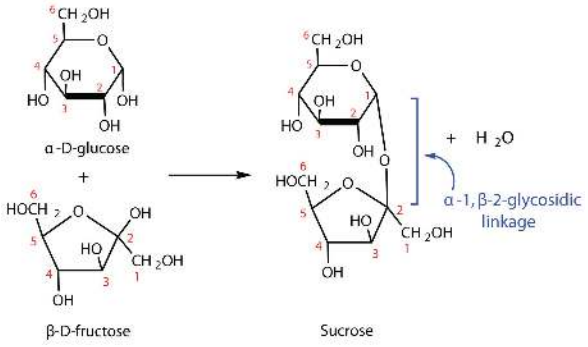
The symptoms disappear if milk or other sources of lactose are excluded from the diet or consumed only sparingly. Alternatively, many food stores now carry special brands of milk that have been pretreated with lactase to hydrolyze the lactose. Cooking or fermenting milk causes at least partial hydrolysis of the lactose, so some people with lactose intolerance are still able to enjoy cheese, yogurt, or cooked foods containing milk. The most common treatment for lactose intolerance, however, is the use of lactase preparations (e.g., Lactaid), which are available in liquid and tablet form at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

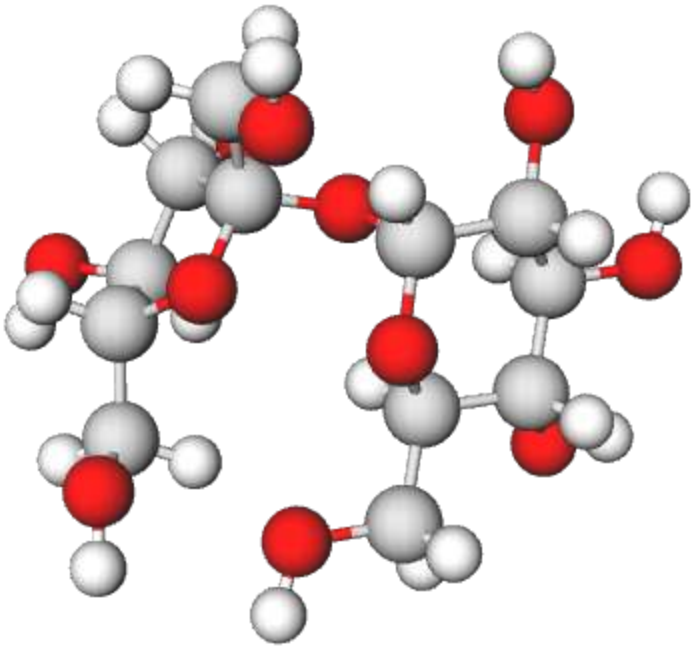
Galactosemia is a condition in which one of the enzymes needed to convert galactose to glucose is missing. Consequently, the blood galactose level is markedly elevated, and galactose is found in the urine. An infant with galactosemia experiences a lack of appetite, weight loss, diarrhea, and jaundice. The disease may result in impaired liver function, cataracts, mental retardation, and even death. If galactosemia is recognized in early infancy, its effects can be prevented by the exclusion of milk and all other sources of galactose from the diet. As a child with galactosemia grows older, he or she usually develops an alternate pathway for metabolizing galactose, so the need to restrict milk is not permanent. The incidence of galactosemia in the United States is 1 in every 65,000 newborn babies.

SUCROSE

Sucrose, probably the largest-selling pure organic compound in the world, is known as *beet sugar*, *cane sugar*, *table sugar*, or simply *sugar*. Most of the sucrose sold commercially is obtained from sugar cane and sugar beets (whose juices are 14%–20% sucrose) by evaporation of the water and recrystallization. The dark brown liquid that remains after the recrystallization of sugar is sold as molasses.

The sucrose molecule is unique among the common disaccharides in having an α-1,β-2-glycosidic (head-to-head) linkage. Because this glycosidic linkage is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.





This linkage gives sucrose certain properties that are quite different from those of maltose and lactose. As long as the sucrose molecule remains intact, neither monosaccharide is in equilibrium with its open-chain form. Thus, sucrose is incapable of mutarotation and exists in only one form both in the solid state and in solution. In addition, sucrose does not undergo reactions that are typical of aldehydes and ketones. Therefore, sucrose is a nonreducing sugar.

The hydrolysis of sucrose in dilute acid or through the action of the enzyme *sucrase* (also known as invertase) gives an equimolar mixture of glucose and fructose. This 1:1 mixture is referred to as *invert sugar* because it rotates plane-polarized light in the opposite direction than sucrose. The hydrolysis reaction has several practical applications. Sucrose readily recrystallizes from a solution, but invert sugar has a much greater tendency to remain in solution. In the manufacture of jelly and candy and in the canning of fruit, the recrystallization of sugar is undesirable. Therefore, conditions leading to the hydrolysis of sucrose are employed in these processes. Moreover, because fructose is sweeter than sucrose, the hydrolysis adds to the sweetening effect. Bees carry out this reaction when they make honey.

The average American consumes more than 100 lb of sucrose every year. About two-thirds of this amount is ingested in soft drinks, presweetened cereals, and other highly processed foods. The widespread use of sucrose is a contributing factor to obesity and tooth decay. Carbohydrates such as sucrose, are converted to fat when the caloric intake exceeds the body's requirements, and sucrose causes tooth decay by promoting the formation of plaque that sticks to teeth.

SUMMARY

Maltose is composed of two molecules of glucose joined by an α-1,4-glycosidic linkage. It is a reducing sugar that is found in sprouting grain. Lactose is composed of a molecule of galactose joined to a molecule of glucose by a β-1,4-glycosidic linkage. It is a reducing sugar that is found in milk. Sucrose is composed of a molecule of glucose joined to a molecule of fructose by an α-1,β-2-glycosidic linkage. It is a nonreducing sugar that is found in sugar cane and sugar beets.

? EXERCISE 25.8.1

What monosaccharides are obtained by the hydrolysis of each disaccharide?

a. sucrose
b. maltose
c. lactose

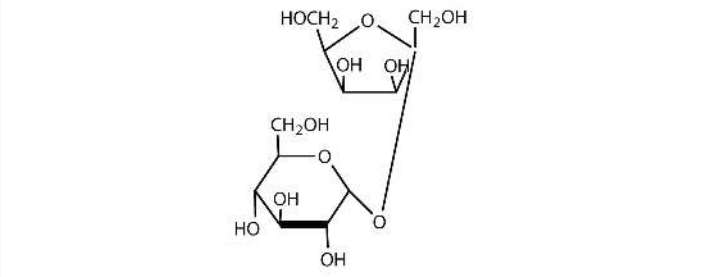
Answer

a. D-glucose and D-fructose
b. two molecules of D-glucose
c. D-glucose and D-galactose

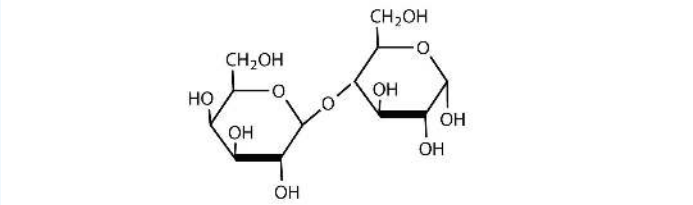
? EXERCISE 25.8.2

For each disaccharide, indicate whether the glycosidic linkage is α or β.

a)

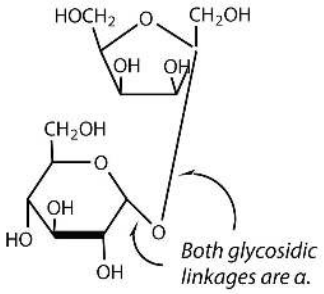


b)

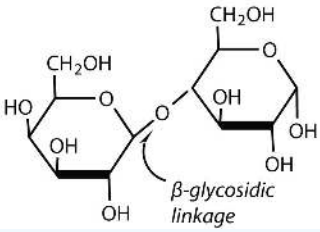


Answer

a)



b)



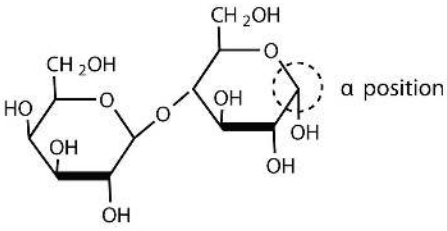
EXERCISE 25.8.3

Identify each disaccharide in Exercise 2 as a reducing or nonreducing sugar. If it is a reducing sugar, draw its structure and circle the anomeric carbon. State if the OH group at the anomeric carbon is in the α or the β position.

Answer

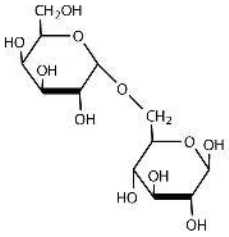
a) nonreducing

b) reducing



EXERCISE 25.8.4

Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:



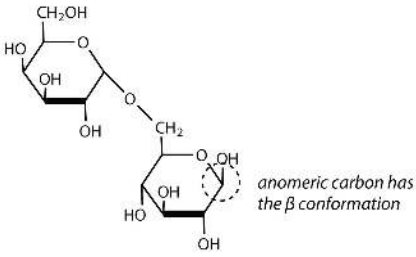
a. What monosaccharide units are incorporated into melibiose?

b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?

c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answer

a) galactose and glucose



.

b) α-glycosidic linkage

c) β.

CONTRIBUTORS AND ATTRIBUTIONS

- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.9: POLYSACCHARIDES AND THEIR SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

1. identify the structural difference between cellulose and the cold-water-insoluble fraction of starch (amylose), and identify both of these substances as containing many glucose molecules joined by 1,4′-glycoside links.
2. identify the cold-water-soluble fraction of starch (amylopectin) as having a more complex structure than amylose because of the existence of 1,6′-glycoside links in addition to the 1,4′-links.
3. compare and contrast the structures and uses of starch, glycogen and cellulose.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- amylopectin
- amylose
- polysaccharide

The polysaccharides are the most abundant carbohydrates in nature and serve a variety of functions, such as energy storage or as components of plant cell walls. Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages. The three most abundant polysaccharides are starch, glycogen, and cellulose. These three are referred to as *homopolymers* because each yields only one type of monosaccharide (glucose) after complete hydrolysis. *Heteropolymers* may contain sugar acids, amino sugars, or noncarbohydrate substances in addition to monosaccharides. Heteropolymers are common in nature (gums, pectins, and other substances) but will not be discussed further in this textbook. The polysaccharides are nonreducing carbohydrates, are not sweet tasting, and do not undergo mutarotation.

STARCH

Starch is the most important source of carbohydrates in the human diet and accounts for more than 50% of our carbohydrate intake. It occurs in plants in the form of granules, and these are particularly abundant in seeds (especially the cereal grains) and tubers, where they serve as a storage form of carbohydrates. The breakdown of starch to glucose nourishes the plant during periods of reduced photosynthetic activity. We often think of potatoes as a “starchy” food, yet other plants contain a much greater percentage of starch (potatoes 15%, wheat 55%, corn 65%, and rice 75%). Commercial starch is a white powder.

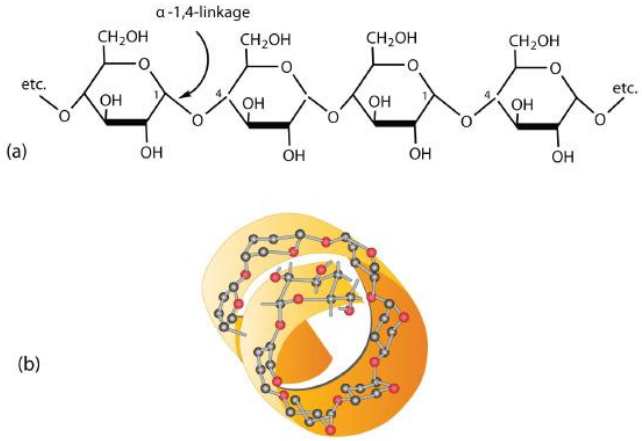


Figure 25.9.1: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

Starch is a mixture of two polymers: amylose and amylopectin. Natural starches consist of about 10%–30% amylose and 70%–90% amylopectin. Amylose is a linear polysaccharide composed entirely of D-glucose units joined by the α-1,4-glycosidic linkages we saw in maltose (part (a) of Figure 25.9.1). Experimental evidence indicates that amylose is not a straight chain of glucose units but instead is coiled like a spring, with six glucose monomers per turn (part (b) of Figure 25.9.1). When coiled in this fashion, amylose has just enough room in

its core to accommodate an iodine molecule. The characteristic blue-violet color that appears when starch is treated with iodine is due to the formation of the amylose-iodine complex. This color test is sensitive enough to detect even minute amounts of starch in solution.

Amylopectin is a branched-chain polysaccharide composed of glucose units linked primarily by α-1,4-glycosidic bonds but with occasional α-1,6-glycosidic bonds, which are responsible for the branching. A molecule of amylopectin may contain many thousands of glucose units with branch points occurring about every 25–30 units (Figure **25.9.2**). The helical structure of amylopectin is disrupted by the branching of the chain, so instead of the deep blue-violet color amylose gives with iodine, amylopectin produces a less intense reddish brown.

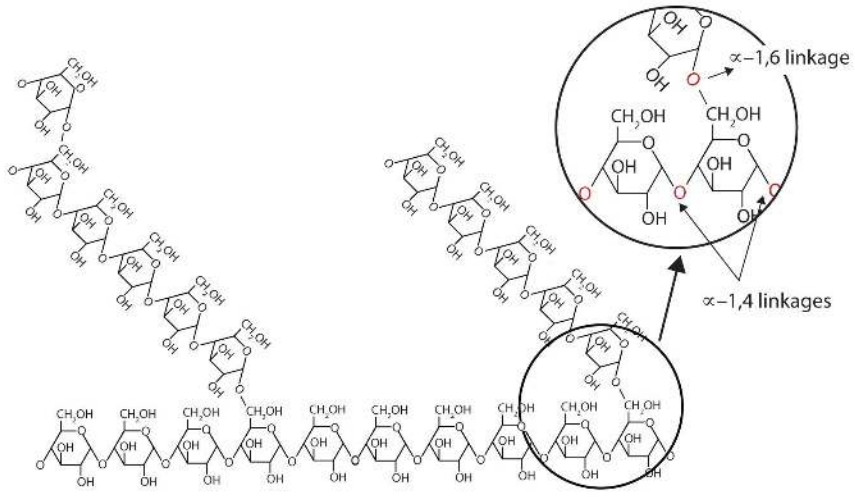


Figure **25.9.2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

Dextrins are glucose polysaccharides of intermediate size. The shine and stiffness imparted to clothing by starch are due to the presence of dextrins formed when clothing is ironed. Because of their characteristic stickiness with wetting, dextrins are used as adhesives on stamps, envelopes, and labels; as binders to hold pills and tablets together; and as pastes. Dextrins are more easily digested than starch and are therefore used extensively in the commercial preparation of infant foods.

The complete hydrolysis of starch yields, in successive stages, glucose:

$$\text{starch} \rightarrow \text{dextrins} \rightarrow \text{maltose} \rightarrow \text{glucose}$$

In the human body, several enzymes known collectively as amylases degrade starch sequentially into usable glucose units.

GLYCOGEN

Glycogen is the energy reserve carbohydrate of animals. Practically all mammalian cells contain some stored carbohydrates in the form of glycogen, but it is especially abundant in the liver (4%–8% by weight of tissue) and in skeletal muscle cells (0.5%–1.0%). Like starch in plants, glycogen is found as granules in liver and muscle cells. When fasting, animals draw on these glycogen reserves during the first day without food to obtain the glucose needed to maintain metabolic balance.

Glycogen is structurally quite similar to amylopectin, although glycogen is more highly branched (8–12 glucose units between branches) and the branches are shorter. When treated with iodine, glycogen gives a reddish brown color. Glycogen can be broken down into its D-glucose subunits by acid hydrolysis or by the same enzymes that catalyze the breakdown of starch. In animals, the enzyme phosphorylase catalyzes the breakdown of glycogen to phosphate esters of glucose.

> About 70% of the total glycogen in the body is stored in muscle cells. Although the percentage of glycogen (by weight) is higher in the liver, the much greater mass of skeletal muscle stores a greater total amount of glycogen.

CELLULOSE

Cellulose, a fibrous carbohydrate found in all plants, is the structural component of plant cell walls. Because the earth is covered with vegetation, cellulose is the most abundant of all carbohydrates, accounting for over 50% of all the carbon found in the vegetable kingdom. Cotton fibrils and filter paper are almost entirely cellulose (about 95%), wood is about 50% cellulose, and the dry weight of leaves is about 10%–20% cellulose. The largest use of cellulose is in the manufacture of paper and paper products. Although the use of non-cellulose synthetic fibers is increasing, rayon (made from cellulose) and cotton still account for over 70% of textile production.

Like amylose, cellulose is a linear polymer of glucose. It differs, however, in that the glucose units are joined by β-1,4-glycosidic linkages, producing a more extended structure than amylose (part (a) of Figure **25.9.3**). This extreme linearity allows a great deal of hydrogen bonding between OH groups on adjacent chains, causing them to pack closely into fibers (part (b) of Figure **25.9.3**). As a result, cellulose exhibits little interaction with water or any other solvent. Cotton and wood, for example, are completely insoluble in water and have considerable mechanical strength. Because cellulose does not have a helical structure, it does not bind to iodine to form a colored product.

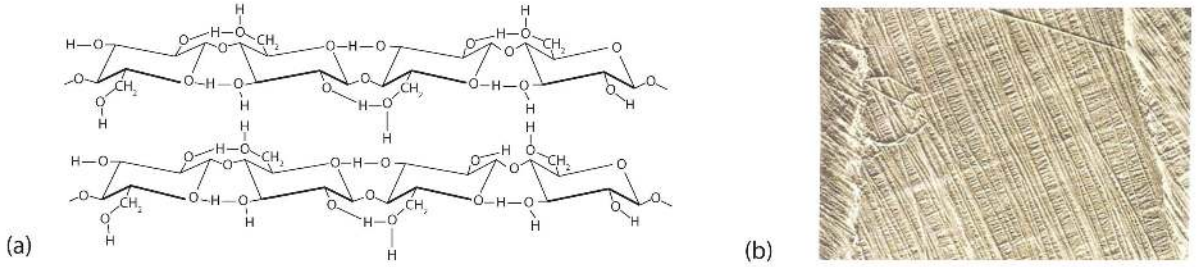
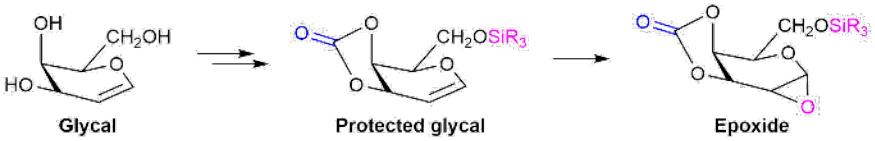


Figure **25.9.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

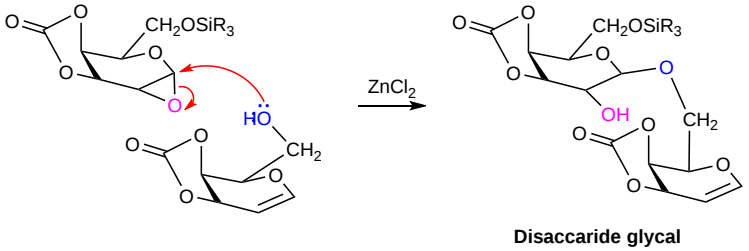
Cellulose yields D-glucose after complete acid hydrolysis, yet humans are unable to metabolize cellulose as a source of glucose. Our digestive juices lack enzymes that can hydrolyze the β-glycosidic linkages found in cellulose, so although we can eat potatoes, we cannot eat grass. However, certain microorganisms can digest cellulose because they make the enzyme cellulase, which catalyzes the hydrolysis of cellulose. The presence of these microorganisms in the digestive tracts of herbivorous animals (such as cows, horses, and sheep) allows these animals to degrade the cellulose from plant material into glucose for energy. Termites also contain cellulase-secreting microorganisms and thus can subsist on a wood diet. This example once again demonstrates the extreme stereospecificity of biochemical processes.

POLYSACCARIDE SYNTHESIS

The presence of multiple -OH groups in monosaccarides makes the laboratory synthesis of polysaccharides difficult. One modern method for the synthesis of polysaccharides is called the **glycal assembly method**. A glycal is a sugar which has been dehydrated to form a double bond. Glycals are typically prepared from the corresponding monosaccharide. As part of the synthesis pathway, the primary alcohol of the glycal is protected by forming a silyl ether (Section 17-8). Also, two adjacent secondary alcohols are protected by forming a cyclic carbonate ester. Now there are no -OH groups remanding in the protected glycal. The double bond of the protected glycal is then converted into a epoxide functional groups.



Epoxides ring can be opened by the acid-catalyzed S_N2 backside attack by an alcohol (section 18-6). This reaction is exploited by reacting a protected glycal epoxide with a second glycal with an unprotected primary alcohol in the presence $ZnCl_2$ as a Lewis acid. The disaccharide formed in this reaction is a glycal so it can be epoxidized and coupled with another glycal to form a trisaccharide etc. Once the monosaccharides are combined to form a chain of the desired length, the remaining silyl ether and cyclic carbonate protecting groups are removed by hydrolysis and the polysaccharide is formed.



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25.10: OTHER IMPORTANT CARBOHYDRATES

OBJECTIVES

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

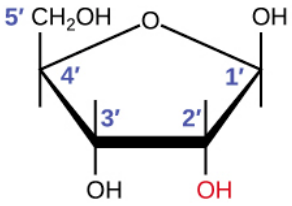
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

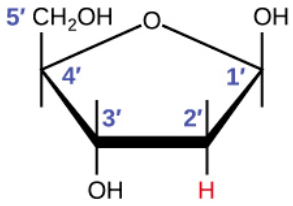
- amino sugar
- deoxy sugar

DEOXY SUGARS

As shown in **Section 25-7**, deoxy sugars are missing an oxygen atom. The most common deoxy sugar is 2-deoxyribose, a modified form of another sugar called ribose. When compared to ribose, 2-deoxyribose has an -OH group replaced with an -H at the 2 position. 2-deoxyribose is best known for being the sugar found in the structure of deoxyribonucleic acid (DNA).

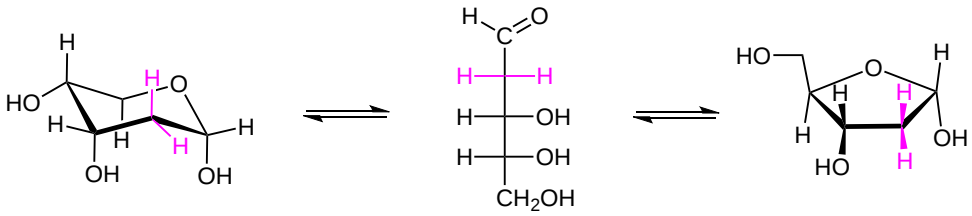


Ribose



Deoxyribose

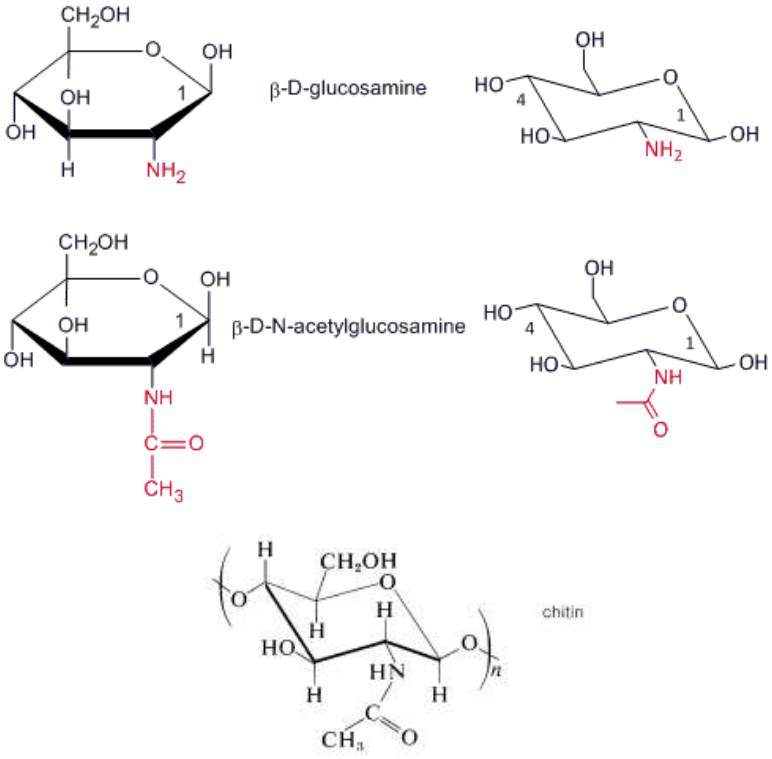
In water, 2-deoxyribose is an equilibrium mixture of both the furanose and pyranose ring forms. The pyranose form the most stable (40% alpha anomer and 35% beta anomer), followed by the furanose structures (13% alpha anomer and 12% beta), with the uncyclized form making up the remaining 0.7%.



Pyranose, uncyclized and furanose forms of 2-deoxyribose. The more stable alpha isomer is shown for both the pyranose and furanose forms. Note the missing hydroxide at the 2 position (highlighted magenta)

AMINO SUGARS

An amino sugar (or more technically a 2-amino-2-deoxysugar) is a sugar molecule in which a hydroxyl group has been replaced with an amine group. More than 60 amino sugars are known, with one of the most abundant being *N*-acetylglucosamine, which is the main component of chitin.



Chitin is a polymer of 2-deoxy-2- N -ethanamidoglucose (N-acetyl-β-D-glucosamine) and is found in many places throughout the natural world. It is a characteristic component of the cell walls of fungi, the exoskeletons of arthropods such as crustaceans (e.g., crabs, lobsters and shrimps) and insects, the radulae of molluscs, and the beaks and internal shells of cephalopods, including squid and octopuses and on the scales and other soft tissues of fish and lissamphibians. Amino sugars are also found in antibiotics such as amikacin and tobramicin.

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25.11: CELL-SURFACE CARBOHYDRATES AND INFLUENZA VIRUSES

OBJECTIVES

After completing this section, you should be able to:

1. Explain how carbohydrates are related to blood type.
2. Explain how influenza works and how it is influenced by carbohydrates.

OLIGOSACCHARIDES

An **oligosaccharide** is a saccharide polymer containing a small number (typically two to ten) of monosaccharides. Oligosaccharides can have many functions; for example, they are commonly found on the plasma membrane of animal cells where they can play a role in cell-cell recognition. In general, they are found attached to compatible amino acid side-chains in proteins or to lipids. Oligosaccharides are often found as a component of **glycoproteins** or **glycolipids**. They can be used as chemical markers on the outside of cells, often for cell recognition. Oligosaccharides are also responsible for determining blood type.

GLYCOPROTEINS

Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins. Glycoproteins and glycolipids are often found in biological membranes, to which they are anchored by through nonpolar interactions. What is the function of these carbohydrates? Two are apparent. First, glycosylation of proteins helps protect the protein from degradation by enzyme catalysts within the body. However, their main functions arises from the fact that covalently attached carbohydrates that "decorate" the surface of glycoproteins or glycolipids provide new binding site interactions that allow interactions with other biomolecules. Hence glycosylation allows for cell:cell, cell:protein, or protein:protein interactions. Unfortunately, bacteria and viruses often recognize glycosylated molecules on cell membranes as well, allowing for their import into the cell.

BLOOD TYPE

Cell markers are carbohydrate chains on the surface of cells where they act as “road signs” allowing molecules to distinguish one cell from another. Blood markers are exclusively made from four monosaccharides: D-galactose, L-fucose, N-acetylgalactosamine, and N-acetylglucosamine.

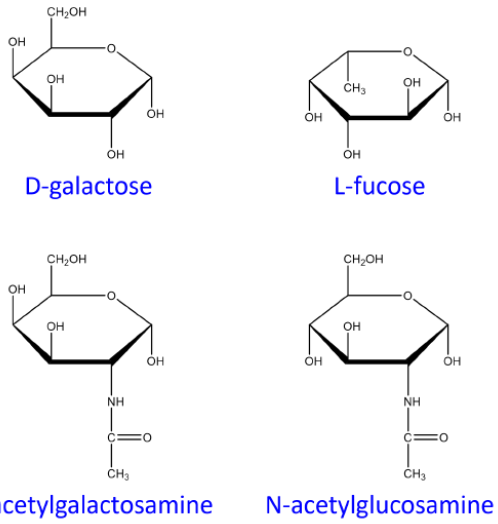


Figure 25.11.1: Structures of monosaccharide units present in ABO blood markers

ABO blood markers found on red blood cells are made up of oligosaccharides that contain either three or four sugar units as shown below. Oligosaccharides attached to red blood cells determine the ABO blood type.

Of the four blood types, type O has the fewest types of saccharides attached to it while type AB has the most. As a result, type O blood is considered the universal donor because it doesn't have any saccharides present that will appear as foreign when transfused into blood of another type. The reverse is not true. For example:

- If type A blood is given to a patient with type O blood, it will be rejected by the body because there is an unknown species being introduced to the body. Type A blood cells contain N-acetylgalactosamine which is not present in type O blood.
- Since type AB blood has all possible saccharides, type AB blood is considered the **universal acceptor**.

The Rhesus factor (Rh) in blood also affects donor and acceptor properties but it does not depend on carbohydrates. The Rh factor is determined by the presence (Rh+) or absence (Rh-) of a specific protein on the surface of red blood cells.

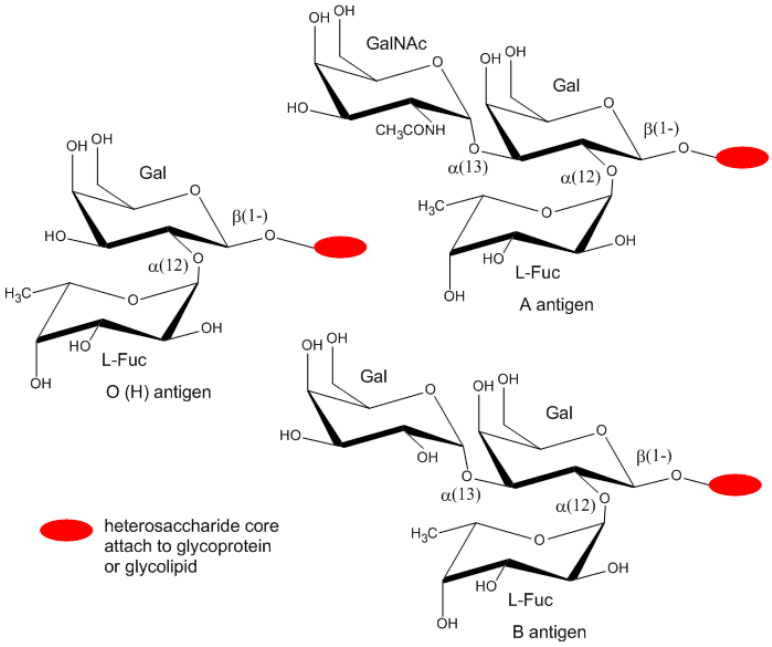


Figure **25.11.2**: ABO blood types.

INFLUENZA AND THE AVIAN FLU

Three pandemics of influenza have swept the world since the "Spanish" flu of 1918.

- The "Asian" flu pandemic of 1957;
- the "Hong Kong" flu pandemic of 1968;
- the "Swine" flu pandemic that began in April of 2009.

The influenza virus is a simple yet deadly virus. It interacts with human cells through a surface protein, hemagglutinin (HA). The virus binds to host cells through interaction of HA with cell surface carbohydrates. Once bound the virus internalizes, ultimately leading to release of the RNA genome of the virus into the host cell. The HA protein is the most abundant protein on the viral surface (as surmised by antibody formation).

The influenza virus is typically classified by two kinds of glycoproteins on the surface of the virus: in addition to HA is the enzyme neuraminidase. Two viral strains which have been often discussed are H5N1 and H1N1 which stands for hemagglutinin (H: type 5 or type 1) and neuraminidase (N: type 1). 15 avian and mammalian variants have been identified (based on antibody studies). Only 3 adapted to humans in the last 100 yr, giving pandemic strains H1 (1918), H2 (957) and H3 (1968). Three recent avian variants (H5, H7, and H9) have jumped directly to humans recently but have low human to human transmissibility.

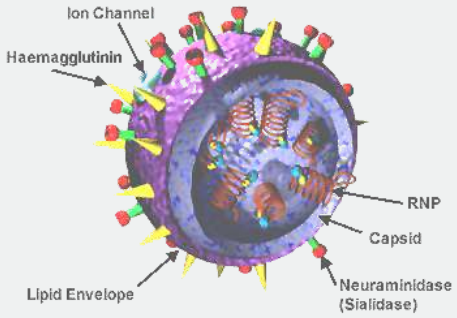
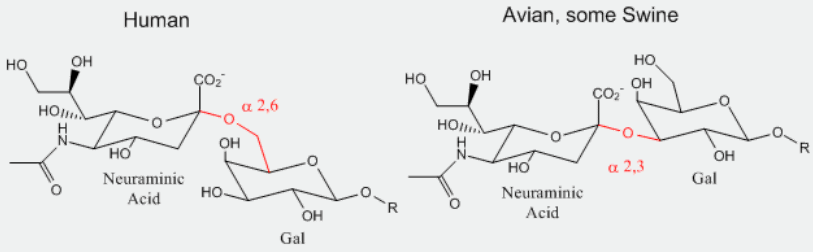


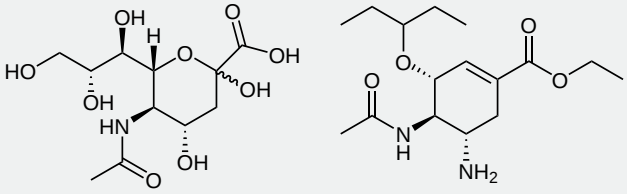
Figure **25.11.3**: Structure (3D) of the Influenza Virus: The image depicts the major components of the virus structure, including the neuraminidase. (Public Domain; National Institutes of Health via Wikipedia)

Influenza Virus binds to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus. Hemagluttinin binds to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins. The sialic acid is usually connected through an alpha (2,3) or alpha (2,6) link to galactose on N-linked glycoproteins. The subtypes found in avian (and equine) influenza isolates bind preferentially to Sia (alpha 2,3) Gal which predominates in avian GI tract where viruses replicate. Human virus of H1, H2, and H3 subtype (cause of the 1918, 1957, and 1968 pandemics) recognize Sia (alpha 2,6) Gal, as the major form in the human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3) both of which are commonly found in swine.

Binding Site for Influenza Hemagluttinin Protein



The virus, before it leaves the cell, forms a bud on the intracellular side of the cell with the HA and NA in the cell membrane of the host cell. The virus in this state would not leave the cell since its HA molecules would interact with sialic acid residues in the host cell membrane, holding the virus in the membrane. Neuraminidase hydrolyzes sialic acid from cell surface glycoproteins, allowing the virus to complete the budding process and be released from the cell as new viruses. By mimicking the structure of sialic acid, the drugs Oseltamivir (Tamiflu) and zanamivir (Relenza) bind to and inhibit neuraminidase whose activity is necessary for viral release from infected cells. Tamiflu appears to work against N1 of the present H5N1 avian influenza viruses. Governments across the world are stockpiling this drug in case of a pandemic caused by the avian virus jumping directly to humans and becoming transmissible from human to human.



Sialic Acid **Tamiflu**

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25.S: BIOMOLECULES- CARBOHYDRATES (SUMMARY)

CONCEPTS & VOCABULARY

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrogen, and oxygen atoms and are polyhydroxy aldehydes and ketones.
- Examples of carbohydrates are starch, fibers, sugar, and cellulose.
- Green plants use glucose for energy or making larger carbohydrates.
- Carbohydrates are needed for the synthesis of nucleic acids, proteins, and lipids.
- Animals rely on plants to provide them with carbohydrates, which are used for food and clothing.

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynthesis.
- The generic formula is $C_n(H_2O)_n$.
- Carbohydrates play a vital role in a major food source, but are also used as structural material, recognition sites on cells, and other tasks.
- Carbohydrates are called saccharides and can be classified as simple or complex.

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multiple chiral centers are present in a molecule.
- In a Fischer projection:
  - the four bonds to a chiral carbon make a cross with the carbon atom at the intersection of the horizontal and vertical lines.
  - the two horizontal bonds are directed toward the viewer (forward of the stereogenic carbon).
  - the two vertical bonds are directed behind the central carbon (away from the viewer).
- Determining whether a chiral carbon is R or S
  - If the lowest priority group is on a vertical bond, the configuration is given directly from the relative positions of the three higher-ranked substituents.
  - If the lowest priority group is on a horizontal bond, the positions of the remaining groups give the wrong answer, so you reverse it.
- Epimer is used to designate diastereomers that differ in configuration at only one chiral center.

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arbitrary choice that (+)-glucose would be the D-family and related aldoses.
- The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Emil Fischer as the D / L designator site.
- The L-family is the mirror image of the D-family.
- If the hydroxyl group in the projection formula pointed to the right, it was defined as a member of the D-family.
- A left directed hydroxyl group then represented the L-family.
- It is important to recognize that the sign of a compound's specific rotation (an experimental number) does not correlate with its configuration (D or L).
- Determining an absolute configuration usually requires chemical interconversion with known compounds by stereospecific reaction paths.

25.5 Configurations of Aldoses

- The aldose family is composed of three to six carbon atoms.
- Emil Fischer determined a way to determine absolute configuration of aldoses.
- In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet, proved that Fischer's choice was correct.

25.6 Anomers

- The preferred structural form of monosaccharides is a cyclic hemiacetal, especially for five and six-membered rings due to low angle strain and eclipsing strain.
- Five-membered cyclic sugars are termed furanose and six-membered cyclic sugars are pyranose.

- By convention for the D-family, the five-membered furanose ring is drawn in an edgewise projection with the ring oxygen positioned away from the viewer.
- The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula.
- In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring.
- The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features.
- Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.
- When a straight-chain monosaccharide forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers.
    - When the OH group on the first carbon atom projected downward, this is called the *alpha (α) form*.
    - When the OH group on the first carbon atom pointed upward, is the *beta (β) form*.
- These two stereoisomers of a cyclic monosaccharide are known as anomers.
- You can start with a pure crystalline sample of glucose consisting entirely of one anomer, but as soon as the molecules dissolve in water, they open to form the carbonyl group and then reclose to form either the α or the β anomer.
- The opening and closing repeats continuously in an ongoing interconversion between anomeric forms and is referred to as mutarotation.

25.7 Reactions of Monosaccharides

- The -OH groups on a monosaccharide can be readily converted to esters and ethers.
- Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides.
- Phosphorylation of the -OH group using ATP.
- Oxidation can occur with the monosaccharides, which is why some sugars are classified as reducing.
- When the aldehyde function of an aldose is oxidized to a carboxylic acid the product is called an aldonic acid.
- If both ends of an aldose chain are oxidized to carboxylic acids the product is called an aldaric acid.
- Sodium borohydride reduction of an aldose makes the ends of the resulting alditol chain identical like aldaric acid.
- Monosaccharides can react to have the chain length increased or decreased, which can be important in elucidation of the carbohydrate's structure.

25.8 The Eight Essential Monosaccharides

- The eight essential monosaccharides are: L-fructose, D-galactose, D-glucose, D-mannose, N-acetyl-D-glucosamine, N-acetyl-D-galacosamine, D-xylose, N-acetyl-D-neuraminic acid.
- These eight monosaccaharides are obtained through diet.

25.9 Disaccharides

- Disaccharides are sugars composed of two monosaccharide units that are joined by a carbon–oxygen-carbon linkage known as a glycosidic linkage.
- The glycosidic linkage is formed from the reaction of the anomeric carbon of one cyclic monosaccharide with the OH group of a second monosaccharide.
- The disaccharides differ from one another in their monosaccharide constituents and in the specific type of glycosidic linkage connecting them.
- There are three common disaccharides: maltose, lactose, and sucrose.
- Maltose is two glucose molecules linked in a *head-to-tail* fashion through an α-linkage from the first carbon atom of one glucose molecule to the fourth carbon atom of the second glucose molecule.
- Lactose is composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond.
- Sucrose is has an α-1,β-2-glycosidic (head-to-head) linkage, which is formed by the OH group on the anomeric carbon of α-D-glucose and the OH group on the anomeric carbon of β-D-fructose, it ties up the anomeric carbons of both glucose and fructose.

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers composed of tens to thousands of monosaccharides joined together by glycosidic linkages.
- The three most abundant polysaccharides are starch, glycogen, and cellulose.

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group, the sugar present - deoxyribose.
- An amino sugar is a sugar molecule in which a hydroxyl group has been replaced with an amine group.

25.12 Cell-Surface Carbohydrates and Influenza Viruses

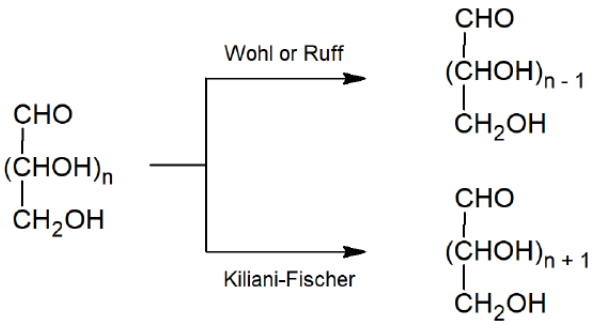
- Carbohydrates are covalently attached to many different biomolecules, including lipids, to form glycolipids, and proteins, to form glycoproteins.
- Glycoproteins and glycolipids are often found in biological membranes that allow other biomolecules to interact and bind to the protein.
- Bacteria and viruses often recognize glycosylated molecules on cell membranes, allowing for their import into the cell.
- This is how the influenza virus enters the body.

SKILLS TO MASTER

- Skill 25.1 Determine which molecules can be classified as carbohydrates.
- Skill 25.2 Distinguish between monosaccharide, disaccharide, and trisaccharides given the structure.
- Skill 25.3 Classify a monosaccharide according to the number of carbon atoms present and whether it contains an aldehyde or ketone group.
- Skill 25.4 Draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
- Skill 25.5 Draw the wedge-and-broken-line structure of a monosaccharide, given its Fischer projection or a molecular model.
- Skill 25.6 Construct a molecular model of a monosaccharide, given its Fischer projection or wedge-and-broken-line structure.
- Skill 25.7 Identify a specific enantiomer of a monosaccharide as being D or L, given its Fischer projection.
- Skill 25.8 Assign an *R* or *S* configuration to each of the chiral carbon atoms present in a monosaccharide, given its Fischer projection.
- Skill 25.9 Draw the Fischer projection formula for a monosaccharide, given its systematic name, complete with the configuration of each chiral carbon atom.
- Skill 25.10 Draw configurations of aldoses.
- Skill 25.11 Determine whether a given monosaccharide will exist as a pyranose or furanose.
- Skill 25.12 Draw the cyclic pyranose form of a monosaccharide, given its Fischer projection.
- Skill 25.13 Determine whether a given cyclic pyranose form represents the D or L form of the monosaccharide concerned.
- Skill 25.14 Describe the phenomenon known as mutarotation.
- Skill 25.15 Explain why certain ketoses, such as fructose, behave as reducing sugars even though they do not contain an aldehyde group.
- Skill 25.16 Predict the product that would be produced by the Kiliani-Fischer synthesis of a given aldose.
- Skill 25.17 Identify the aldose that would yield a given product following Kiliani-Fischer synthesis.
- Skill 25.18 Predict the product that would be produced by the Wohl degradation of a given aldose.
- Skill 25.19 Identify the aldose that would yield a given product following Wohl degradation synthesis.
- Skill 25.20 Identify disaccharides as compounds consisting of two monosaccharide units joined by a glycoside link between the C1 of one sugar and one of the hydroxyl groups of a second sugar.
- Skill 25.21 Identify the two monosaccharide units in a given disaccharide.
- Skill 25.22 Identify the type of glycoside link (e.g., 1,4′-β) present in a given disaccharide structure.
- Skill 25.23 Draw the structure of a specific disaccharide, given the structure of the monosaccharide units and the type of glycoside link involved.
- Skill 25.24 Identify the products formed from the hydrolysis of a given disaccharide.

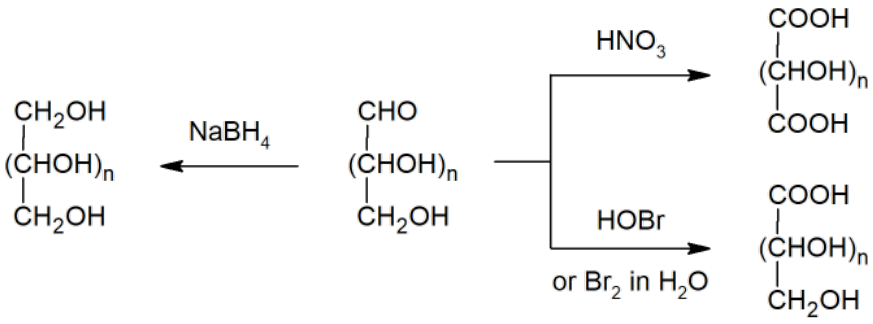
SUMMARY OF REACTIONS

Chain Length

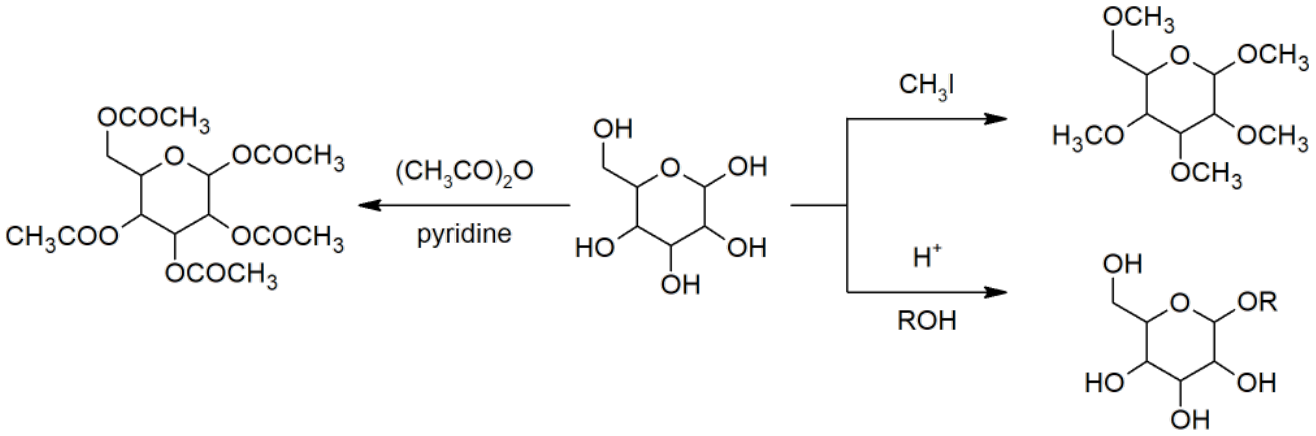


Oxidation - Reduction

https://chem.libretexts.org/@go/page/206873



Ester and Ether Formation



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CHAPTER OVERVIEW

26: BIOMOLECULES- AMINO ACIDS, PEPTIDES, AND PROTEINS

LEARNING OBJECTIVES

When you have completed Chapter 26, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. use the information provided by an amino acid analysis, an Edman degradation and a carboxypeptidase hydrolysis to determine the structure of an unknown polypeptide.
3. outline the approach that you would use to synthesize a given peptide, providing appropriate mechanistic details if requested to do so.
4. define, and use in context, the key terms introduced in this chapter.

Amino acids are important biochemicals, as they are the building blocks from which proteins and polypeptides are assembled. We begin this chapter with an examination of some of the fundamental chemistry of amino acids: their structures, stereochemistry and synthesis. We then discuss the nature of peptides and of the peptide bond, and present the complex issue of determining the order in which the various amino-acid residues occur in a given peptide. Once a chemist knows the exact order the of the residues in a given peptide, the next challenge is to determine a method by which the same peptide can be prepared in the laboratory. Thus, two sections are devoted to the problem of protein synthesis. The final sections in the chapter deal with the classification, overall structure and denaturation of proteins.

26.0: Chapter Objectives
26.1: Introduction
26.2: Structures of Amino Acids
26.3: Amino Acids, the Henderson-Hasselbalch Equation, and Isoelectric Points
26.4: Synthesis of Amino Acids
26.5: Peptides and Proteins
26.6: Amino Acid Analysis of Peptides
26.7: The Edman Degradation
26.8: Peptide Synthesis
26.9: The Merrifield Solid-Phase Technique
26.10: Protein Structure
26.11: Enzymes and Coenzymes
26.12: How do Enzymes Work? Citrate Synthase

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26.0: CHAPTER OBJECTIVES

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26.1: INTRODUCTION

OBJECTIVES

After completing this section, you should be able to

1. give examples of the various biological roles played by proteins.
2. identify amino acids as being the building blocks from which all proteins are made.
3. show, in a general way, how the joining together of a number of amino acids through the formation of peptide bonds results in the formation of proteins.

KEY TERMS

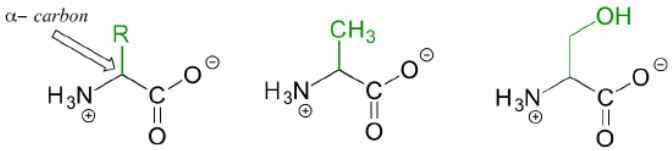
Make certain that you can define, and use in context, the key terms below.

- amino acid
- enzyme
- peptide bond
- protein

STUDY NOTES

The “peptide bond” or “peptide linkage” that is formed between the amino group of one amino acid and the carboxyl group of a second amino acid is identical to the C$\ce{-}$N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

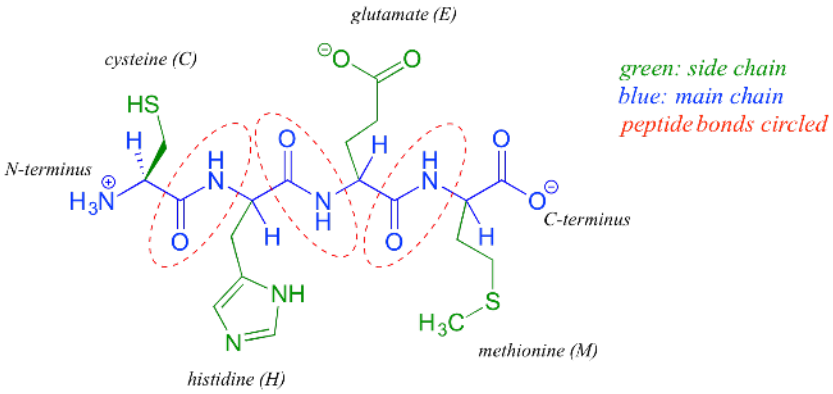
Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded to the alpha-carbon.



amino acid alanine serine

There are twenty different side chains in naturally occurring amino acids, and it is the identity of the side chain that determines the identity of the amino acid: for example, if the side chain is a -CH_3 group, the amino acid is alanine, and if the side chain is a -CH_2OH group, the amino acid is serine. Many amino acid side chains contain a functional group (the side chain of serine, for example, contains a primary alcohol), while others, like alanine, lack a functional group, and contain only a simple alkane.

The two 'hooks' on an amino acid monomer are the amine and carboxylate groups. Proteins (polymers of ~50 amino acids or more) and peptides (shorter polymers) are formed when the amino group of one amino acid monomer reacts with the carboxylate carbon of another amino acid to form an amide linkage, which in protein terminology is a **peptide bond**. Which amino acids are linked, and in what order - the protein **sequence** - is what distinguishes one protein from another, and is coded for by an organism's DNA. Protein sequences are written in the amino terminal (N-terminal) to carboxylate terminal (C-terminal) direction, with either three-letter or single-letter abbreviations for the amino acids (see amino acid table). Below is a four amino acid peptide with the sequence "cysteine - histidine - glutamate - methionine". Using the single-letter code, the sequence is abbreviated CHEM.



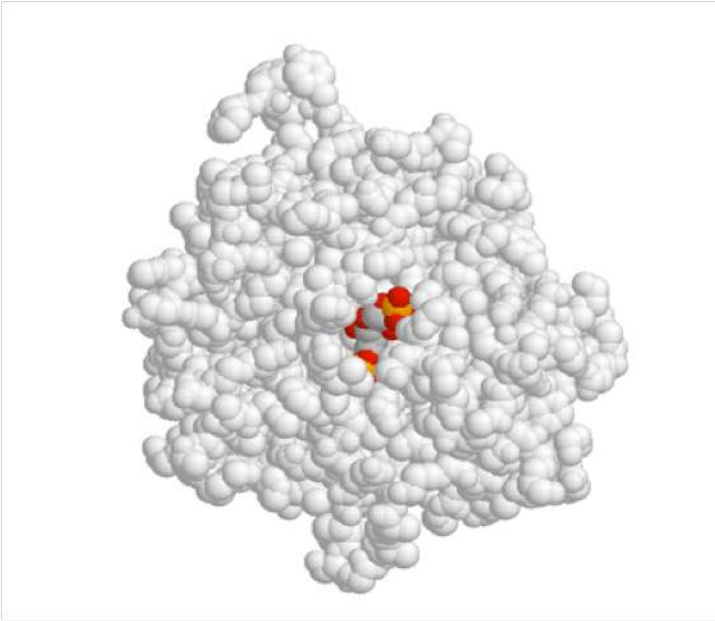
CHEM peptide

When an amino acid is incorporated into a protein it loses a molecule of water and what remains is called a **residue** of the original amino acid. Thus we might refer to the 'glutamate residue' at position 3 of the CHEM peptide above.

Once a protein polymer is constructed, it in many cases folds up very specifically into a three-dimensional structure, which often includes one or more 'binding pockets' in which other molecules can be bound. It is this shape of this folded structure, and the precise arrangement of the functional groups within the structure (especially in the area of the binding pocket) that determines the function of the protein.

Enzymes are proteins which catalyze biochemical reactions. One or more reacting molecules - often called **substrates** - become bound in the **active site** pocket of an enzyme, where the actual reaction takes place. **Receptors** are proteins that bind specifically to one or more molecules - referred to as **ligands** - to initiate a biochemical process. For example, we saw in the introduction to this chapter that the TrpVI receptor in mammalian tissues binds capsaicin (from hot chili peppers) in its binding pocket and initiates a heat/pain signal which is sent to the brain.

Shown below is an image of the glycolytic enzyme fructose-1,6-bisphosphate aldolase (in grey), with the substrate molecule bound inside the active site pocket.



(x-ray crystallographic data are from *Protein Science* **1999**, 8, *291*; pdb code 4ALD. Image produced with JMol First Glance)

Intro to nucleic acids ⇒

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26.2: STRUCTURES OF AMINO ACIDS

OBJECTIVES

After completing this section, you should be able to

1. identify the structural features present in the 20 amino acids commonly found in proteins.

   Note: You are not expected to remember the detailed structures of all these amino acids, but you should be prepared to draw the structures of the two simplest members, glycine and alanine.

2. draw the Fischer projection formula of a specified enantiomer of a given amino acid.

   Note: To do so, you must remember that in the *S* enantiomer, the carboxyl group appears at the top of the projection formula and the amino group is on the left.

3. classify an amino acid as being acidic, basic or neutral, given its Kekulé, condensed or shorthand structure.
4. draw the zwitterion form of a given amino acid.
5. account for some of the typical properties of amino acids (e.g., high melting points, solubility in water) in terms of zwitterion formation.
6. write appropriate equations to illustrate the amphoteric nature of amino acids.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- α-amino acids
- amphoteric
- essential amino acids
- zwitterion

STUDY NOTES

This is a good point at which to review some of the principles of stereochemistry presented in Chapter 5. Be sure to make full use of molecular models when any stereochemical issues arise.

You should recognize that a three-letter shorthand code is often used to represent individual amino acids. You need not memorize this code.

The distinction between essential and nonessential amino acids is not as clear-cut as one might suppose. For example, arginine is often regarded as being nonessential.

INTRODUCTION TO AMINO ACIDS

Amino acids form polymers through a nucleophilic attack by the amino group of an amino acid at the electrophilic carbonyl carbon of the carboxyl group of another amino acid. The carboxyl group of the amino acid must first be activated to provide a better leaving group than OH^-. (We will discuss this activation by ATP later in the course.) The resulting link between the amino acids is an amide link which biochemists call a peptide bond. In this reaction, water is released. In a reverse reaction, the peptide bond can be cleaved by water (hydrolysis).

- Structure and Property of the Naturally-Occurring Amino Acids (Too large to include in text: print separately)

When two amino acids link together to form an amide link, the resulting structure is called a dipeptide. Likewise, we can have tripeptides, tetrapeptides, and other polypeptides. At some point, when the structure is long enough, it is called a protein. There are many different ways to represent the structure of a polypeptide or protein, each showing differing amounts of information.

Figure: Different Representations of a Polypeptide (Heptapeptide)

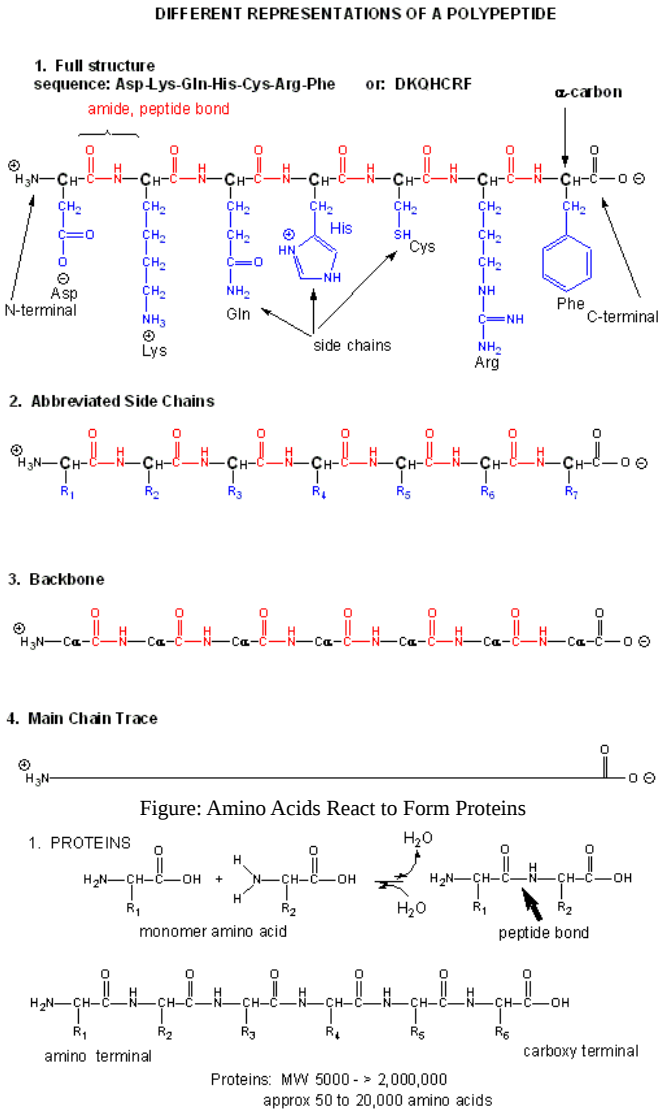


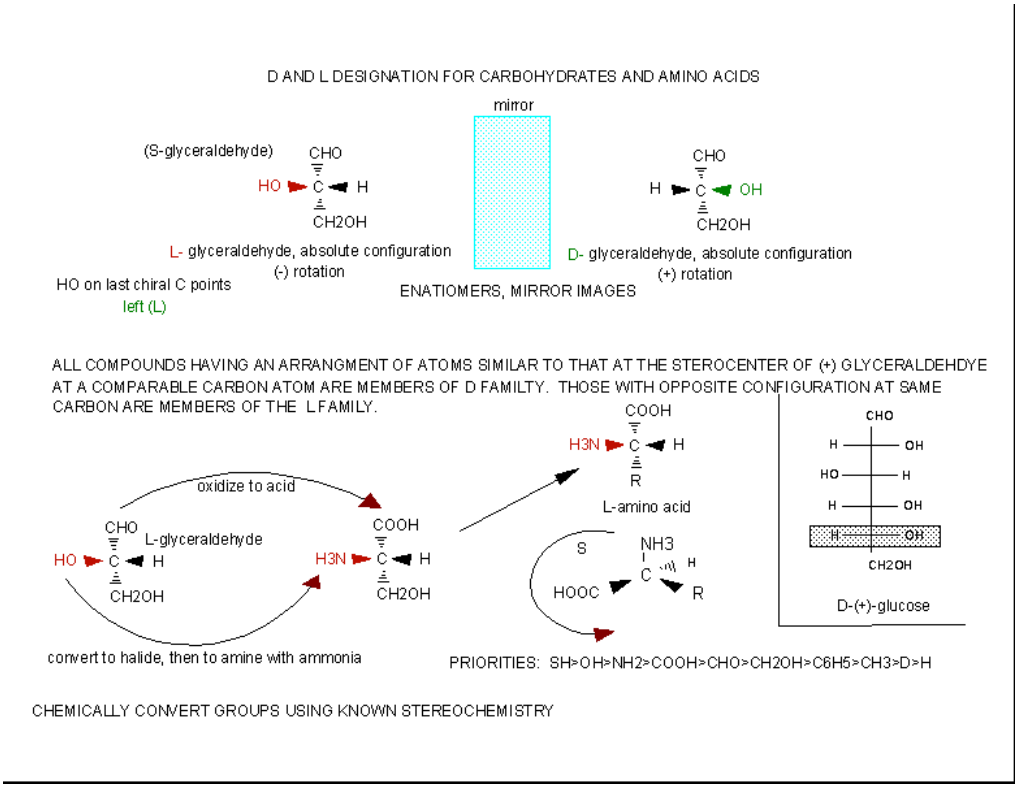
Figure: Amino Acids React to Form Proteins

(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. In contrast, nucleic acids are polymers of just 4 different monomeric nucleotides. Both the sequence of a protein and its total length differentiate one protein from another. Just for an octapeptide, there are over 25 billion different possible arrangements of amino acids. Compare this to just 65536 different oligonucleotides of 8 monomeric units (8mer). Hence the diversity of possible proteins is enormous.

STEREOCHEMISTRY

The amino acids are all chiral, with the exception of glycine, whose side chain is H. As with lipids, biochemists use the L and D nomenclature. All naturally occuring proteins from all living organisms consist of L amino acids. The absolute stereochemistry is related to L-glyceraldehyde, as was the case for triacylglycerides and phospholipids. Most naturally occurring chiral amino acids are S, with the exception of cysteine. As the diagram below shows, the absolute configuration of the amino acids can be shown with the H pointed to the rear, the COOH groups pointing out to the left, the R group to the right, and the NH_3 group upwards. You can remember this with the anagram CORN.

Figure: *Stereochemistry of Amino Acids.*



Why do biochemists still use D and L for sugars and amino acids? This explanation (taken from the link below) seems reasonable.

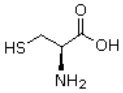
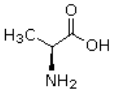
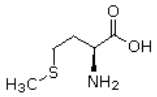
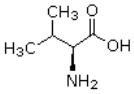
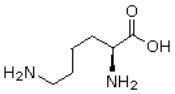
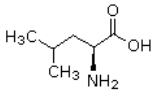
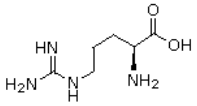
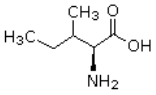
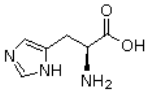
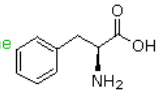
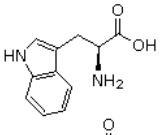
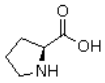
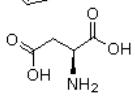
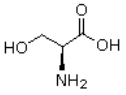
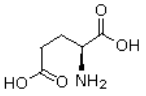
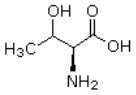
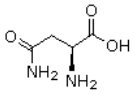
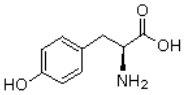
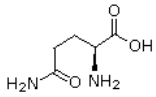
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied to biochemical molecules. For example, as we have seen, all of the common amino acids are L, because they all have exactly the same structure, including the position of the R group if we just write the R group as R. However, they do not all have the same configuration in the (R,S) system: L-cysteine is also (R)-cysteine, but all the other L-amino acids are (S), but this just reflects the human decision to give a sulphur atom higher priority than a carbon atom, and does not reflect a real difference in configuration. Worse problems can sometimes arise in substitution reactions: sometimes inversion of configuration can result in no change in the (R) or (S) prefix; and sometimes retention of configuration can result in a change of prefix.

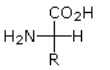
It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given above of why the (R,S) system is little used in biochemistry is thus almost the exact opposite of reality. This system is actually the only practical way of unambiguously representing the stereochemistry of complicated molecules with several asymmetric centres, but it is inconvenient with regular series of molecules like amino acids and simple sugars. "

NATURAL A-AMINO ACIDS

Hydrolysis of proteins by boiling aqueous acid or base yields an assortment of small molecules identified as α-aminocarboxylic acids. More than twenty such components have been isolated, and the most common of these are listed in the following table. Those amino acids having green colored names are **essential** diet components, since they are not synthesized by human metabolic processes. The best food source of these nutrients is protein, but it is important to recognize that not all proteins have equal nutritional value. For example, peanuts have a higher weight content of protein than fish or eggs, but the proportion of essential amino acids in peanut protein is only a third of that from the two other sources. For reasons that will become evident when discussing the structures of proteins and peptides, each amino acid is assigned a one or three letter abbreviation.

NATURAL A-AMINO ACIDS

Name	Formula	Abbreviations		Name	Formula	Abbreviations	
Glycine		Gly	G	Cysteine		Cys	C
Alanine		Ala	A	Methionine		Met	M
Valine		Val	V	Lysine		Lys	K
Leucine		Leu	L	Arginine		Arg	R
Isoleucine		Ile	I	Histidine		His	H
Phenylalanine		Phe	F	Tryptophan		Trp	W
Proline		Pro	P	Aspartic Acid		Asp	D
Serine		Ser	S	Glutamic Acid		Glu	E
Threonine		Thr	T	Asparagine		Asn	N
Tyrosine		Tyr	Y	Glutamine		Gln	Q


L-Amino Acid

Some common features of these amino acids should be noted. With the exception of proline, they are all 1°-amines; and with the exception of glycine, they are all chiral. The configurations of the chiral amino acids are the same when written as a Fischer projection formula, as in the drawing on the right, and this was defined as the **L-configuration** by Fischer. The R-substituent in this structure is the remaining structural component that varies from one amino acid to another, and in proline R is a three-carbon chain that joins the nitrogen to the alpha-carbon in a five-membered ring. Applying the Cahn-Ingold-Prelog notation, all these natural chiral amino acids, with the exception of cysteine, have an **S**-configuration. For the first seven compounds in the left column the R-substituent is a hydrocarbon. The last three entries in the left column have hydroxyl functional groups, and the first two amino acids in the right column incorporate thiol and sulfide groups respectively. Lysine and arginine have basic amine functions in their side-chains; histidine and tryptophan have less basic nitrogen heterocyclic rings as substituents. Finally, carboxylic acid side-chains are substituents on aspartic and glutamic acid, and the last two compounds in the right column are their corresponding amides.

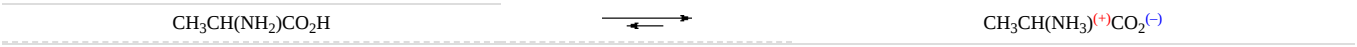
The formulas for the amino acids written above are simple covalent bond representations based upon previous understanding of mono-functional analogs. **The formulas are in fact incorrect**. This is evident from a comparison of the physical properties listed in the following table. All four compounds in the table are roughly the same size, and all have moderate to excellent water solubility. The first two are simple carboxylic acids, and the third is an amino alcohol. All three compounds are soluble in organic solvents (e.g. ether) and have relatively low melting points. The carboxylic acids have pK_a's near 4.5, and the conjugate acid of the amine has a pK_a of 10. The simple amino acid alanine is the last entry. By contrast, it is very high melting (with decomposition), insoluble in organic solvents, and a million times weaker as an acid than ordinary carboxylic acids.

Physical Properties of Selected Acids and Amines

Compound	Formula	Mol.Wt.	Solubility in Water	Solubility in Ether	Melting Point	pK_a
isobutyric acid	$(CH_3)_2CHCO_2H$	88	20g/100mL	complete	-47 ºC	5.0
lactic acid	$CH_3CH(OH)CO_2H$	90	complete	complete	53 ºC	3.9
3-amino-2-butanol	$CH_3CH(NH_2)CH(OH)CH_3$	89	complete	complete	9 ºC	10.0
alanine	$CH_3CH(NH_2)CO_2H$	89	18g/100mL	insoluble	ca. 300 ºC	9.8

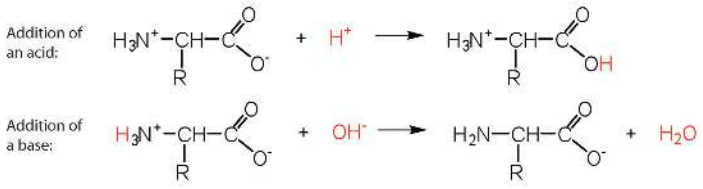
ZWITTERION

These differences above all point to internal salt formation by a proton transfer from the acidic carboxyl function to the basic amino group. The resulting ammonium carboxylate structure, commonly referred to as a **zwitterion**, is also supported by the spectroscopic characteristics of alanine.



As expected from its ionic character, the alanine zwitterion is high melting, insoluble in nonpolar solvents and has the acid strength of a 1º-ammonium ion. Examples of a few specific amino acids may also be viewed in their favored neutral zwitterionic form. Note that in lysine the amine function farthest from the carboxyl group is more basic than the alpha-amine. Consequently, the positively charged ammonium moiety formed at the chain terminus is attracted to the negative carboxylate, resulting in a coiled conformation.

The structure of an amino acid allows it to act as both an acid and a base. An amino acid has this ability because at a certain pH value (different for each amino acid) nearly all the amino acid molecules exist as zwitterions. If acid is added to a solution containing the zwitterion, the carboxylate group captures a hydrogen (H^+) ion, and the amino acid becomes positively charged. If base is added, ion removal of the H^+ ion from the amino group of the zwitterion produces a negatively charged amino acid. In both circumstances, the amino acid acts to maintain the pH of the system—that is, to remove the added acid (H^+) or base (OH^-) from solution.

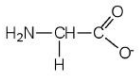


EXAMPLE 26.1

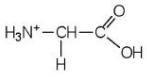
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.



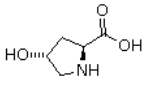
The acid adds H^+ to the carboxylate group.

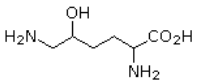


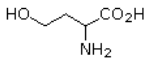
OTHER NATURAL AMINO ACIDS

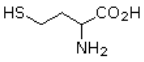
The twenty alpha-amino acids listed above are the primary components of proteins, their incorporation being governed by the genetic code. Many other naturally occurring amino acids exist, and the structures of a few of these are displayed below. Some, such as hydroxylysine and hydroxyproline, are simply functionalized derivatives of a previously described compound. These two amino acids are found only in collagen, a common structural protein. Homoserine and homocysteine are higher homologs of their namesakes. The amino group in beta-alanine has moved to the end of the three-carbon chain. It is a component of pantothenic acid, $HOCH_2C(CH_3)_2CH(OH)CONHCH_2CH_2CO_2H$, a member of the vitamin B complex and an essential nutrient. Acetyl coenzyme A is a

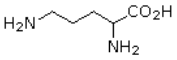
pyrophosphorylated derivative of a pantothenic acid amide. The gamma-amino homolog GABA is a neurotransmitter inhibitor and antihypertensive agent.

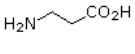

4-hydroxyproline

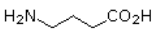

5-hydroxylysine

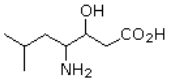

homoserine


homocysteine


ornithine


β-alanine


γ-aminobutyric acid (GABA)


statine

Many unusual amino acids, including D-enantiomers of some common acids, are produced by microorganisms. These include ornithine, which is a component of the antibiotic bacitracin A, and statin, found as part of a pentapeptide that inhibits the action of the digestive enzyme **pepsin**.

EXERCISES

QUESTIONS

Q26.1.1

Why is cysteine the only L amino acid with an R configuration at the alpha carbon?

Q26.1.2

Isoleucine has two stereogenic centers.

(a) Draw a Fischer projection of isoleucine.

(b) Draw a Fischer projection of an isoleucine diastereomer, and label each stereocenter as R or S.

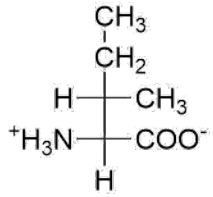
SOLUTIONS

S26.1.1

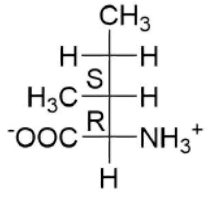
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

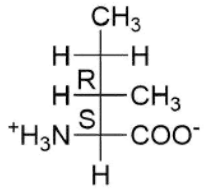
S26.1.2

(a)



(b)





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26.3: AMINO ACIDS, THE HENDERSON-HASSELBALCH EQUATION, AND ISOELECTRIC POINTS

OBJECTIVES

After completing this section, you should be able to

1. draw the predominant form of a given amino acid in a solution of known pH, given the isoelectric point of the amino acid.
2. describe, briefly, how a mixture of amino acids may be separated by paper electrophoresis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- electrophoresis
- isoelectric point

Since amino acids, as well as peptides and proteins, incorporate both acidic and basic functional groups, the predominant molecular species present in an aqueous solution will depend on the pH of the solution. In order to determine the nature of the molecular and ionic species that are present in aqueous solutions at different pH's, we make use of the **Henderson-Hasselbalch Equation**, written below. Here, the pK_a represents the acidity of a specific conjugate acid function (HA). When the pH of the solution equals pK_a, the concentrations of HA and $A^{(-)}$ must be equal (log 1 = 0).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]}$$

The titration curve for alanine in Figure **26.3.2** demonstrates this relationship. At a pH lower than 2, both the carboxylate and amine functions are protonated, so the alanine molecule has a net positive charge. At a pH greater than 10, the amine exists as a neutral base and the carboxyl as its conjugate base, so the alanine molecule has a net negative charge. At intermediate pH's the zwitterion concentration increases, and at a characteristic pH, called the **isoelectric point** (**pI**), the negatively and positively charged molecular species are present in equal concentration. This behavior is general for simple (difunctional) amino acids. Starting from a fully protonated state, the pK_a's of the acidic functions range from 1.8 to 2.4 for $-CO_2H$, and 8.8 to 9.7 for $-NH_3^{(+)}$. The isoelectric points range from 5.5 to 6.2. Titration curves show the neutralization of these acids by added base, and the change in pH during the titration.

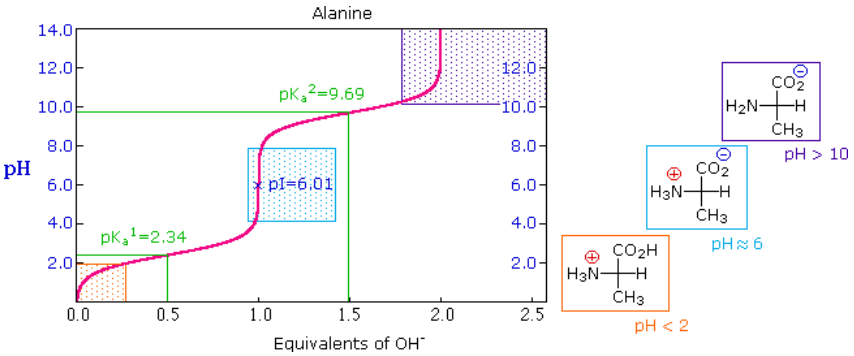


Figure **26.3.1**: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

The distribution of charged species in a sample can be shown experimentally by observing the movement of solute molecules in an electric field, using the technique of **electrophoresis** (Figure **26.3.2**). For such experiments an ionic buffer solution is incorporated in a solid matrix layer, composed of paper or a crosslinked gelatin-like substance. A small amount of the amino acid, peptide or protein sample is placed near the center of the matrix strip and an electric potential is applied at the ends of the strip, as shown in the following diagram. The solid structure of the matrix retards the diffusion of the solute molecules, which will remain where they are inserted, unless acted upon by the electrostatic potential.

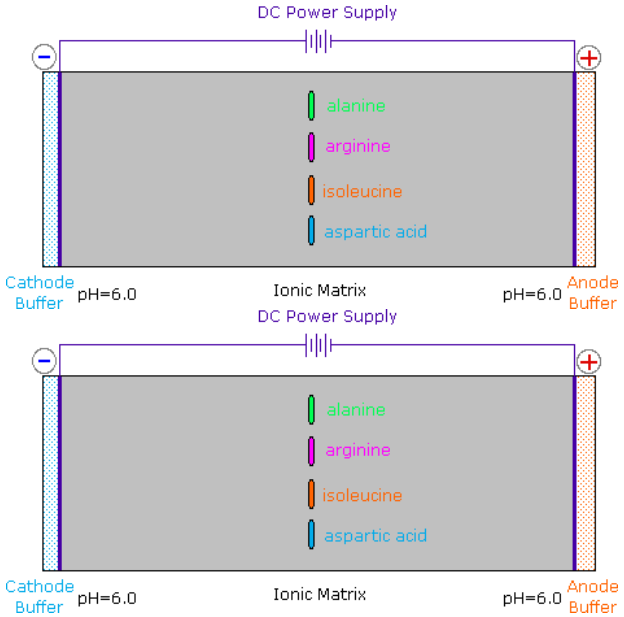
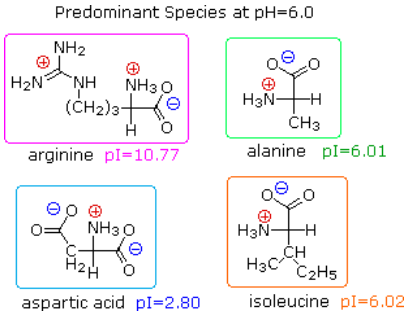


Figure **26.3.2**: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

At pH 6.00 alanine and isoleucine exist on average as neutral zwitterionic molecules, and are not influenced by the electric field. Arginine is a basic amino acid. Both base functions exist as "onium" conjugate acids in the pH 6.00 matrix. The solute molecules of arginine therefore carry an excess positive charge, and they move toward the cathode. The two carboxyl functions in aspartic acid are both ionized at pH 6.00, and the negatively charged solute molecules move toward the anode in the electric field. Structures for all these species are shown to the right of the display.



It should be clear that the result of this experiment is critically dependent on the pH of the matrix buffer. If we were to repeat the electrophoresis of these compounds at a pH of 3.80, the aspartic acid would remain at its point of origin, and the other amino acids would move toward the cathode. Ignoring differences in molecular size and shape, the arginine would move twice as fast as the alanine and isoleucine because its solute molecules on average would carry a double positive charge.

As noted earlier, the titration curves of simple amino acids display two inflection points, one due to the strongly acidic carboxyl group (pK_a^1 = 1.8 to 2.4), and the other for the less acidic ammonium function (pK_a^2 = 8.8 to 9.7). For the 2º-amino acid proline, pK_a^2 is 10.6, reflecting the greater basicity of 2º-amines.

Table **26.3.1**: pKa Values of Polyfunctional Amino Acids

Amino Acid	α-CO_2H pK_a^1	α-NH_3 pK_a^2	Side Chain pK_a^3	pI
Arginine	2.1	9.0	12.5	10.8
Aspartic Acid	2.1	9.8	3.9	3.0
Cysteine	1.7	10.4	8.3	5.0
Glutamic Acid	2.2	9.7	4.3	3.2
Histidine	1.8	9.2	6.0	7.6
Lysine	2.2	9.0	10.5	9.8
Tyrosine	2.2	9.1	10.1	5.7

Some amino acids have additional acidic or basic functions in their side chains. These compounds are listed in Table **26.3.1**. A third pK_a, representing the acidity or basicity of the extra function, is listed in the fourth column of the table. The pI's of these amino acids (last column) are often very different from those noted above for the simpler members. As expected, such compounds display three inflection points in their titration curves, illustrated by the titrations of arginine and aspartic acid (Figure\ (\PageIndex{3}\)). For each of these compounds four possible charged species are possible, one of which has no overall charge. Formulas for these species are written to the right of the titration curves, together with the pH at which each is expected to predominate. The very high pH required to remove the last acidic proton from arginine reflects the exceptionally high basicity of the guanidine moiety at the end of the side chain.

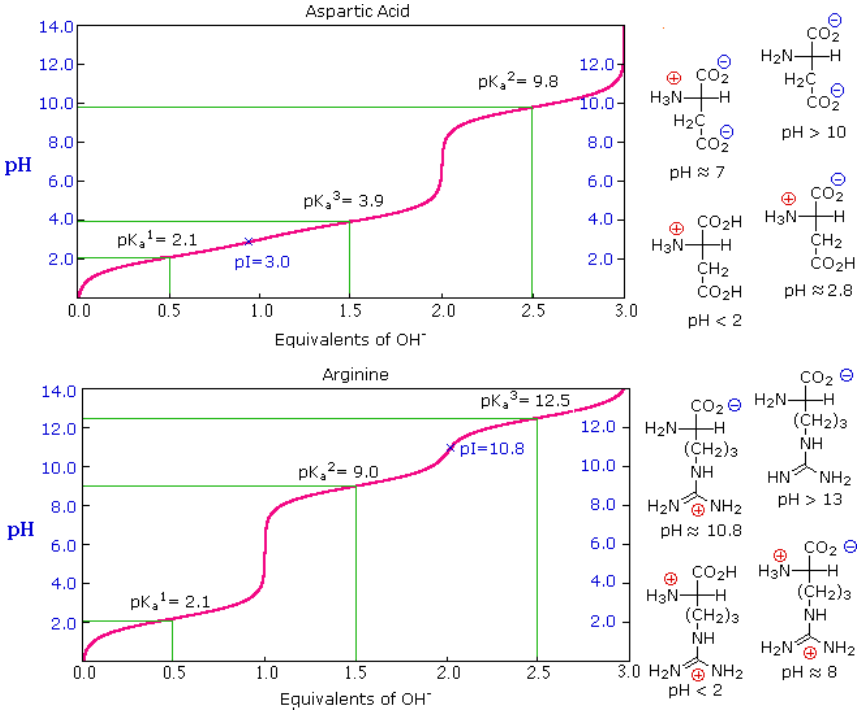


Figure **26.3.3**

THE ISOELECTRIC POINT

The isoelectric point, **pI**, is the pH of an aqueous solution of an amino acid (or peptide) at which the molecules on average have no net charge. In other words, the positively charged groups are exactly balanced by the negatively charged groups. For simple amino acids such as alanine, the pI is an average of the pK_a's of the carboxyl (2.34) and ammonium (9.69) groups. Thus, the pI for alanine is calculated to be: (2.34 + 9.69)/2 = 6.02, the experimentally determined value. If additional acidic or basic groups are present as side-chain functions, the pI is the average of the pK_a's of the two most similar acids. To assist in determining similarity we define two classes of acids. The first consists of acids that are neutral in their protonated form (e.g. CO_2H & SH). The second includes acids that are positively charged in their protonated state (e.g. $-NH_3^+$). In the case of aspartic acid, the similar acids are the alpha-carboxyl function (pK_a = 2.1) and the side-chain carboxyl function (pK_a = 3.9), so pI = (2.1 + 3.9)/2 = 3.0. For arginine, the similar acids are the guanidinium species on the side-chain (pK_a = 12.5) and the alpha-ammonium function (pK_a = 9.0), so the calculated pI = (12.5 + 9.0)/2 = 10.75

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26.4: SYNTHESIS OF AMINO ACIDS

OBJECTIVES

After completing this section, you should be able to

1. outline, by means of equations, how a racemic mixture of given amino acid can be prepared from a carboxylic acid using reactions you studied earlier in the course.
2. a. outline, by means of equations, the preparation of a given amino acid by the amidomalonate synthesis.
   b. identify the amino acid formed from using a given alkyl halide in an amidomalonate synthesis.
   c. identify the alkyl halide needed to produce a given amino acid by the amidomalonate synthesis.
3. describe, by means of equations, how an α-keto acid can be transformed to an amino acid by reductive amination.
4. a. describe a general method for resolving a racemic mixture of a given amino acid.
   b. provide a brief example of how a biological method may be employed to resolve a racemic mixture of a given amino acid.
   c. show the enantioselective preparation of an amino acid from the corresponding *Z* enamido acid.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

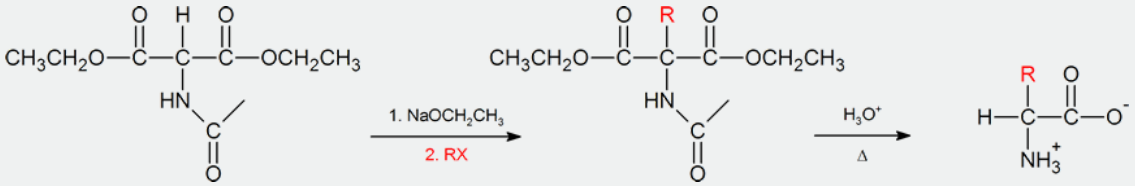
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

STUDY NOTES

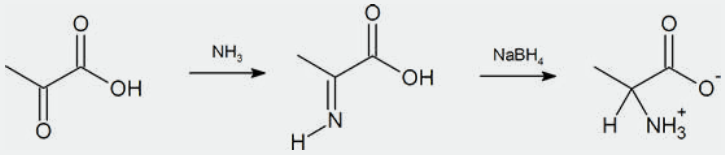
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

To fulfill the requirements of Objective 1, review the Hell-Volhard-Zelinskii reaction (Section 22.4) and the Gabriel phthalimide synthesis (Section 24.6).

The **amidomalonate synthesis** is a simple variation of the malonic ester synthesis (Section 22.7). A base abstracts a proton from the alpha carbon, which is then alkylated with an alkyl halide. Then both the hydrolysis of the esters and the amide protecting group under aqueous acidic conditions generates the α-amino acid.

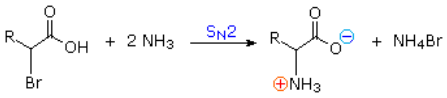


Another method of getting to the α-amino acid is by **reductive amination** of the α-keto acid which you have also previously encountered (Section 24.6).

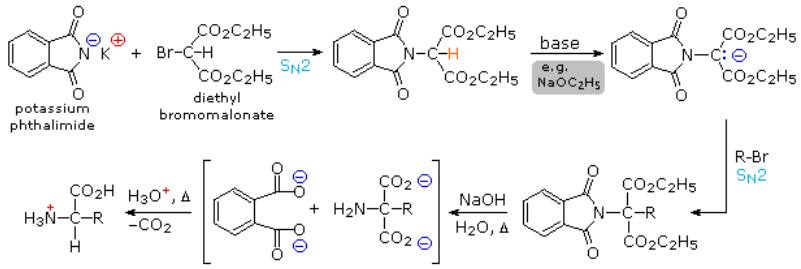


SYNTHESIS OF A-AMINO ACIDS

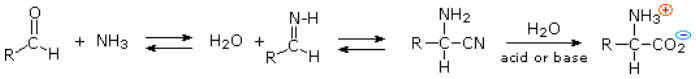
1) Amination of alpha-bromocarboxylic acids, illustrated by the following equation, provides a straightforward method for preparing alpha-aminocarboxylic acids. The bromoacids, in turn, are conveniently prepared from carboxylic acids by reaction with Br_2 + PCl_3. Although this direct approach gave mediocre results when used to prepare simple amines from alkyl halides, it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



2) By modifying the nitrogen as a phthalimide salt, the propensity of amines to undergo multiple substitutions is removed, and a single clean substitution reaction of 1º- and many 2º-alkylhalides takes place. This procedure, known as the Gabriel synthesis, can be used to advantage in aminating bromomalonic esters, as shown in the upper equation of the following scheme. Since the phthalimide substituted malonic ester has an acidic hydrogen (colored orange), activated by the two ester groups, this intermediate may be converted to an ambident anion and alkylated. Finally, base catalyzed hydrolysis of the phthalimide moiety and the esters, followed by acidification and thermal decarboxylation, produces an amino acid and phthalic acid (not shown).

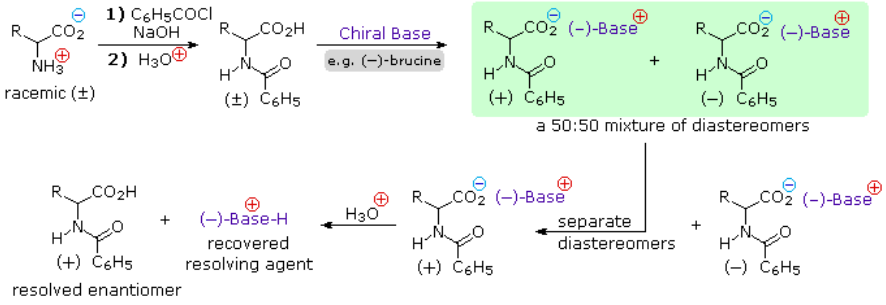


3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this way can then be hydrolyzed to an amino acid by either acid or base catalysis.

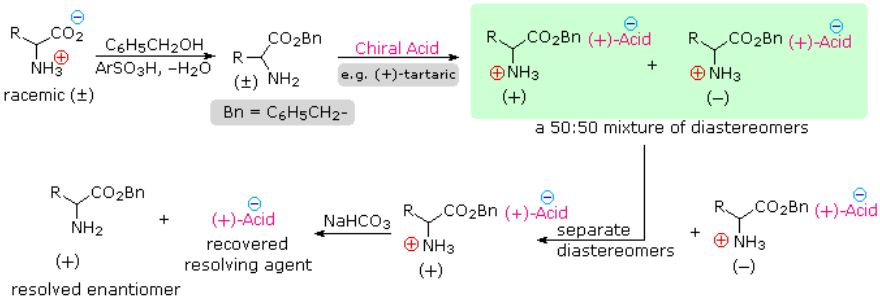


4) Resolution The three synthetic procedures described above, and many others that can be conceived, give racemic amino acid products. If pure **L** or **D** enantiomers are desired, it is necessary to resolve these racemic mixtures. A common method of resolving racemates is by diastereomeric salt formation with a pure chiral acid or base. This is illustrated for a generic amino acid in the following diagram. Be careful to distinguish charge symbols, shown in colored circles, from optical rotation signs, shown in parenthesis.

In the initial display, the carboxylic acid function contributes to diastereomeric salt formation. The racemic amino acid is first converted to a benzamide derivative to remove the basic character of the amino group. Next, an ammonium salt is formed by combining the carboxylic acid with an optically pure amine, such as brucine (a relative of strychnine). The structure of this amine is not shown, because it is not a critical factor in the logical progression of steps. Since the amino acid moiety is racemic and the base is a single enantiomer (levorotatory in this example), an equimolar mixture of diastereomeric salts is formed (drawn in the green shaded box). Diastereomers may be separated by crystallization, chromatography or other physical manipulation, and in this way one of the isomers may be isolated for further treatment, in this illustration it is the (+):(-) diastereomer. Finally the salt is broken by acid treatment, giving the resolved (+)-amino acid derivative together with the recovered resolving agent (the optically active amine). Of course, the same procedure could be used to obtain the (-)-enantiomer of the amino acid.



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Since amino acids are amphoteric, resolution could also be achieved by using the basic character of the amine function. For this approach we would need an enantiomerically pure chiral acid such as tartaric acid to use as the resolving agent. This alternative resolution strategy will be illustrated. Note that the carboxylic acid function is first esterified, so that it will not compete with the resolving acid.

Resolution of aminoacid derivatives may also be achieved by enzymatic discrimination in the hydrolysis of amides. For example, an aminoacylase enzyme from pig kidneys cleaves an amide derivative of a natural L-amino acid much faster than it does the D-enantiomer. If the racemic mixture of amides shown in the green shaded box above is treated with this enzyme, the L-enantiomer (whatever its rotation) will be rapidly converted to its free zwitterionic form, whereas the D-enantiomer will remain largely unchanged. Here, the diastereomeric species are transition states rather than isolable intermediates. This separation of enantiomers, based on very different rates of reaction, is called **kinetic resolution**.

ENANTIOSELECTIVE SYNTHESIS

Till now all of the synthetic routes to α-amino acids we have discussed yield a racemic mixture. Once produced one could resolve the mixture to obtain pure **L** or **D** enantiomers. However, enantioselective synthetic methods to produce pure compounds directly are being developed. For instance, several catalysts are now available for reduction of C=C to expose enantiopure amino acids. A good example is the industrial synthesis of L-DOPA, a drug used in the treatment of Parkinson's disease. W.S. Knowles shared the 2001 Nobel Price with R. Noyori and K.B. Sharpless for their contributions in the area of asymmetric catalytic reductions**.** Knowles developed several chiral phosphine–metal catalysts for asymmetric reductions. The rhodium(I) catalyst shown, which is complexed by large organic ligands, facilitates production of almost pure L-DOPA.

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26.5: PEPTIDES AND PROTEINS

OBJECTIVES

After completing this section, you should be able to

1. a. show, by means of a diagram, how two different amino acid residues can be combined to give two different dipeptides.
   b. draw the structure of a relatively simple peptide, given its full or abbreviated name and the structures of the appropriate amino acids.
   c. draw, or name, the six possible isomeric tripeptides that can be formed by combining three different amino acid residues (amino acid units) of given structure.
2. account for the fact that there is restricted rotation about the C$\ce{-}$N bonds in peptides.
3. illustrate the formation of a disulfide linkage between two cysteine residues, and show how such bonds can link together two separate peptide chains or can provide a bridge between two cysteine residues present in a single peptide molecule.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

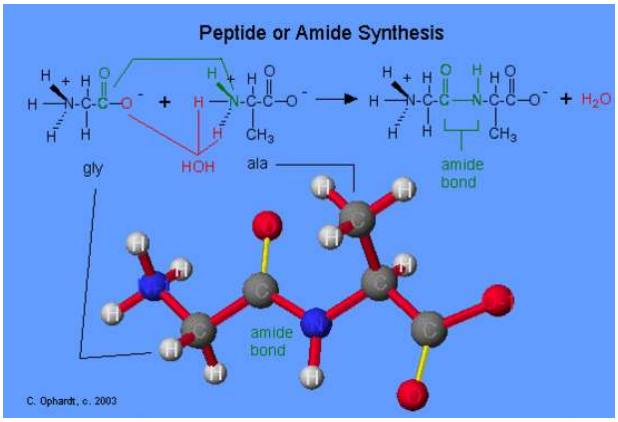
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

STUDY NOTES

If necessary, review the discussion of the delocalization of the nitrogen lone-pair electrons in amides that was presented in Section 24.3. Similarly, you may wish to refer back to Section 18.8 to review the interconversion of thiols and disulfides.

PEPTIDE BOND FORMATION OR AMIDE SYNTHESIS

The formation of peptides is nothing more than the application of the **amide synthesis reaction**. By convention, the amide bond in the peptides should be made in the order that the amino acids are written. The amine end (N terminal) of an amino acid is always on the left, while the acid end (C terminal) is on the right. The reaction of glycine with alanine to form the dipeptide glyclalanine is written as shown in the graphic on the left. Oxygen (red) from the acid and hydrogens (red) on the amine form a water molecule. The carboxyl oxygen (green) and the amine nitrogen (green) join to form the amide bond.



If the order of listing the amino acids is reversed, a different dipeptide is formed such as alaninylglycine.

? EXERCISE 26.5.1

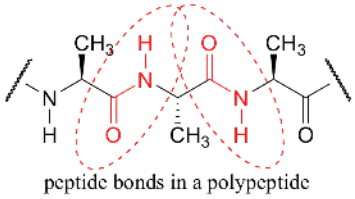
Write the reactions for:

a. ala + gly ---> Answer graphic

b. phe + ser ----> Answer graphic

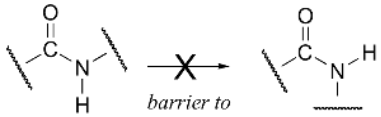
RESONANCE CONTRIBUTORS FOR THE PEPTIDE BONDS

A consideration of resonance contributors is crucial to any discussion of the amide functional group. One of the most important examples of amide groups in nature is the 'peptide bond' that links amino acids to form polypeptides and proteins.

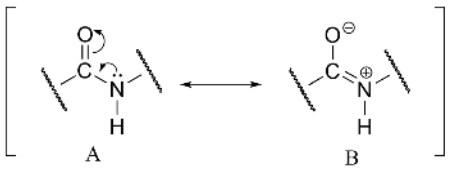


peptide bonds in a polypeptide

Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, the C-N bond in a peptide linkage has a significant barrier to rotation, almost as if it were a double bond.



This, along with the observation that the bonding around the peptide nitrogen has trigonal planar geometry, strongly suggests that the nitrogen is sp^2-hybridized. An important resonance contributor has a C=N double bond and a C-O single bond, with a separation of charge between the oxygen and the nitrogen.



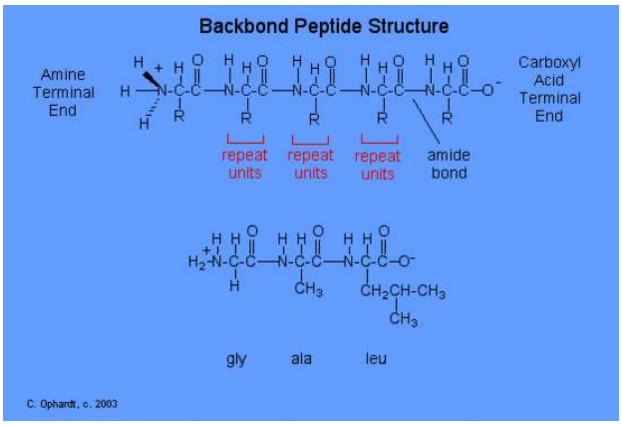
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

BACKBONE PEPTIDE OR PROTEIN STRUCTURE

The structure of a peptide can be written fairly easily without showing the complete amide synthesis reaction by learning the structure of the "backbone" for peptides and proteins.

The peptide backbone consists of repeating units of "N-H 2, CH, C double bond O; N-H 2, CH, C double bond O; etc. See the graphic on the left .

After the backbone is written, go back and write the specific structure for the side chains as represented by the "R" as gly-ala-leu for this example. The amine end (N terminal) of an amino acid is always on the left (gly), while the acid end (C terminal) is on the right (leu).



EXERCISE 26.5.2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

Answer graphic

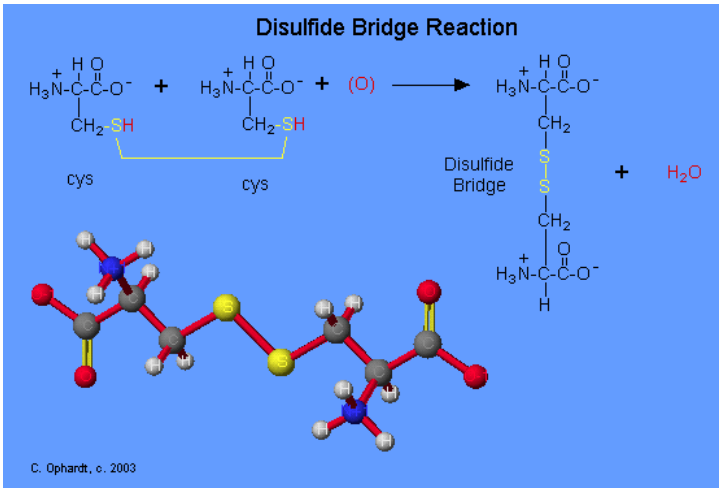
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

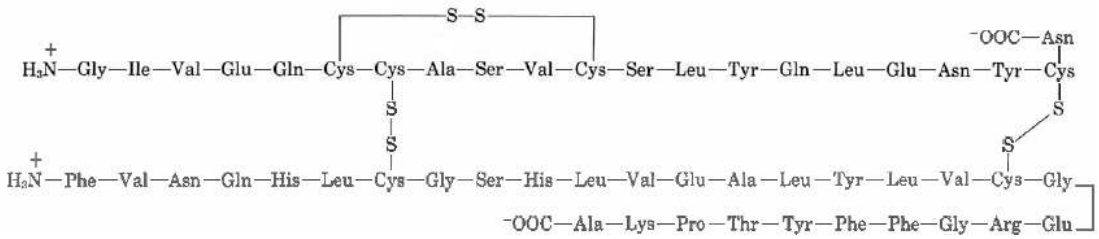
2 b) phe-tyr-asn ---> Answer graphic

DISULFIDE BRIDGES AND OXIDATION-REDUCTION

The amino acid cysteine undergoes oxidation and reduction reactions involving the -SH (sulfhydryl group). The oxidation of two sulfhydryl groups results in the formation of a **disulfide bond** by the removal of two hydrogens. The **oxidation** of two cysteine amino acids is shown in the graphic. An unspecified oxidizing agent (O) provides an oxygen which reacts with the hydrogen (red) on the -SH group to form water. The sulfurs (yellow) join to make the **disulfide bridge**. This is an important bond to recognize in protein tertiary structure. The reduction of a disulfide bond is the opposite reaction which again leads to two separate cysteine molecules. Remember that reduction is the addition of hydrogen.



Cysteine residues in the the peptide chain can form a loop buy forming the disulfide bond (—S—S—), while cysteine residues in different peptide chains can actually link what were otherwise separate chains. Insulin was the first protein whose amino acid sequence was determined. This pioneering work, completed in 1953 after some 10 years of effort, earned a Nobel Prize for British biochemist Frederick Sanger (born 1918). He found the primary structure to comprise of two chains linked by two cysteine disulfide bridges. Also note the first peptide chain possesses an internal loop.



Insulin

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26.6: AMINO ACID ANALYSIS OF PEPTIDES

OBJECTIVES

After completing this section, you should be able to describe, briefly, how the identity and amounts of each amino acid residue present in a peptide of unknown structure may be determined.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- amino acid analyzer

STUDY NOTES

You need not memorize the reaction between ninhydrin and an α-amino acid.

ION-EXCHANGE CHROMATOGRAPHY

When a protein is to be analysed, it is first heated with acid to hydrolyse all the peptide bonds. When such a mixture of amino acids is to be purified and estimated quantitatively, ion-exchange chromatography is the technique of choice. Fully automated amino acid analyzers are now available, which are equipped with a solvent pump to deliver the required buffer(s) in a programmed manner. There is a column, filled with Dowex 50 resin (Fig 26.5.1). This solid support is made up of polymeric beads. Chemically speaking they are polymers bearing arylsulfonic acid groups. The cation exchange resin helps in the separation of amino acids. In a typical run (Fig 26.5.2), the eluent is a buffer. The pH value of the buffer could be varied as step elution or as gradient elution. The chromatogram shown in Fig 26.5.2 is a chromatogram run with gradient elution technique, using **ninhydrin** as the post column treatment. The detector is a UV detector scanning the wavelengths 570 nm and 440 nm.

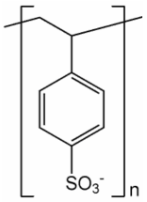


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

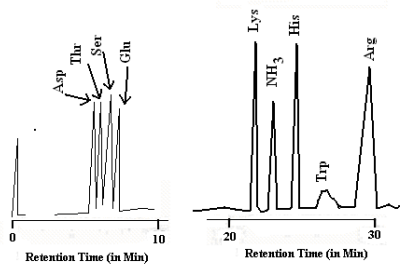
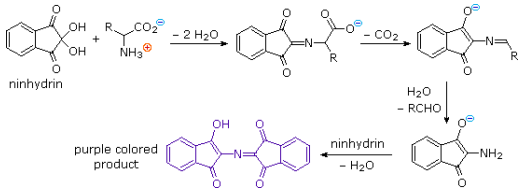


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

THE NINHYDRIN REACTION

Alpha-amino acids show reactivity at their the carboxylic acid and amine sites typical of those functional groups. In addition to these common reactions of amines and carboxylic acids, common alpha-amino acids, except proline, undergo a unique reaction with the triketohydrindene hydrate known as ninhydrin. Among the products of this unusual reaction (shown on the left below) is a purple colored imino derivative, which provides as a useful color test for these amino acids, most of which are colorless. A common application of the ninhydrin test is the visualization of amino acids in paper chromatography. As shown in the graphic on the right, samples of amino acids or mixtures thereof are applied along a line near the bottom of a rectangular sheet of paper (the baseline). The bottom edge of the paper is immersed in an aqueous buffer, and this liquid climbs slowly toward the top edge. As the solvent front passes the sample spots, the compounds in each sample are carried along at a rate which is characteristic of their functionality, size and interaction with the cellulose matrix of the paper. Some compounds move rapidly up the paper, while others may scarcely move at all. The ratio of the distance a compound moves from the baseline to the distance of the solvent front from the baseline is defined as the retardation (or retention) factor R_f. Different amino acids usually have different R_f's under suitable conditions. In the example on the right, the three sample compounds (1, 2 & 3) have respective R_f values of 0.54, 0.36 & 0.78.



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26.7: THE EDMAN DEGRADATION

OBJECTIVES

After completing this section, you should be able to

1. describe how an Edman degradation is used to determine the sequence of the amino acid residues in peptides containing up to 20 such residues.
2. describe, briefly, how the procedure is modified to deal with peptides and proteins containing more than 20 amino acid residues.
3. write a detailed mechanism for the Edman degradation.
4. determine the structure of a peptide, given a list of the fragments that are produced by a partial acid hydrolysis.
5. determine the structure of a peptide, given a list of the fragments that are produced when the peptide is cleaved by a specific enzyme and the details of the types of bonds cleaved by that enzyme.
6. predict the fragments that would be produced when a peptide of known structure is cleaved by a specific enzyme, given sufficient information about the types of bonds that are cleaved by the enzyme in question.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- Edman degradation

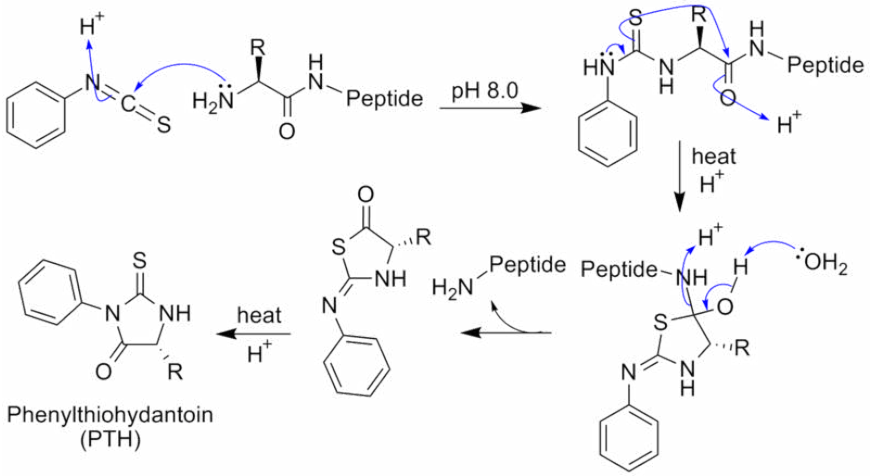
STUDY NOTES

The reagent used in the Edman degradation is phenyl isothiocyanate. You may find it helpful to review the relationship between cyanates, isocyanates, thiocyanates and isothiocyanates.

R–O–C≡N	cyanate (such compounds do not exist)
R–N=C=O	isocyanate
R–S–C≡N	thiocyanate
R–N=C=S	isothiocyanate

You need not memorize the specific peptide bonds that are broken by the enzymes trypsin and chymotrypsin.

Edman degradation is the process of purifying protein by sequentially removing one residue at a time from the amino end of a peptide. To solve the problem of damaging the protein by hydrolyzing conditions, Pehr Edman created a new way of labeling and cleaving the peptide. Edman thought of a way of removing only one residue at a time, which did not damage the overall sequencing. This was done by adding Phenyl isothiocyanate, which creates a phenylthiocarbamoyl derivative with the N-terminal. The N-terminal is then cleaved under less harsh acidic conditions, creating a cyclic compound of phenylthiohydantoin PTH-amino acid. This does not damage the protein and leaves two constituents of the peptide. This method can be repeated for the rest of the residues, separating one residue at a time.



Edman degradation is very useful because it does not damage the protein. This allows sequencing of the protein to be done in less time. Edman sequencing is done best if the composition of the amino acid is known. As we saw in Section 26.5, to determine the composition of the amino acid, the peptide must be hydrolyzed. This can be done by denaturing the protein and heating it and adding HCl for a long time. This causes the individual amino acids to be separated, and they can be separated by ion exchange chromatography. They are then dyed with ninhydrin and the amount of amino acid can be determined by the amount of optical absorbance. This way, the composition but not the sequence can be determined

SEQUENCING LARGER PROTEINS

Larger proteins cannot be sequenced by the Edman sequencing because of the less than perfect efficiency of the method. A strategy called divide and conquer successfully cleaves the larger protein into smaller, practical amino acids. This is done by using a certain chemical or enzyme which can cleave the protein at specific amino acid residues. The separated peptides can be isolated by chromatography. Then they can be sequenced using the Edman method, because of their smaller size.

In order to put together all the sequences of the different peptides, a method of overlapping peptides is used. The strategy of divide and conquer followed by Edman sequencing is used again a second time, but using a different enzyme or chemical to cleave it into different residues. This allows two different sets of amino acid sequences of the same protein, but at different points. By comparing these two sequences and examining for any overlap between the two, the sequence can be known for the original protein.

For example, trypsin can be used on the initial peptide to cleave it at the carboxyl side of arginine and lysine residues. Using trypsin to cleave the protein and sequencing them individually with Edman degradation will yield many different individual results. Although the sequence of each individual cleaved amino acid segment is known, the order is scrambled. Chymotrypsin, which cleaves on the carboxyl side of aromatic and other bulky nonpolar residues, can be used. The sequence of these segments overlap with those of the trypsin. They can be overlapped to find the original sequence of the initial protein. However, this method is limited in analyzing larger sized proteins (more than 100 amino acids) because of secondary hydrogen bond interference. Other weak intermolecular bonding such as hydrophobic interactions cannot be properly predicted. Only the linear sequence of a protein can be properly predicted assuming the sequence is small enough.

CONTRIBUTORS AND ATTRIBUTIONS

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26.8: PEPTIDE SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

1. describe why it is necessary to protect certain amino and carboxyl groups during the synthesis of a peptide.
2. describe, using appropriate equations, how carboxyl groups are protected by ester formation and amino groups are protected by the formation of their *tert*-butoxycarbonyl amide derivatives.
3. write a detailed mechanism for the formation of a peptide link between an amino acid with a protected amino group and an amino acid with a protected carboxyl group using dicyclohexylcarbodiimide.
4. outline the five steps required in order to form a dipeptide from two given amino acids.

In order to synthesize a peptide from its component amino acids, two obstacles must be overcome. The first of these is statistical in nature, and is illustrated by considering the dipeptide Ala-Gly as a proposed target. If we ignore the chemistry involved, a mixture of equal molar amounts of alanine and glycine would generate four different dipeptides. These are: **Ala-Ala, Gly-Gly, Ala-Gly & Gly-Ala**. In the case of tripeptides, the number of possible products from these two amino acids rises to eight. Clearly, some kind of selectivity must be exercised if complex mixtures are to be avoided.

The second difficulty arises from the fact that carboxylic acids and 1º or 2º-amines do not form amide bonds on mixing, but will generally react by proton transfer to give salts (the intermolecular equivalent of zwitterion formation).

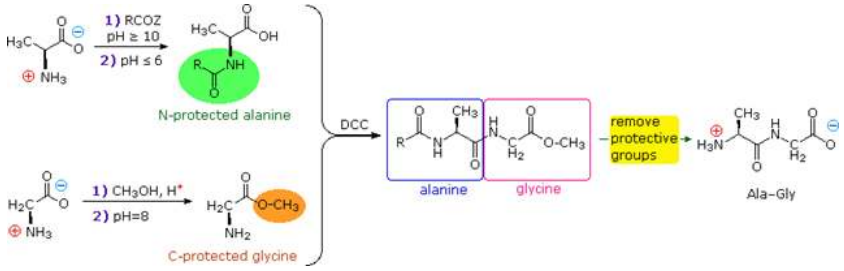
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated carboxyl function so that it will acylate the one remaining free amine. Fortunately, chemical reactions that permit us to accomplish these selections are well known.

First, the basicity and nucleophilicity of amines are substantially reduced by amide formation. Consequently, the acylation of amino acids by treatment with acyl chlorides or anhydrides at pH > 10, as described earlier, serves to protect their amino groups from further reaction.

Second, acyl halide or anhydride-like activation of a specific carboxyl reactant must occur as a prelude to peptide (amide) bond formation. This is possible, provided competing reactions involving other carboxyl functions that might be present are precluded by preliminary ester formation. Remember, esters are weaker acylating reagents than either anhydrides or acyl halides, as noted earlier.

Finally, dicyclohexylcarbodiimide (DCC) effects the dehydration of a carboxylic acid and amine mixture to the corresponding amide under relatively mild conditions. The structure of this reagent and the mechanism of its action have been described. Its application to peptide synthesis will become apparent in the following discussion.

The strategy for peptide synthesis, as outlined here, should now be apparent. The following example shows a selective synthesis of the dipeptide Ala-Gly.



An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the amino acids in the resulting peptide. This problem strikes at the heart of our strategy, so it is important to give careful thought to the design of specific N-protective groups. In particular, three qualities are desired:

1. The protective amide should be easy to attach to amino acids.
2. The protected amino group should not react under peptide forming conditions.
3. The protective amide group should be easy to remove under mild conditions.

A number of protective groups that satisfy these conditions have been devised; and two of the most widely used, **carbobenzoxy** (Cbz) and **t-butoxycarbonyl** (BOC or t-BOC), are described here.

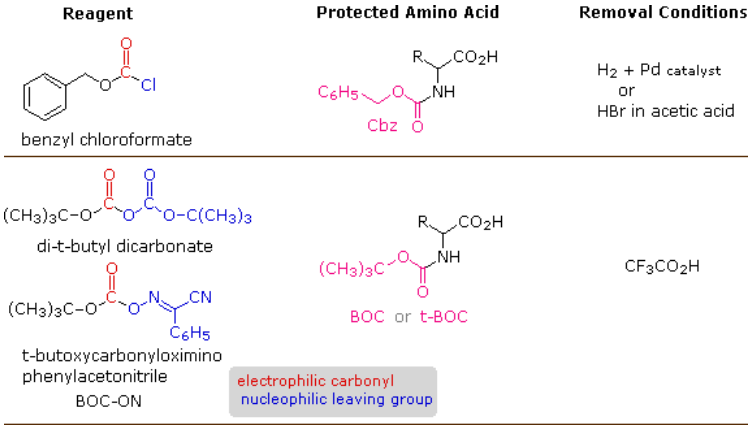


Figure_3.png" />

The reagents for introducing these N-protective groups are the acyl chlorides or anhydrides shown in the left portion of the above diagram. Reaction with a free amine function of an amino acid occurs rapidly to give the "protected" amino acid derivative shown in the center. This can then be used to form a peptide (amide) bond to a second amino acid. Once the desired peptide bond is created the protective group can be removed under relatively mild non-hydrolytic conditions. Equations showing the protective group removal will be displayed above by are shown above. Cleavage of the reactive benzyl or tert-butyl groups generates a common carbamic acid intermediate (HOCO-NHR) which spontaneously loses carbon dioxide, giving the corresponding amine. If the methyl ester at the C-terminus is left in place, this sequence of reactions may be repeated, using a different N-protected amino acid as the acylating reagent. Removal of the protective groups would then yield a specific tripeptide, determined by the nature of the reactants and order of the reactions.

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26.9: THE MERRIFIELD SOLID-PHASE TECHNIQUE

OBJECTIVES

After completing this section, you should be able to describe, briefly, the Merrifield solid-phase technique for the synthesis of polypeptides.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- solid-phase method (solid-phase synthesis)

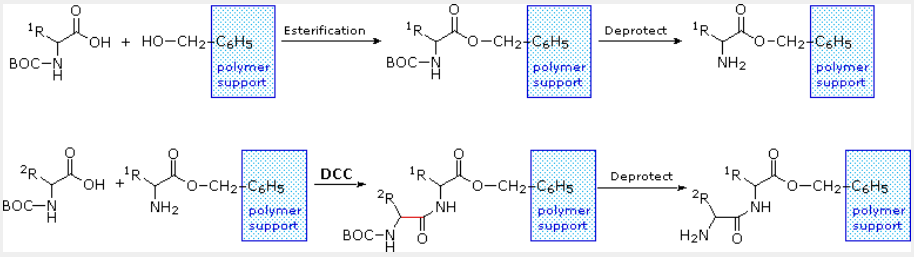
STUDY NOTES

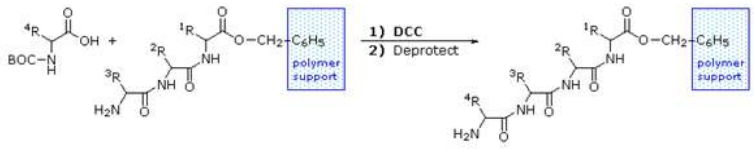
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

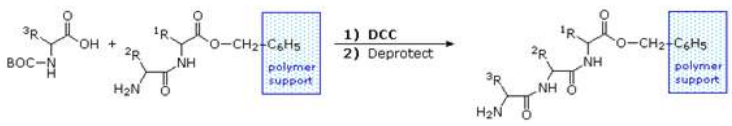
For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

The synthesis of a peptide of significant length (e.g. ten residues) by this approach requires many steps, and the product must be carefully purified after each step to prevent unwanted cross-reactions. To facilitate the tedious and time consuming purifications, and reduce the material losses that occur in handling, a clever modification of this strategy has been developed. This procedure, known as the **Merrifield Synthesis** after its inventor R. Bruce Merrifield, involves attaching the C-terminus of the peptide chain to a polymeric solid, usually having the form of very small beads. Separation and purification is simply accomplished by filtering and washing the beads with appropriate solvents. The reagents for the next peptide bond addition are then added, and the purification steps repeated. The entire process can be automated, and peptide synthesis machines based on the Merrifield approach are commercially available. A series of equations illustrating the Merrifield synthesis may be viewed below. The final step, in which the completed peptide is released from the polymer support, is a simple benzyl ester cleavage. This is not shown in the display.

The Merrifield Peptide Synthesis







https://chem.libretexts.org/@go/page/36474

Two or more moderately sized peptides can be joined together by selective peptide bond formation, provided side-chain functions are protected and do not interfere. In this manner good sized peptides and small proteins may be synthesized in the laboratory. However, even if chemists assemble the primary structure of a natural protein in this or any other fashion, it may not immediately adopt its native secondary, tertiary and quaternary structure. Many factors, such as pH, temperature and inorganic ion concentration influence the conformational coiling of peptide chains. Indeed, scientists are still trying to understand how and why these higher structures are established in living organisms.

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26.10: PROTEIN STRUCTURE

OBJECTIVES

After completing this section, you should be able to

1. discuss, with reference to a suitable example (either given or of your own choice), the structure of proteins, paying particular attention to distinguishing between the primary, secondary, tertiary and quaternary structure.
2. describe the α-helical secondary structure displayed by many proteins.
3. describe the β-pleated-sheet structure displayed by many proteins.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

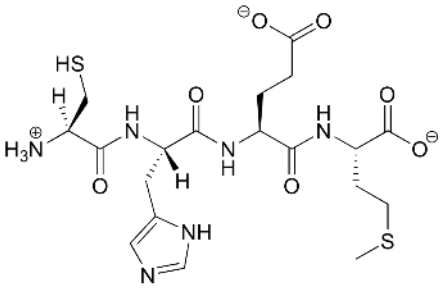
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

STUDY NOTES

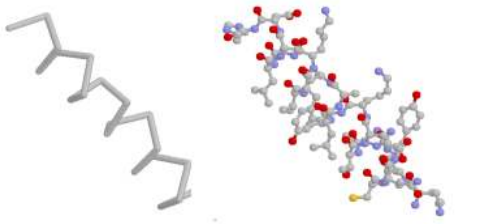
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

THE FOUR LEVELS OF PROTEIN STRUCTURE

Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)



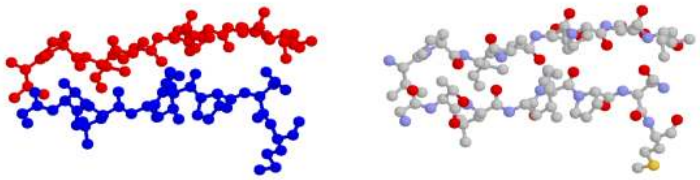
Secondary structure is three-dimensional, but is a local phenomenon, confined to a relatively short stretch of amino acids. For the most part, there are three important elements of secondary structure: helices, beta-sheets, and loops. In a helix, the main chain of the protein adopts the shape of a clockwise spiral staircase, and the side chains point out laterally.



main chain view main chain + side chain

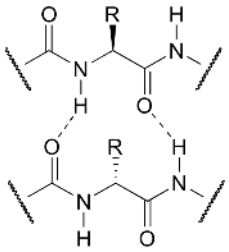
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In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



Loops are relatively disordered segments of protein chain, but often assume a very ordered structure when in contact with a second protein or a smaller organic compound.

Both helix and the beta-sheet structures are held together by very specific hydrogen-bonding interactions between the amide nitrogen on one amino acid and the carbonyl oxygen on another. The hydrogen bonding pattern in a section of a beta-strand is shown below.



hydrogen bonding in a β-strand

Secondary structure refers to the shape of a folding protein due exclusively to hydrogen bonding between its backbone amide and carbonyl groups. Secondary structure does not include bonding between the R-groups of amino acids, hydrophobic interactions, or other interactions associated with tertiary structure. The two most commonly encountered secondary structures of a polypeptide chain are α-helices and beta-pleated sheets. These structures are the first major steps in the folding of a polypeptide chain, and they establish important topological motifs that dictate subsequent tertiary structure and the ultimate function of the protein.

A-HELICES

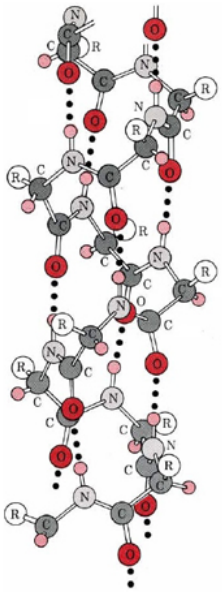


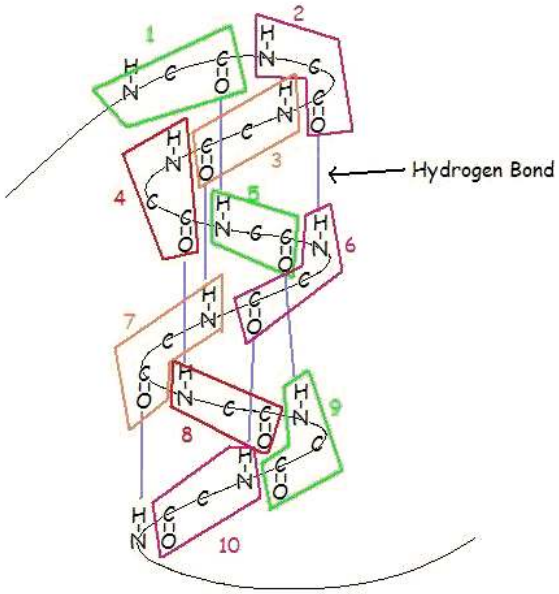
Figure 26.9.1 *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

An α-helix is a right-handed coil of amino-acid residues on a polypeptide chain, typically ranging between 4 and 40 residues. This coil is held together by hydrogen bonds between the oxygen of C=O on top coil and the hydrogen of N-H on the bottom coil. Such a hydrogen bond is formed exactly every 4 amino acid residues, and every complete turn of the helix is only 3.6 amino acid residues. This regular

pattern gives the α-helix very definite features with regards to the thickness of the coil and the length of each complete turn along the helix axis.

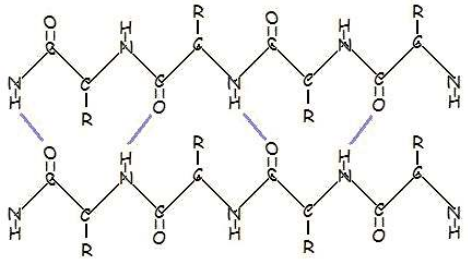
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the nitrogen of the amide group, which causes steric hindrance. In addition, the lack of a hydrogen on Proline's nitrogen prevents it from participating in hydrogen bonding.

Another factor affecting α-helix stability is the total dipole moment of the entire helix due to individual dipoles of the C=O groups involved in hydrogen bonding. Stable α-helices typically end with a charged amino acid to neutralize the dipole moment.



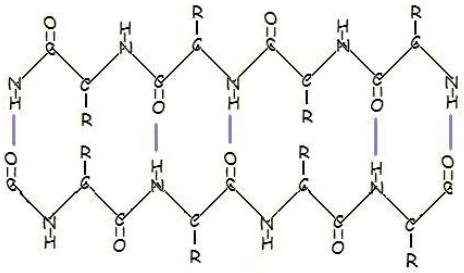
BETA-PLEATED SHEETS

This structure occurs when two (or more, e.g. ψ-loop) segments of a polypeptide chain overlap one another and form a row of hydrogen bonds with each other. This can happen in a parallel arrangement:



Parallel

Or in anti-parallel arrangement:



Anti-Parallel

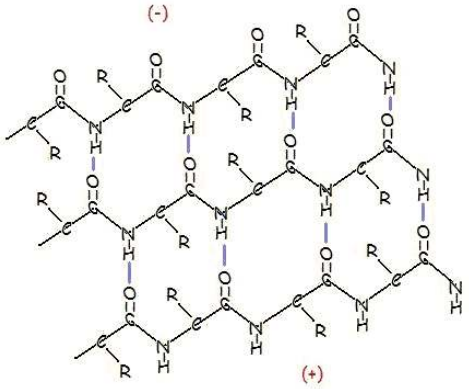
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus end are on the same sides for both segments. The "pleat" occurs because of the alternating planes of the peptide bonds between amino acids; the aligned amino and carbonyl group of each opposite segment alternate their orientation from facing towards each other to facing opposite directions.

The parallel arrangement is less stable because the geometry of the individual amino acid molecules forces the hydrogen bonds to occur at an angle, making them longer and thus weaker. Contrarily, in the anti-parallel arrangement the hydrogen bonds are aligned directly opposite each other, making for stronger and more stable bonds.

Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of a polypeptide chain to form beta-pleated sheets, but for proximal segments it is a definite requirement. For short distances, the two segments of a beta-pleated sheet are separated by 4+2n amino acid residues, with 4 being the minimum number of residues.

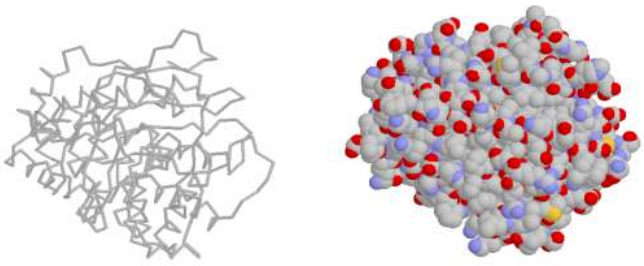
A-PLEATED SHEETS

A similar structure to the beta-pleated sheet is the α-pleated sheet. This structure is energetically less favorable than the beta-pleated sheet, and is fairly uncommon in proteins. An α-pleated sheet is characterized by the alignment of its carbonyl and amino groups; the carbonyl groups are all aligned in one direction, while all the N-H groups are aligned in the opposite direction. The polarization of the amino and carbonyl groups results in a net dipole moment on the α-pleated sheet. The carbonyl side acquires a net negative charge, and the amino side acquires a net positive charge.



Alpha-Pleated Sheet

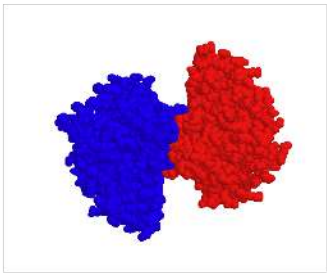
A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.



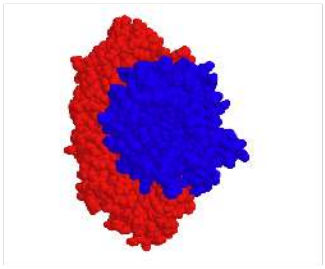
folded protein chain (main chain view)

folded protein chain ('space-filling' view)

While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have no quaternary structure. Many other proteins consist of two identical subunits (these are called homodimers) or two non-identical subunits (these are called heterodimers).

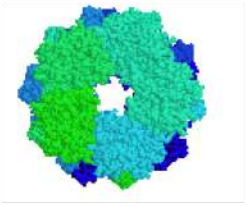


a homodimer

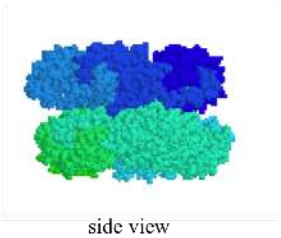


a heterodimer

Quaternary structures can be quite elaborate: below we see a protein whose quaternary structure is defined by ten identical subunits arranged in two five-membered rings, forming what can be visualized as a 'double donut' shape (this is fructose 1,6-bisphosphate aldolase):



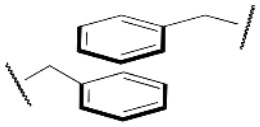
top view



side view

THE MOLECULAR FORCES THAT HOLD PROTEINS TOGETHER

The question of exactly how a protein 'finds' its specific folded structure out of the vast number of possible folding patterns is still an active area of research. What *is* known, however, is that the forces that cause a protein to fold properly and to remain folded are the same basic noncovalent forces that we talked about in chapter 2: ion-ion, ion-dipole, dipole-dipole, hydrogen bonding, and hydrophobic (van der Waals) interactions. One interesting type of hydrophobic interaction is called 'aromatic stacking', and occurs when two or more planar aromatic rings on the side chains of phenylalanine, tryptophan, or tyrosine stack together like plates, thus maximizing surface area contact.



Hydrogen bonding networks are extensive within proteins, with both side chain and main chain atoms participating. Ionic interactions often play a role in protein structure, especially on the protein surface, as negatively charged residues such as aspartate interact with positively-charged groups on lysine or arginine.

One of the most important ideas to understand regarding tertiary structure is that *a protein, when properly folded, is polar on the surface and nonpolar in the interior*. It is the protein's surface that is in contact with water, and therefore the surface must be hydrophilic in order for the whole structure to be soluble. If you examine a three dimensional protein structure you will see many charged side chains (e.g. lysine, arginine, aspartate, glutamate) and hydrogen-bonding side chains (e.g. serine, threonine, glutamine, asparagine) exposed on the surface, in direct contact with water. Inside the protein, out of contact with the surrounding water, there tend to be many more hydrophobic residues such as alanine, valine, phenylalanine, etc. If a protein chain is caused to come unfolded (through exposure to heat, for example, or extremes of pH), it will usually lose its solubility and form solid precipitates, as the hydrophobic residues from the interior come into contact with water. You can see this phenomenon for yourself if you pour a little bit of vinegar (acetic acid) into milk. The solid clumps that form in the milk are proteins that have come unfolded due to the sudden acidification, and precipitated out of solution.

In recent years, scientists have become increasing interested in the proteins of so-called 'thermophilic' (heat-loving) microorganisms that thrive in hot water environments such as geothermal hot springs. While the proteins in most organisms (including humans) will rapidly unfold and precipitate out of solution when put in hot water, the proteins of thermophilic microbes remain completely stable, sometimes even in water that is just below the boiling point. In fact, these proteins typically only gain full biological activity when in appropriately hot water - at room-temperature they act is if they are 'frozen'. Is the chemical structure of these thermostable proteins somehow unique and exotic? As it turns out, the answer to this question is 'no': the overall three-dimensional structures of thermostable proteins look very much like those of 'normal' proteins. The critical difference seems to be simply that thermostable proteins have more extensive networks of noncovalent interactions, particularly ion-ion interactions on their surface, that provides them with a greater stability to heat. Interestingly, the proteins of 'psychrophilic' (cold-loving) microbes isolated from pockets of water in arctic ice show the opposite characteristic: they have

far fewer ion-ion interactions, which gives them greater flexibility in cold temperatures but leads to their rapid unfolding in room temperature water.

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26.11: ENZYMES AND COENZYMES

OBJECTIVES

After completing this section, you should be able to

1. describe the catalytic role of an enzyme in a biochemical reaction.
2. give an example of one fat-soluble and one water-soluble vitamin.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- coenzyme
- cofactor
- enzyme
- substrate
- vitamin

STUDY NOTES

You should have a general knowledge of the function of enzymes, but you need not memorize specific names or the classification system.

A **catalyst** is any substance that increases the *rate* or speed of a chemical reaction without being changed or consumed in the reaction. **Enzymes** are biological catalysts, and nearly all of them are proteins. In addition, enzymes are highly specific in their action; that is, each enzyme catalyzes only one type of reaction in only one compound or a group of structurally related compounds. The compound or compounds on which an enzyme acts are known as its **substrates**. Enzymes are classified by reaction type into six categories show in Table **26.11.1**.

Table **26.11.1**: ***Classes of Enzymes***

Class	Type of Reaction Catalyzed	Examples
oxidoreductases	oxidation-reduction reactions	Dehydrogenases catalyze oxidation-reduction reactions involving hydrogen and reductases catalyze reactions in which a substrate is reduced.
transferases	transfer reactions of groups, such as methyl, amino, and acetyl	Transaminases catalyze the transfer of amino group, and kinases catalyze the transfer of a phosphate group.
hydrolases	hydrolysis reactions	Lipases catalyze the hydrolysis of lipids, and proteases catalyze the hydrolysis of proteins
lyases	reactions in which groups are removed without hydrolysis or addition of groups to a double bond	Decarboxylases catalyze the removal of carboxyl groups.
isomerases	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a ketose, and mutases catalyze reactions in which a functional group is transferred from one atom in a substrate to another.
ligases	reactions in which new bonds are formed between carbon and another atom; energy is required	Synthetases catalyze reactions in which two smaller molecules are linked to form a larger one.

Enzyme-catalyzed reactions occur in at least two steps. In the first step, an enzyme molecule (E) and the substrate molecule or molecules (S) collide and react to form an intermediate compound called the *enzyme-substrate* (E–S) *complex* (Equation 26.11.1). This step is reversible because the complex can break apart into the original substrate or substrates and the free enzyme. Once the E–S complex forms, the enzyme is able to catalyze the formation of product (P), which is then released from the enzyme surface (Equation 26.11.2):

$$S + E \rightleftharpoons E\text{–}S \tag{26.11.1}$$

$$E\text{–}S \rightarrow P + E \tag{26.11.2}$$

Hydrogen bonding and other electrostatic interactions hold the enzyme and substrate together in the complex. The structural features or functional groups on the enzyme that participate in these interactions are located in a cleft or pocket on the enzyme surface. This pocket, where the enzyme combines with the substrate and transforms the substrate to product is called the active site of the enzyme (Figure **26.11.1**).

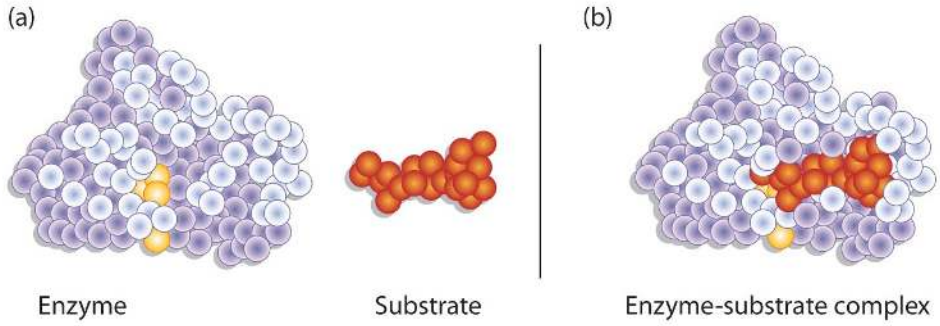


Figure* 26.11.1*: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

The active site possesses a unique conformation (including correctly positioned bonding groups) that is complementary to the structure of the substrate, so that the enzyme and substrate molecules fit together in much the same manner as a key fits into a tumbler lock. In fact, an early model describing the formation of the enzyme-substrate complex was called the lock-and-key model (Figure 26.11.2). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

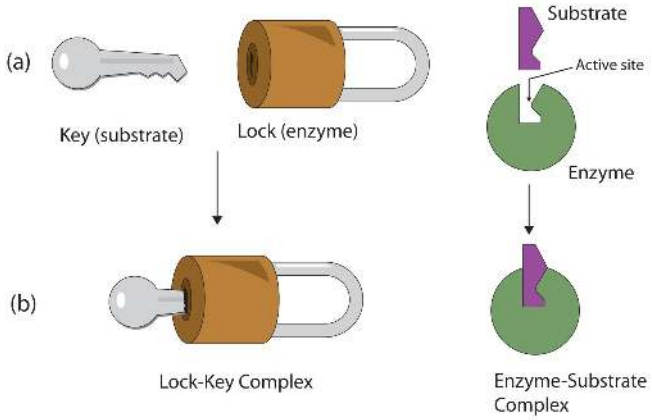


Figure 26.11.2: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate complex.

Working out the precise three-dimensional structures of numerous enzymes has enabled chemists to refine the original lock-and-key model of enzyme actions. They discovered that the binding of a substrate often leads to a large conformational change in the enzyme, as well as to changes in the structure of the substrate or substrates. The current theory, known as theinduced-fit model, says that enzymes can undergo a change in conformation when they bind substrate molecules, and the active site has a shape complementary to that of the substrate only after the substrate is bound, as shown for hexokinase in Figure 26.11.3. After catalysis, the enzyme resumes its original structure.

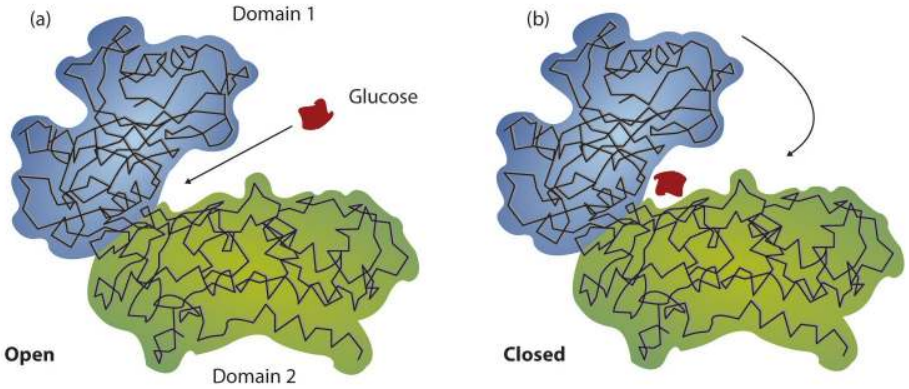


Figure **26.11.3**: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and glucose.

The structural changes that occur when an enzyme and a substrate join together bring specific parts of a substrate into alignment with specific parts of the enzyme's active site. Amino acid side chains in or near the binding site can then act as acid or base catalysts, provide binding sites for the transfer of functional groups from one substrate to another or aid in the rearrangement of a substrate. The participating amino acids, which are usually widely separated in the primary sequence of the protein, are brought close together in the active site as a result of the folding and bending of the polypeptide chain or chains when the protein acquires its tertiary and quaternary structure. Binding to enzymes brings reactants close to each other and aligns them properly, which has the same effect as increasing the concentration of the reacting compounds.

✔ EXAMPLE 26.11.1

a. What type of interaction would occur between an OH group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

Solution

a. An OH group would most likely engage in hydrogen bonding with an appropriate functional group present in the active site of an enzyme.
b. Several amino acid side chains would be able to engage in hydrogen bonding with an OH group. One example would be asparagine, which has an amide functional group.

? EXERCISE 26.11.1

a. What type of interaction would occur between an COO^- group present on a substrate molecule and a functional group in the active site of an enzyme?
b. Suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you just identified.

ENZYME COFACTORS AND VITAMINS

Many enzymes are simple proteins consisting entirely of one or more amino acid chains. Other enzymes contain a nonprotein component called a **cofactor** that is necessary for the enzyme's proper functioning. There are two types of cofactors: inorganic ions [e.g., zinc or Cu(I) ions] and organic molecules known as coenzymes. Most **coenzymes** are vitamins or are derived from vitamins.

Vitamins are organic compounds that are essential in very small (trace) amounts for the maintenance of normal metabolism. They generally cannot be synthesized at adequate levels by the body and must be obtained from the diet. The absence or shortage of a vitamin may result in a vitamin-deficiency disease. In the first half of the 20th century, a major focus of biochemistry was the identification, isolation, and characterization of vitamins. Despite accumulating evidence that people needed more than just carbohydrates, fats, and proteins in their diets for normal growth and health, it was not until the early 1900s that research established the need for trace nutrients in the diet.

Table **26.11.2**: Fat-Soluble Vitamins and Physiological Functions

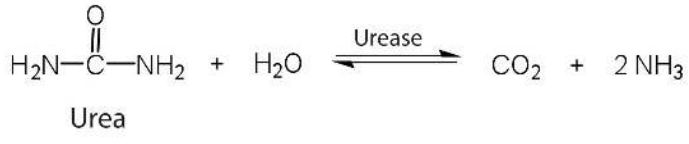
Vitamin	Physiological Function	Effect of Deficiency
vitamin A (retinol)	formation of vision pigments; differentiation of epithelial cells	night blindness; continued deficiency leads to total blindness
vitamin D (cholecalciferol)	increases the body's ability to absorb calcium and phosphorus	osteomalacia (softening of the bones); known as rickets in children
vitamin E (tocopherol)	fat-soluble antioxidant	damage to cell membranes
vitamin K (phylloquinone)	formation of prothrombin, a key enzyme in the blood-clotting process	increases the time required for blood to clot

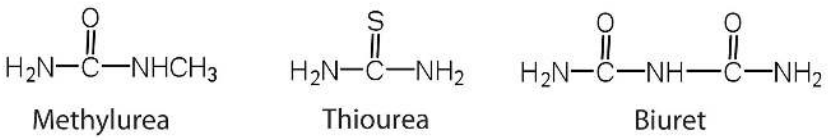
Because organisms differ in their synthetic abilities, a substance that is a vitamin for one species may not be so for another. Over the past 100 years, scientists have identified and isolated 13 vitamins required in the human diet and have divided them into two broad categories: the *fat-soluble vitamins* (Table **26.11.2**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **26.11.3**). All fat-soluble vitamins contain a high proportion of hydrocarbon structural components. There are one or two oxygen atoms present, but the compounds as a whole are nonpolar. In contrast, water-soluble vitamins contain large numbers of electronegative oxygen and nitrogen atoms, which can engage in hydrogen bonding with water. Most water-soluble vitamins act as coenzymes or are required for the synthesis of coenzymes. The fat-soluble vitamins are important for a variety of physiological functions.

Table **26.11.3**: ***Water-Soluble Vitamins and Physiological Functions***

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vitamin B_3 (niacin)	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_{12} (cyanocobalamin)	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic Acid	coenzyme A	carrier of acyl groups	—
vitamin C (ascorbic acid)	none	antioxidant; formation of collagen, a protein found in tendons, ligaments, and bone	scurvy

One characteristic that distinguishes an enzyme from all other types of catalysts is its *substrate specificity*. An inorganic acid such as sulfuric acid can be used to increase the reaction rates of many different reactions, such as the hydrolysis of disaccharides, polysaccharides, lipids, and proteins, with complete impartiality. In contrast, enzymes are much more specific. Some enzymes act on a single substrate, while other enzymes act on any of a group of related molecules containing a similar functional group or chemical bond. Some enzymes even distinguish between D- and L-stereoisomers, binding one stereoisomer but not the other. Urease, for example, is an enzyme that catalyzes the hydrolysis of a single substrate—urea—but not the closely related compounds methyl urea, thiourea, or biuret. The enzyme carboxypeptidase, on the other hand, is far less specific. It catalyzes the removal of nearly any amino acid from the carboxyl end of any peptide or protein.





Enzyme specificity results from the uniqueness of the active site in each different enzyme because of the identity, charge, and spatial orientation of the functional groups located there. It regulates cell chemistry so that the proper reactions occur in the proper place at the proper time. Clearly, it is crucial to the proper functioning of the living cell.

CONCEPT REVIEW EXERCISES

1. Distinguish between the lock-and-key model and induced-fit model of enzyme action.
2. Which enzyme has greater specificity—urease or carboxypeptidase? Explain.

ANSWERS

1. The lock-and-key model portrays an enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site. The induced fit model portrays the enzyme structure as more flexible and is complementary to the substrate only after the substrate is bound.
2. Urease has the greater specificity because it can bind only to a single substrate. Carboxypeptidase, on the other hand, can catalyze the removal of nearly any amino acid from the carboxyl end of a peptide or protein.

TAKEAWAYS

- A substrate binds to a specific region on an enzyme known as the active site, where the substrate can be converted to product.
- The substrate binds to the enzyme primarily through hydrogen bonding and other electrostatic interactions.
- The induced-fit model says that an enzyme can undergo a conformational change when binding a substrate.
- Enzymes exhibit varying degrees of substrate specificity.

EXERCISES

1. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. COOH
   b. NH_3^+
   c. OH
   d. $CH(CH_3)_2$
2. What type of interaction would occur between each group present on a substrate molecule and a functional group of the active site in an enzyme?
   a. SH
   b. NH_2
   c. C_6H_5
   d. COO^-
3. For each functional group in Exercise 1, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.
4. For each functional group in Exercise 2, suggest an amino acid whose side chain might be in the active site of an enzyme and form the type of interaction you identified.

ANSWERS

1. a. hydrogen bonding
   b. ionic bonding
   c. hydrogen bonding
   d. dispersion forces
3. a. The amino acid has a polar side chain capable of engaging in hydrogen bonding; serine (answers will vary).
   b. The amino acid has a negatively charged side chain; aspartic acid (answers will vary).
   c. The amino acid has a polar side chain capable of engaging in hydrogen bonding; asparagine (answers will vary).
   d. The amino acid has a nonpolar side chain; isoleucine (answers will vary).

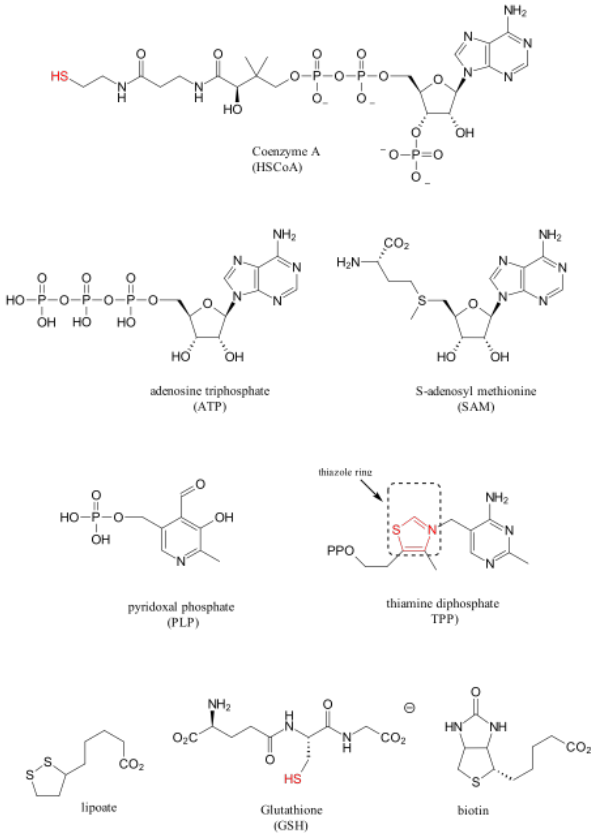
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26.12: HOW DO ENZYMES WORK? CITRATE SYNTHASE

OBJECTIVES

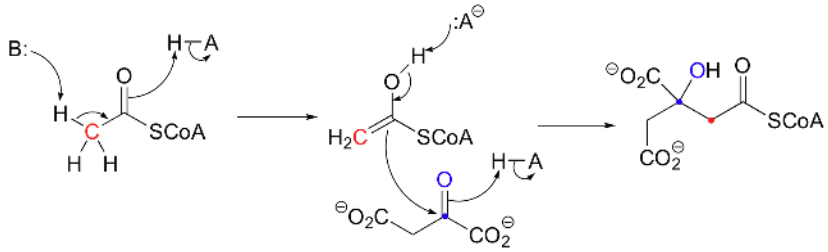
After completing this section, you should be able to

1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

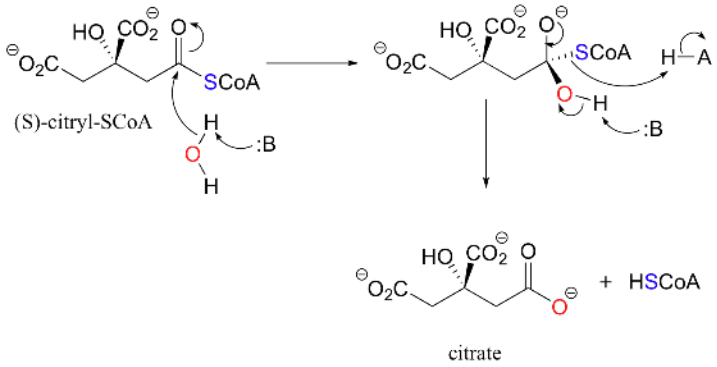


OXALOACETATE TO CITRATE CATALYZED BY CITRATE SYNTHASE

Citrate synthase is a protein with 433 amino acids with various functional groups that can react with substrates. This enzyme catalyzes oxaloacetate to eventually produce citrate as part of the citric acid (Krebs) cycle. In the first step of the citric acid (Krebs) cycle, acetyl CoA condenses with oxaloacetate to form (S)-citryl CoA. The carboxylate group of an aspartic acid (B:) on citrate synthase removes the acidic alpha proton on acetyl CoA, while a histidine site (H-A) donates a proton to form the enol. Then a second histidine site (H-A) protonates the carbonyl oxygen of oxaloacetate, while the carbon of the carbonyl is attacked by the enol. Simultaeously, that first histidine ($:A^-$) deprotonates the acetyl CoA enol. (S)-citryl CoA is generated.



The acyl group of a thioester of (S)-citryl CoA can be transferred to a water molecule in a hydrolysis reaction to converting (S)-citryl CoA to citrate. Again histidine sites on citrate synthase are an integral part of the mechanism and assist with removal and addition of protons.



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CHAPTER OVERVIEW

27: BIOMOLECULES - LIPIDS

LEARNING OBJECTIVES

- When you have completed Chapter 27, you should be able to
- fulfill all of the detailed objectives listed under each individual section.
- distinguish among fats and oils, phospholipids, prostaglandins, terpenes and steroids, and be familiar with the sources and biological roles of these substances.
- define, and use in context, the key terms introduced in this chapter.

27.0: Introduction to Lipids
27.1: Waxes, Fats, and Oils
27.2: Soap
27.3: Phospholipids
27.4: Prostaglandins and Other Eicosanoids
27.5: Terpenoids
27.6: Steroids
27.7: Biosynthesis of Steroids
27.S: Biomolecules - Lipids (Summary)

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27.0: INTRODUCTION TO LIPIDS

OBJECTIVES

After completing this section, you should be able to identify fats and steroids as being examples of lipids.

KEY TERMS

Make certain that you can define, and use in context, the key term below.

- lipid

Lipids are naturally occurring organic compounds that can be extracted from cells and tissues using nonpolar solvents. Although many lipids have complex structures, their chemistry can often be understood quite readily by applying the basic concepts you have studied in previous chapters. We begin the chapter with a study of fats and oils, and explain the different origins of these structurally similar substances. A discussion of soaps follows, as soap is obtained by the reaction of a fat with sodium hydroxide. Phospholipids are substances whose structures are somewhat similar to those of fats, except that the former contain a phosphate group. Prostaglandins are lipids that play important roles in biological systems and are of great interest to those involved in the medical and pharmaceutical professions. Terpenoids form a series of compounds whose structural similarity can be seen through the application of the isoprene rule. The chapter concludes with a discussion of steroids, with particular attention being paid to the stereochemistry of these substances.

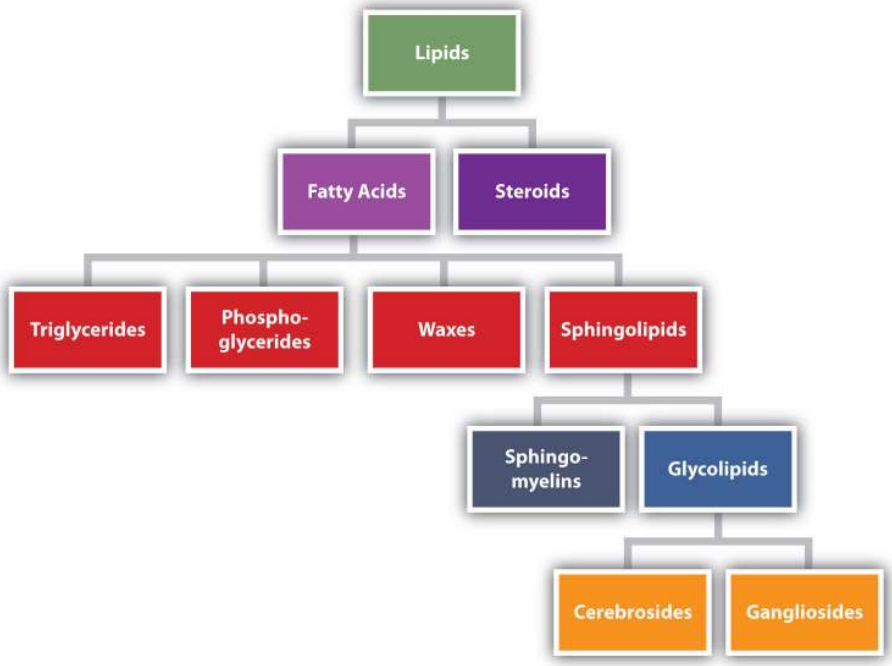


Figure **27.0.1**: Lipid Organization Based on Structural Relationships

Lipids are not defined by the presence of specific functional groups, as carbohydrates are, but by a physical property—solubility. Compounds isolated from body tissues are classified as lipids if they are more soluble in organic solvents, such as dichloromethane, than in water. By this criterion, the lipid category includes not only **fats and oils**, which are esters of the trihydroxy alcohol glycerol and fatty acids, but also compounds that incorporate functional groups derived from phosphoric acid, carbohydrates, or amino alcohols, as well as **steroid compounds** such as cholesterol. Figure **27.0.1** presents one scheme for classifying the various kinds of lipids.

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27.1: WAXES, FATS, AND OILS

OBJECTIVES

After completing this section, you should be able to

1. identify waxes as being mixtures of long-chain esters, and write the general structure for such compounds.
2. identify fats and oils as being triacylglycerols, and write a general structure for such compounds.
3. relate the physical properties of animal fats and vegetable oils to their structures.
4. predict the behaviour of a given fat or oil when it is subjected to some of the more common reactions discussed in previous units; examples would include hydrolysis, reduction and ozonolysis.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- fat
- fatty acids
- triacylglycerols

STUDY NOTES

You are not expected to memorize the trivial names or formulas of the fatty acids listed in Table **27.1.1**. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table **27.1.1**: Systematic names of some common saturated fatty acids

Trivial Name	Systematic Name
lauric acid	dodecanoic acid
myristic acid	tetradecanoic acid
palmitic acid	hexadecanoic acid
stearic acid	octadecanoic acid
arachidic acid	eicosanoic acid

Unsaturated Fatty Acids

Table **27.1.2**: Systematic names of some common unsaturated fatty acids

Trivial Name	Systematic Name
palmitoleic acid	(*Z*)-9-hexadecenoic acid
oleic acid	(*Z*)-9-octadecenoic acid
ricinoleic acid	(*Z*)-12-hydroxy-9-octadecenoic acid
linoleic acid	(*Z*,*Z*)-9,12-octadecadienoic acid
linolenic acid	(*Z*,*Z*,*Z*)-9,12,15-octadecatrienoic acid
arachidonic acid	(*Z*,*Z*,*Z*,*Z*)-5,8,11,14-eicosatetraenoic acid

The systematic names in these tables may be somewhat unfamiliar, but they are derived in exactly the same way as the names of the simpler carboxylic acids that we discussed in Chapter 20. You may wish to review the alkane names (Section 3.2) and the *E*,*Z* system (Section 7.5) to satisfy yourself that you understand how these names originate.

In many older textbooks, the term “fatty acid” is used to describe all carboxylic acids, not only those that are obtained from the hydrolysis of triacylglycerols.

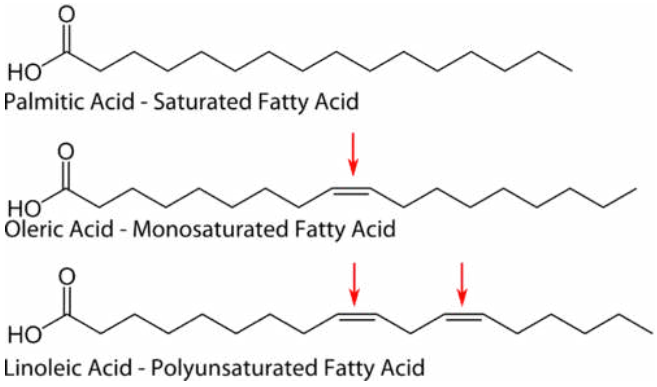
Fats play an important role in human nutrition, and most people are aware of the desirability of limiting their dietary intake of saturated fats, as these compounds have been associated with heart disease. Unsaturated fats are generally considered to be much more desirable from the point of view of good health. Notice that all the fatty acids derived from naturally occurring fats have a *Z* (i.e., cis) configuration.

Linoleic acid is an “essential” nutrient; that is, it cannot be made by the body in sufficient quantity to meet our physiological needs, and must be obtained from food. A deficiency in linoleic acid results in skin problems and liver abnormalities. Historically, linolenic and arachidonic acids were also thought to be essential nutrients, but recent research suggests that they can be synthesized in the body if sufficient linoleic acid is present.

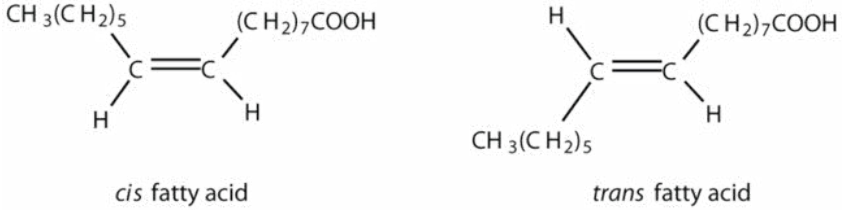
FATTY ACIDS

Fatty acids are structural components of fats, oils, and all other categories of lipids, except steroids. **Fatty acids** are long-chain carboxylic acids that have the general formula $CH_3(CH_2)_nCOOH$, where n usually ranges from 2 to 28 and is always an even number. More than 70 have been identified in nature. They are generally unbranched, and can be classified by the presence and number of carbon-to-carbon double bonds.

A **saturated fat** is a fat that consists of triglycerides whose carbon chains consist entirely of carbon-carbon single bonds. Therefore, the carbon chains are saturated with the maximum number of hydrogen atoms possible. An **unsaturated fat** is a fat that consists of triglycerides whose carbon chains contain one or more carbon-carbon double bonds. A fat with one double bond is called monounsaturated, while a fat with multiple double bonds is called polyunsaturated (see figure below).



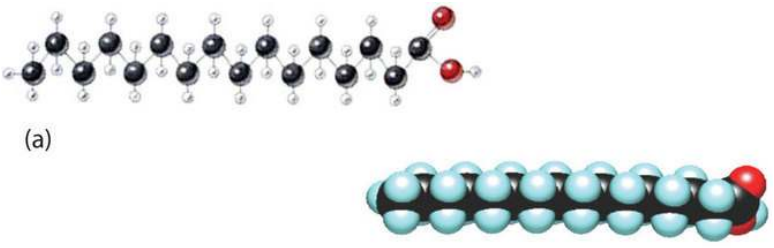
Each of the double bonds in unsaturated fatty acids can have either cis or trans stereochemistry and the type of fatty acid is further defined as a **cis fatty acid** or **trans fatty acid**. These are what are commonly referred to in food as cis or trans fats.



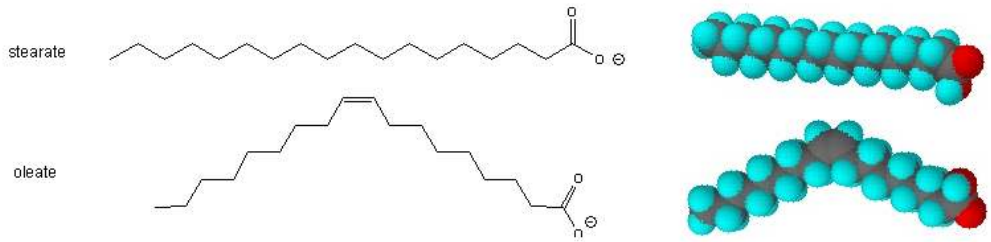
Saturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 °C
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 °C
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 °C
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 °C
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 °C

Unsaturated Fatty Acids		
Formula	**Common Name**	**Melting Point**
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 °C
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 °C

The higher melting points of the saturated fatty acids reflect the uniform rod-like shape of their molecules. Viewed as a whole, however, the saturated fatty acid molecule is relatively straight (Figure 17.1.2b). Such molecules pack closely together into a crystal lattice, maximizing the strength of dispersion forces and causing fatty acids and the fats derived from them to have relatively high melting points.

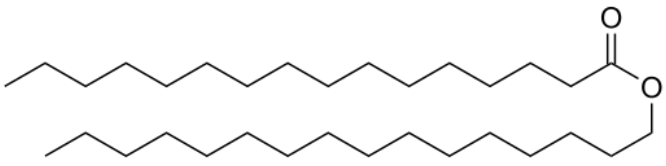


The cis-double bond(s) in the unsaturated fatty acids introduce a kink in their shape, which makes it more difficult to pack their molecules together in a stable repeating array or crystalline lattice. As a result, the intermolecular attractions of unsaturated fatty acids (and unsaturated fats) are weaker, causing these substances to have lower melting points. Most are liquids at room temperature.



WAXES

Waxes are esters of long-chain fatty acids with long-chain monohydric alcohols (one hydroxyl group). The carboxylic acid and the alcohol typically each have an even number of carbons. Cetyl palmitate is a typical wax, it is the ester of cetyl alcohol ($CH_3(CH_2)_{15}OH$) and palmitic acid ($CH_3(CH_2)_{14}COOH$). Most waxes have a similar structure.



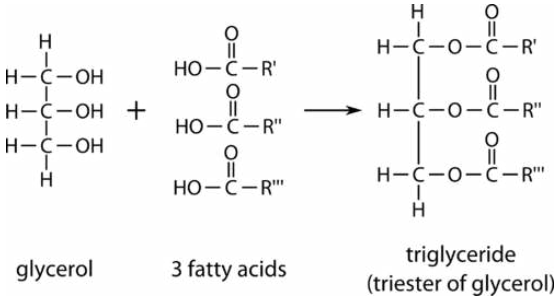
Cetyl palmitate, a typical wax ester.

Waxes are widely distributed in nature. The leaves and fruits of many plants have waxy coatings, which may protect them from dehydration and small predators. The feathers of birds and the fur of some animals have similar coatings which serve as a water repellent. Carnauba wax is valued for its toughness and water resistance. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

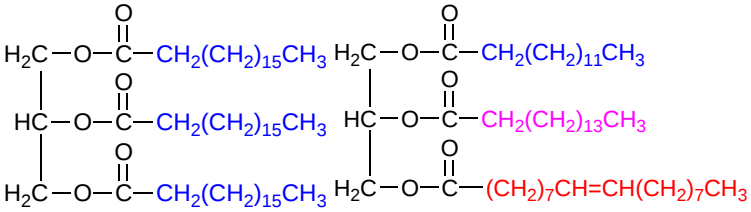
	Spermaceti	Beeswax	Carnauba wax
Alcohol	$CH_3(CH_2)_{14}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH	$CH_3(CH_2)_{28}CH_2$-OH
Fatty Acid	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{24}COOH$
Wax	$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$	$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$	$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

TRIGLYCERIDES

Fats and oils often exist as **triglycerides** (or ***triacylcylgerols*** because they are esters composed of three fatty acid units joined to *glycerol*, a trihydroxy alcohol (IUPAC name is 1,2,3-propanetriol)):



If all three OH groups on the glycerol molecule are esterified with the same fatty acid, the resulting ester is called a ***simple triglyceride***. Although simple triglycerides have been synthesized in the laboratory, they rarely occur in nature. Instead, a typical triglyceride obtained from naturally occurring fats and oils contains two or three different fatty acid components and is thus termed a ***mixed triglyceride***.



Tristearin: a simple triglyceride (left) and a mixed triglyceride (right)

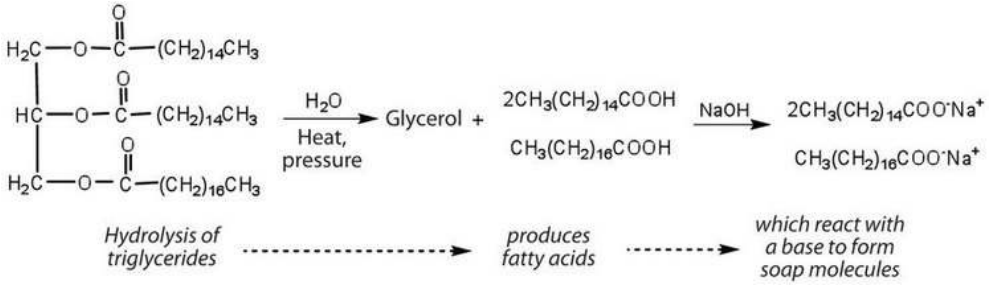
A triglyceride is called a **fat** if it is a solid at 25°C; it is called an **oil** if it is a liquid at that temperature. These differences in melting points reflect differences in the degree of unsaturation (as discussed above) and number of carbon atoms in the constituent fatty acids. Triglycerides obtained from animal sources are usually solids, while those of plant origin are generally oils. Therefore, we commonly speak of animal fats and vegetable oils. No single formula can be written to represent the naturally occurring fats and oils because they are highly complex mixtures of triglycerides in which many different fatty acids are represented. The table below shows the fatty acid compositions of some common fats and oils. The composition of any given fat or oil can vary depending on the plant or animal species it comes from as well as on dietetic and climatic factors.

Table **27.1.3**: Some common fats and oils including fatty acid content are listed below.

	glycerides				
Fat or Oil	**Saturated**		**Unsaturated**		
	Palmitic	Stearic	Oleic	Linoleic	Other
			Animal Origin		
Butter	29	9	27	4	31
Lard	30	18	41	6	5
Beef	32	25	38	3	2
			Vegetable Origin		
Corn oil	10	4	34	48	4
Soybean	7	3	25	56	9
Peanut	7	5	60	21	7
Olive	6	4	83	7	-

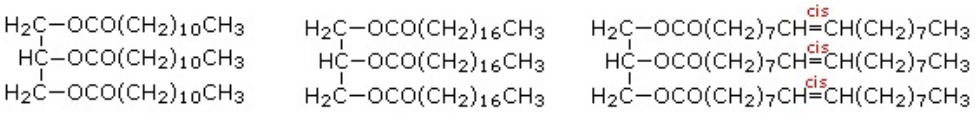
Fats and oils can participate in a variety of chemical reactions—for example, because triglycerides are esters, they can be hydrolyzed in the presence of an acid, a base, or specific enzymes known as lipases. The hydrolysis of fats and oils in the presence of a base is used to make

soap and is called saponification. Today most soaps are prepared through the hydrolysis of triglycerides (often from tallow, coconut oil, or both) using water under high pressure and temperature [(~50 atm or 5,000 kPa) and 200°C]. Sodium carbonate or sodium hydroxide is then used to convert the fatty acids to their sodium salts (soap molecules):

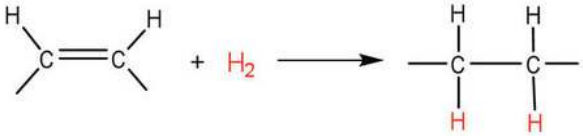


Chemical reaction of the saponification (base hydrolysis) of a triglyceride.

As might be expected from the properties of the fatty acids, fats have a predominance of saturated fatty acids, and oils are composed largely of unsaturated acids. Thus, the melting points of triglycerides reflect their composition, as shown by the following examples. Natural mixed triglycerides have somewhat lower melting points, the melting point of lard being near 30 ° C, whereas olive oil melts near -6 ° C. Since fats are valued over oils by some Northern European and North American populations, vegetable oils are extensively converted to solid triglycerides (e.g. Crisco) by partial hydrogenation of their unsaturated components. Some of the remaining double bonds are isomerized (to trans) in this operation. These saturated and trans-fatty acid glycerides in the diet have been linked to long-term health issues such as atherosclerosis.



The double bonds in fats and oils can undergo hydrogenation and also oxidation. The hydrogenation of vegetable oils to produce semisolid fats is an important process in the food industry. Chemically, it is essentially identical to the catalytic hydrogenation reaction described for alkenes.



In commercial processes, the number of double bonds that are hydrogenated is carefully controlled to produce fats with the desired consistency (soft and pliable). Inexpensive and abundant vegetable oils (canola, corn, soybean) are thus transformed into margarine and cooking fats.

Many people have switched from butter to margarine or vegetable shortening because of concerns that saturated animal fats can raise blood cholesterol levels and result in clogged arteries. However, during the hydrogenation of vegetable oils, an isomerization reaction occurs that produces the trans fatty acids mentioned in the opening essay. However, studies have shown that trans fatty acids also raise cholesterol levels and increase the incidence of heart disease. Trans fatty acids do not have the bend in their structures, which occurs in cis fatty acids and thus pack closely together in the same way that the saturated fatty acids do. Consumers are now being advised to use polyunsaturated oils and soft or liquid margarine and reduce their total fat consumption to less than 30% of their total calorie intake each day.

? EXERCISE 27.1.1

Why do unsaturated fatty acids have lower melting points than saturated fatty acids?

Answer

Unsaturated fatty acids cannot pack as tightly together as saturated fatty acids due to the presence of the cis double bond that puts a “kink” or bend in the hydrocarbon chain.

EXERCISE 27.1.2

Classify each fatty acid as saturated or unsaturated and indicate the number of carbon atoms in each molecule.

a. palmitoleic acid
b. myristic acid
c. linoleic acid

Answer

a. unsaturated; 16 carbon atoms
b. saturated; 14 carbon atoms
c. unsaturated; 18 carbon atoms

EXERCISE 27.1.3

Write the condensed structural formula for each fatty acid.

a. lauric acid
b. palmitoleic acid
c. linoleic acid

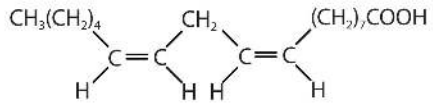
Answer

a. $CH_3(CH_2)_{10}COOH$
b. $CH_3(CH_2)_5CH{=}CH(CH_2)_7COOH$
c. $CH_3(CH_2)_3(CH_2CH{=}CH)_2(CH_2)_7COOH$

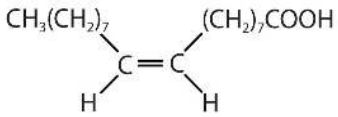
EXERCISE 27.1.4

Arrange these fatty acids (all contain 18 carbon atoms) in order of increasing melting point. Justify your arrangement.

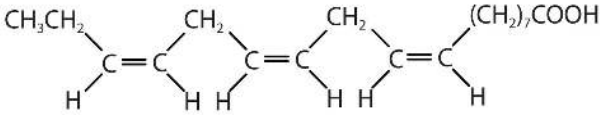
a)



b)



c)



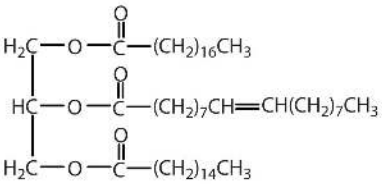
Answer

c < a < b; an increase in the number of double bonds will lower the melting point because it is more difficult to closely pack the fatty acids together.

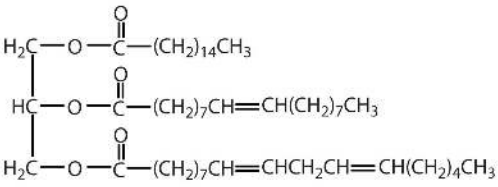
EXERCISE 27.1.5

Which of these triglycerides would you expect to find in higher amounts in oils? In fats? Justify your choice.

https://chem.libretexts.org/@go/page/36482



(a)



(b)

Answer

The triglyceride labeled as (a) is expected to be present in higher amounts in fats because it is composed of a greater number of saturated fatty acids. The triglyceride labeled as (b) is expected to be present in higher amounts in oils because it is composed of a greater number of unsaturated fatty acids.

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27.2: SOAP

LEARNING OBJECTIVES

After completing this section, you should be able to

- write an equation to represent the formation of a soap.
  - identify the structure of the fat required to produce a given soap.
  - identify the structure of a soap, given the structure of the fat from which it is produced.
- describe the mechanism by which soaps exert their cleansing action.
- give a chemical explanation of the problems encountered when carboxylate soaps are used in hard-water areas, and explain how they may be overcome by the use of sulphonate detergents.

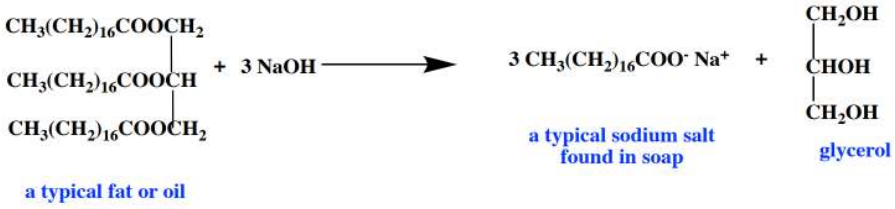
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

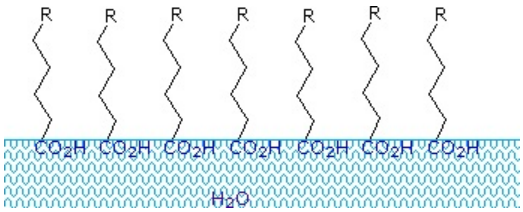
- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

Soap making has remained unchanged over the centuries. The ancient Roman tradition called for mixing rain water, potash and animal tallow (rendered form of beef or mutton fat). Making soap was a long and arduous process. First, the fat had to be rendered (melted and filtered). Then, potash solution was added. Since water and oil do not mix, this mixture had to be continuously stirred and heated sufficiently to keep the fat melted. Slowly, a chemical reaction called saponification would take place between the fat and the hydroxide which resulted in a liquid soap. When the fat and water no longer separated, the mixture was allowed to cool. At this point salt, such as sodium chloride, was added to separate the soap from the excess water. The soap came to the top, was skimmed off, and placed in wooden molds to cure. It was aged many months to allow the reaction to run to completion.

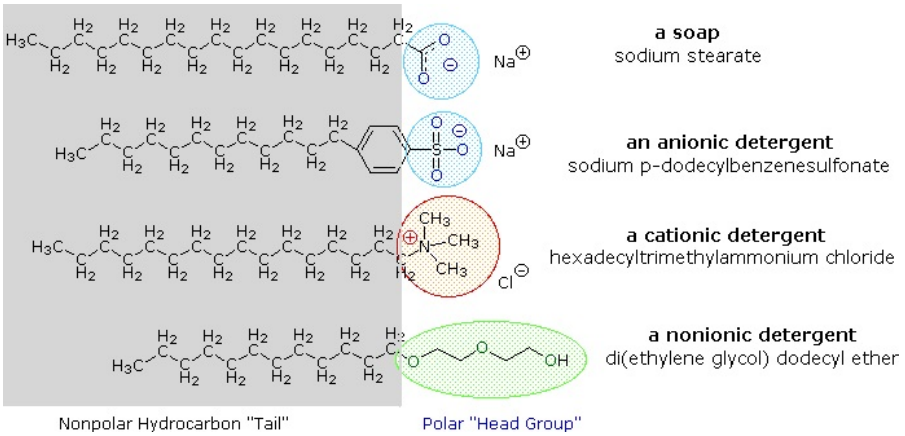
All soap is made from fats and oils, mixed with alkaline (basic) solutions. There are many kinds of fats and oils, both animal and vegetable. As previously discussed, fats are usually solid at room temperature, but many oils are liquid at room temperature. Liquid cooking oils originate from corn, peanuts, olives, soybeans, and many other plants. For making soap, all different types of fats and oils can be used – anything from lard to exotic tropical plant oils.



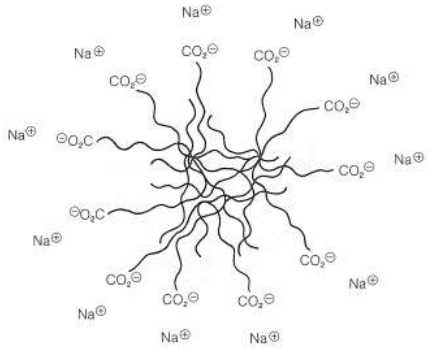
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids made up of ten or more carbon atoms are nearly insoluble in water, and because of their lower density, float on the surface when mixed with water. Unlike paraffin or other alkanes, which tend to puddle on the waters surface, these fatty acids spread evenly over an extended water surface, eventually forming a monomolecular layer in which the polar carboxyl groups are hydrogen bonded at the water interface, and the hydrocarbon chains are aligned together away from the water. This behavior is illustrated in the diagram on the right. Substances that accumulate at water surfaces and change the surface properties are called **surfactants**.



Alkali metal salts of fatty acids are more soluble in water than the acids themselves, and the amphiphilic character of these substances also make them strong surfactants. The most common examples of such compounds are soaps and detergents, four of which are shown below. Note that each of these molecules has a nonpolar hydrocarbon chain, the "tail", and a polar (often ionic) "head group". The use of such compounds as cleaning agents is facilitated by their surfactant character, which lowers the surface tension of water, allowing it to penetrate and wet a variety of materials.



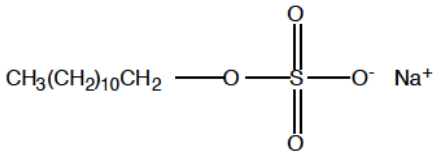
When minute amounts of soaps are put into water, instead of forming simple solutions, the molecules become concentrated at the surface of the water, with the saltlike ends sticking down into the water and the hydrocarbon chains forming a layer on the surface. This arrangement greatly reduces the surface tension of the water and contributes to the startling properties of soap films and bubbles. At higher concentrations, the solutions become turbid as the result of **micelle** formation. Micelles are spherical aggregates of soap molecules, wherein the hydrocarbon chains form a region of low polarity that is stabilized by having the polar salt ends of the molecules in contact with the water. By gathering the hydrophobic chains together in the center of the micelle, disruption of the hydrogen bonded structure of liquid water is minimized, and the polar head groups extend into the surrounding water where they participate in hydrogen bonding.



The importance of soap to human civilization is documented by history, but some problems associated with its use have been recognized. One of these is caused by the weak acidity (pKa ca. 4.9) of the fatty acids. Solutions of alkali metal soaps are slightly alkaline (pH 8 to 9) due to hydrolysis. If the pH of a soap solution is lowered by acidic contaminants, insoluble fatty acids precipitate and form a scum. A second problem soaps are less effective in hard water, which is water that contains a significant concentration of magnesium, calcium and iron ions. These ions form precipitates with soap molecules, and this precipitate is often seen as a gray line on a bathtub or sink and is often called “soap scum”. Since soap forms a precipitate with these ions, it means that many of the soap molecules are no longer present in the solution. Therefore, soap will form fewer suds in hard water. “Soft water” is water that contains very few or no ions that precipitate with soap. Soap will therefore be much more effective in soft water than in hard water.

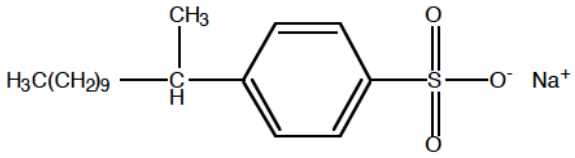
These problems have been alleviated by the development of synthetic soaps called detergents. Detergents are similar to soaps in that they have a charged head group and a long nonpolar tail group, but they are not prepared from natural fats or oils. Detergents are useful because they do not form precipitates with magnesium, iron or calcium ions, which means that they work in both soft and hard water. By using a much stronger acid for the polar head group, water solutions of detergents are less sensitive to pH changes. Also the sulfonate functions used for virtually all anionic detergents confer greater solubility on micelles incorporating the alkaline earth cations found in hard water. Variations on the detergent theme have led to the development of other classes, such as the cationic and nonionic detergents shown above. Cationic detergents often exhibit germicidal properties, and their ability to change surface pH has made them useful as fabric softeners and

hair conditioners. These versatile chemical "tools" have dramatically transformed the household and personal care cleaning product markets over the past fifty years



Sodium Lauryl Sulfate (a non-biodegradable detergent)

After detergents started being widely used, it was discovered that they were not broken down in sewage treatment plants. Many streams and lakes became contaminated with detergents and large amounts of foam appeared in natural waters. Biodegradable detergents were then developed. Shown below is an example of a biodegradable detergent, sodium laurylbenzenesulfonate.



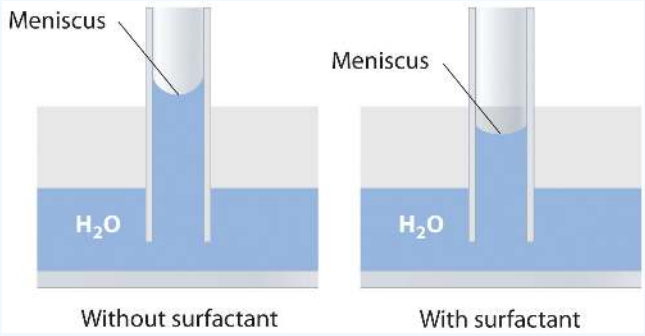
Sodium Laurylbenzenesulfonate (a biodegradable detergent)

EXERCISE 27.2.1

Explain how soaps or surfactants decrease the surface tension of a liquid. How does the meniscus of an aqueous solution in a capillary change if a surfactant is added? Illustrate your answer with a diagram.

Answer

Adding a soap or a surfactant to water disrupts the attractive intermolecular interactions between water molecules, thereby decreasing the surface tension. Because water is a polar molecule, one would expect that a soap or a surfactant would also disrupt the attractive interactions responsible for adhesion of water to the surface of a glass capillary. As shown in the sketch, this would decrease the height of the water column inside the capillary, as well as making the meniscus less concave.



EXERCISE 27.2.2

Draw the structure of calcium stearate, a component of soap scum.

Answer

$(C_{17}H_{35}COO)_2Ca^{2+}$

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27.3: PHOSPHOLIPIDS

LEARNING OBJECTIVES

After completing this section, you should be able to

- draw the general structure of a phosphoglyceride.
- describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

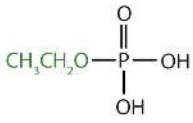
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

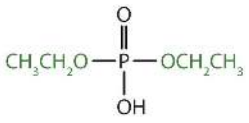
- phosphoglyceride
- phospholipid

PHOSPHATE ESTERS

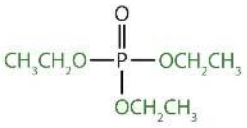
Similarly to carboxylic acids, inorganic acids such as nitric acid (HNO_3), sulfuric acid (H_2SO_4), and phosphoric acid (H_3PO_4) also can form esters. The esters of phosphoric acid are especially important in biochemistry. A phosphoric acid molecule can form a monoalkyl, a dialkyl, or a trialkyl ester by reaction with one, two, or three molecules of an alcohol.



Ethyl dihydrogen phosphate

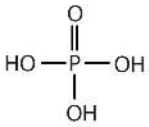


Diethyl hydrogen phosphate

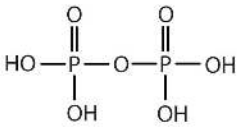


Triethyl phosphate

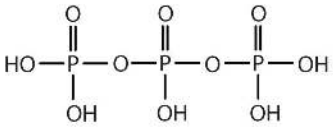
Esters of pyrophosphoric acid and triphosphoric acid are also important in biochemistry.



Phosphoric acid



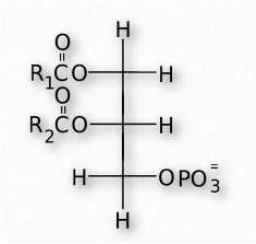
Pyrophosphoric acid



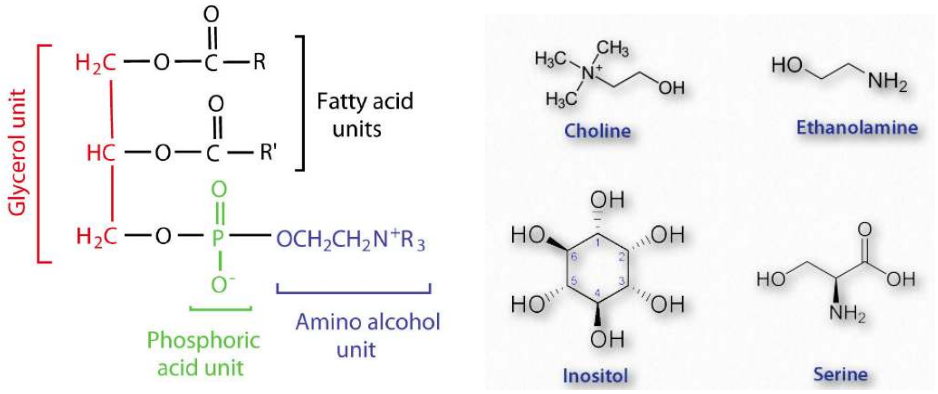
Triphosphoric acid

PHOSPHOLIPIDS

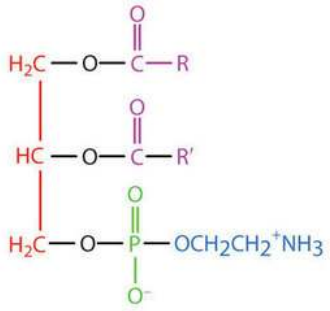
The two main types of phospholipids are **glycerophospholipids** and **sphingomyelins**. Glycerophospholipids are important components of the lipid bilayer of cellular membranes. Glycerophospholipids are structurally related to fats, as both are derived from phosphatidic acid, which has the basic structure of glycerol with two ester bonds with fatty acids and one ester bond with phosphoric acid.



Phosphatidic acid is converted into a glycerophospholipid by esterifying various groups, such as ethanolamine, serine, choline, inositol, and others to the phosphate of phosphatidic acid. These compounds have a chiral center at C2 and have an R configuration when found in nature.

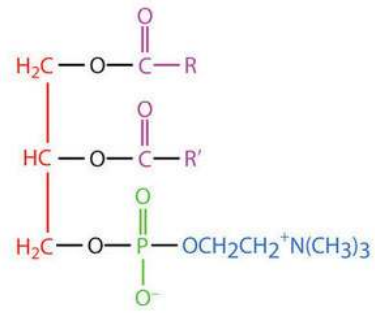


The **phosphatidylethanolamines** are found in all living cells and are one of the most common phosphatides. They are common constituents of brain tissue and in the spinal cord, making up as much as 45% of the total phospholipids. Phosphatidylethanolamines are asymmetrically distributed across membranes, being preferentially located on the inner leaflet (closest to the cytoplasm) of the plasma membrane.



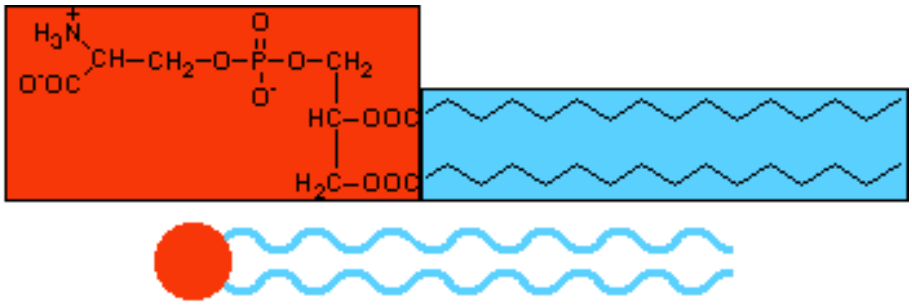
Phosphatidylethanolamine
(cephalin)

Metabolically, phosphatidylethanloamines are precursors of **phosphatidylcholines**. Phosphatidylcholines are another group of important membrane components. They tend to be found more commonly on the outer leaflet of the plasma membrane. Nutritionally, the compounds are readily obtained from eggs and soybeans. Phosphatidylcholines are moved across membranes by Phosphatidylcholine transfer protein (PCTP).



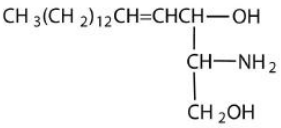
Phosphatidycholine
(lecithin)

Like the phosphatidylethanolamines, **phosphatidylserines** are preferentially located on the inner leaflet of the plasma membrane. When apoptosis (cell suicide) occurs, the preferential distribution is lost and the phosphatidylserines appear on the outer leaflet where they serve as a signal to macrophages to bind and destroy the cell.

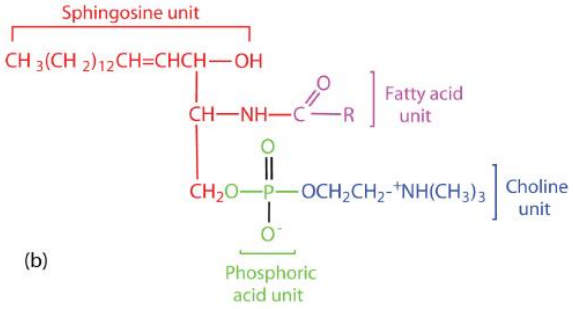


Phosphatidylserine, a polar phospholipid. A serine head group has been added on to a phosphate group on a glycerol functional group, all shown in orange. The fatty acid chains are in blue.

Sphingomyelins, the simplest sphingolipids, each contain a fatty acid, a phosphoric acid, sphingosine, and choline. Because they contain phosphoric acid, they are also classified as phospholipids. Sphingomyelins are important constituents of the myelin sheath surrounding the axon of a nerve cell. Multiple sclerosis is one of several diseases resulting from damage to the myelin sheath.



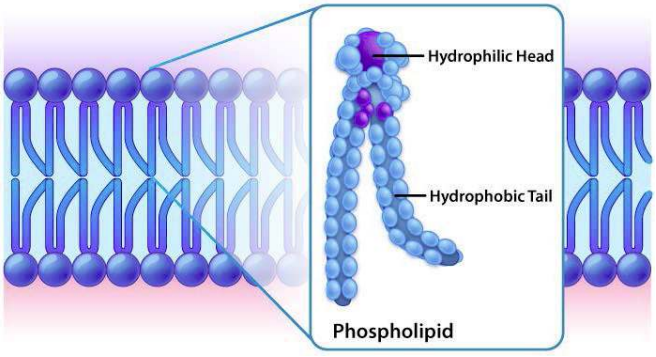
(a) Sphingosine



(b)

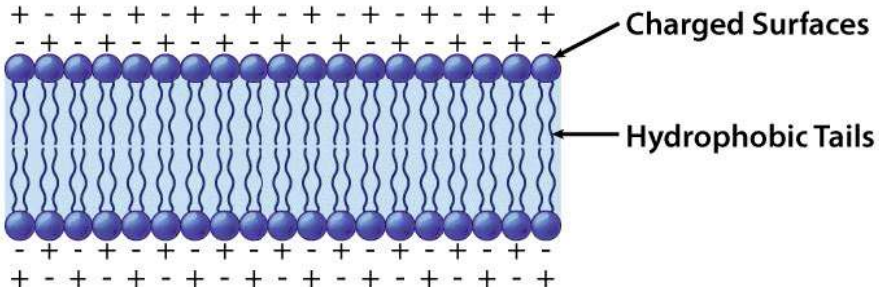
LIPID BILAYER

In one sense the polar lipids are like the anions of fatty acids, only more so. They contain two hydrophobic hydrocarbon tails and a head which may have several electrically charged sites. As in the case of soap and detergent molecules, the tails of polar lipids tend to avoid water and other polar substances, but the heads are quite compatible with such environments.



Lipid bilayer closeup Image by Aleia Kim

As ionic amphiphiles, phospholipids aggregate or self-assemble when mixed with water, but in a different manner than the soaps and detergents. Because of the two pendant alkyl chains present in phospholipids and the unusual mixed charges in their head groups, micelle formation is unfavorable relative to a bilayer structure. If a phospholipid is smeared over a small hole in a thin piece of plastic immersed in water, a stable planar bilayer of phospholipid molecules is created at the hole. As shown in the following diagram, the polar head groups on the faces of the bilayer contact water, and the hydrophobic alkyl chains form a nonpolar interior.



Organization of the lipid bilayer Image by Aleia Ki

The polar lipids are most commonly found as components of cell walls and other membranes. Nearly all hypotheses regarding membrane structure take as a fundamental component a lipid bilayer. Bilayers made in the laboratory have many properties in common with membranes. Ions such as Na^+, K^+, and Cl^- cannot pass through them, but water molecules can. Certain carrier molecules can transport K^+ and other ions across a bilayer, apparently by wrapping a hydrophobic cloak around them to disguise their charges. Membrane proteins in a bilayer also allow for transport of ions and other molecules across the bilayer which could not cross otherwise.

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27.4: PROSTAGLANDINS AND OTHER EICOSANOIDS

LEARNING OBJECTIVES

After completing this section, you should be able to

- describe the general structure of the prostaglandins, and identify a prostaglandin from a given list of organic structures.
- identify at least two important biological functions of prostaglandins.

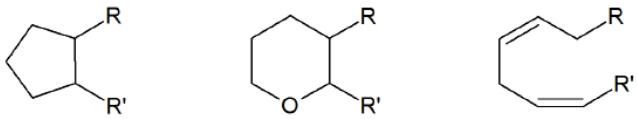
KEY TERMS

Make certain that you can define, and use in context, the key terms below.

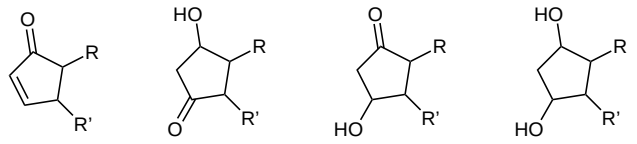
- eicosanoid
- prostaglandin

EICOSANOIDS

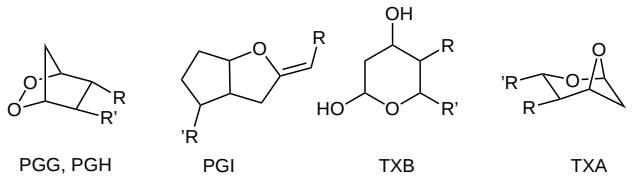
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body tissues is tied to the metabolism of the essential fatty acid arachadonic acid (5,8,11,14-eicosatetraenoic acid) they are classified as **eicosanoids**. Many properties of the common drug aspirin result from its effect on the cascade of reactions associated with these hormones. Eicosanoids include prostaglandins, leukotrienes, and thromboxanes.



Eicosanoids are primarily named off the ring system present in the molecule prostaglandin (PG), thromboxane (TX), leukotriene (LT). Common substitution patterns on the ring system are indicated with a letter in the name. Also, the number of double bonds in the molecule is indicated with a subscript number.

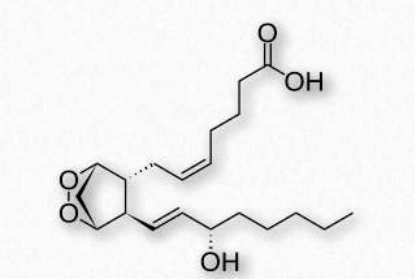


Prostaglandin structures for PGA, PGD, PGE and PGF



Structures for prostaglandins PGG, PGH and PGI and thromboxanes TXA and TXB

Thus the molecule PGH_2 means that it has the prostaglandin ring system with a type H Substitution pattern. The subscript 2 indicated that the molecule contains two double bonds.



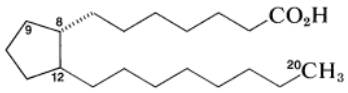
Prostaglandin PGH_2

PROSTAGLANDINS

Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, are like hormones in that they act as chemical messengers, but do not move to other sites, but work right within the cells where they are synthesized.

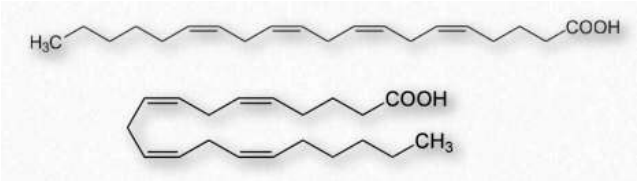
Prostaglandins are found in low concentrations distributed in a large number of organs, tissues, and body fluids of mammals. They exhibit a broad spectrum of physiological activity and are remarkably potent. Their precise biological role is not entirely clear, but they are known to induce strong contractions of smooth muscle tissue (lungs, uterus) and to lower blood pressure and sodium levels. Prostaglandins also have been implicated in the control of pituitary hormones released from the hypothalamus, and in the incidence of "pain" as a response to fever and inflammation. In fact, the analgesic property of aspirin possibly may result from the inhibition of prostaglandin biosynthesis

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon prostanoic acid, which is a C20 fatty acid in which there is a cyclopentane ring formed by connecting the C8 and C12 positions.



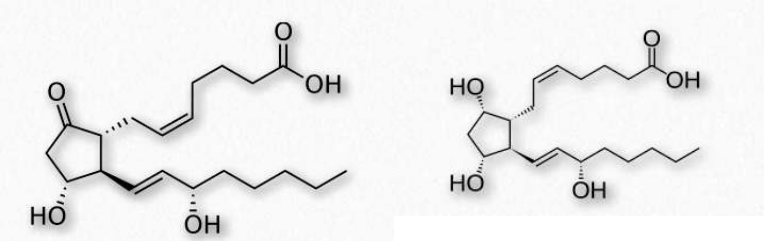
prostanoic acid

They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

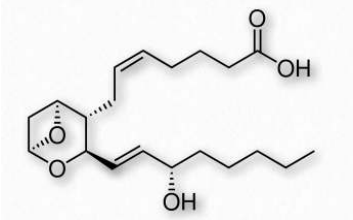
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

THROMBOXANES

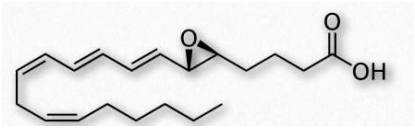
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

LEUKOTRIENES

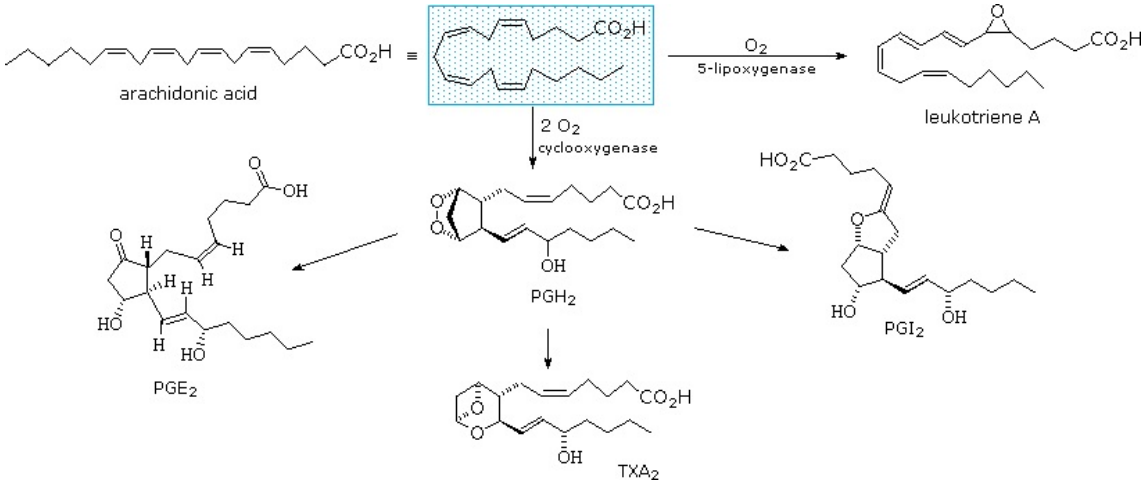
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are found in leukocytes and other immunocompetent cells, such as neutrophils, monocytes, mast cells, eosinophils, and basophils. Leukotrienes are associated with production of histamines and prostaglandins, which act as mediators of inflammation. Leukotrienes also trigger contractions in the smooth muscles of the bronchioles. When overproduced, they may pay a role in asthma and allergic reactions. Some treatments for asthma aim at inhibiting production or action of leukotrienes.



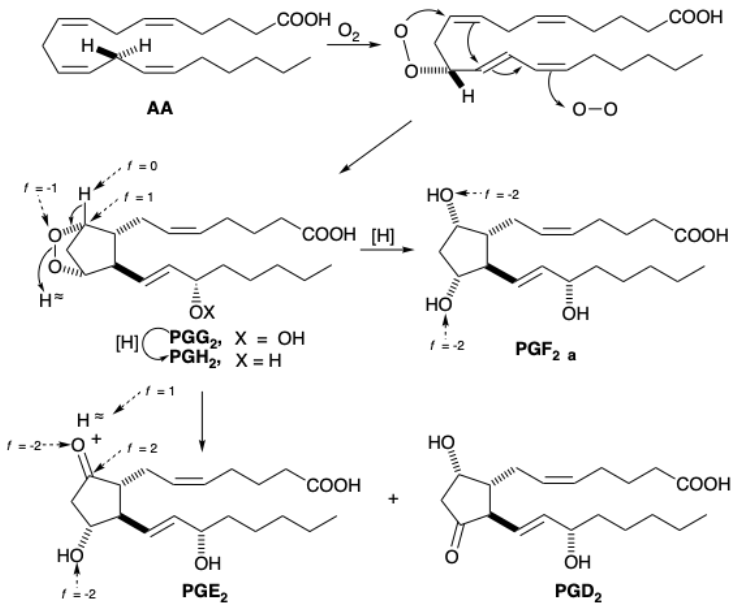
Leukotriene A_4 (LTA_4)

EICOSANOID BIOSYNTHESIS

The biosynthesis of eicosanoids begins with the reaction of arachidonic acid with O_2 which can be catalyzed by two different cyclooxygenase enzymes (COX-1 & COX-2).



In nature, prostaglandins arise by an oxidative cyclization of poly-unsaturated twenty-carbon fatty acids, which begins with enantiospecific removal of the L-hydrogen atom of the prochiral methylene group at C-13 coupled with enantiospecific introduction of oxygen at the allylic C-15 position. Subsequent cyclization and termination by addition of a second molecule of oxygen leads to a 15-hydroperoxy bicyclic peroxide (PGG), that is reduced to a 15-hydroxy bicyclic peroxide (PGH). These intermediates, known as prostaglandin endoperoxides, have been isolated and shown to yield prostaglandins. Reduction of the peroxy bridge gives PGF, while disproportionation gives β-hydroxy ketones PGE and PGD. The carbons in prostaglandins are numbered one to twenty starting at the carboxyl carbon and following the numbering system of the biosynthetic precursor fatty acids.



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27.5: TERPENOIDS

OBJECTIVES

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyze the structure of a given terpene in terms of the isoprene rule.
3. classify a given terpene structure according to the number of isoprene units present; that is, determine whether a given terpene is a monoterpene, sesquiterpene, diterpene, etc.
4. identify and draw the structure of the precursors of isopentenyl diphosphate: (*R*) mevalonate or 1-deoxy-D-xylulose 5-phosphate.

KEY TERMS

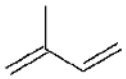
Make certain that you can define, and use in context, the key terms below.

- isoprene rule
- terpenoid
- terpene

STUDY NOTES

You are not expected to memorize all the details of the synthetic mechanisms for terpenoids. However, you should know the overall general synthetic pathway illustrated under "Terpenoid Biosynthesis." As you read through the details of these mechanisms, realize that they may be complex, but they are based on experimental evidence. You should also note the important role of enzymes in many natural systems transformations. Finally, you will recognize that essentially, individual steps are often reactions you have already encountered in previous sections.

The terpenoids (aka isoprenoids) are a large (estimated 60% of known natural products) and diverse group of lipids derived from five-carbon isoprene units assembled in thousands of combinations. Technically a terpenoid contains oxygen, while a terpene is a hydrocarbon. Often the two terms are used to refer collectively to both groups.



isoprene

ISOPRENE RULE

Compounds classified as terpenes constitute what is arguably the largest and most diverse class of natural products. A majority of these compounds are found only in plants, but some of the larger and more complex terpenes (e.g. squalene & lanosterol) occur in animals. Terpenes incorporating most of the common functional groups are known, so this does not provide a useful means of classification. Instead, the number and structural organization of carbons is a definitive characteristic. Terpenes may be considered to be made up of isoprene (more accurately isopentane) units, an empirical feature known as the isoprene rule. Because of this, terpenes usually have $5n$ carbon atoms (n is an integer), and are subdivided as follows:

Classification	Isoprene Units	Carbon Atoms
monoterpenes	2	C_{10}
sesquiterpenes	3	C_{15}
diterpenes	4	C_{20}
sesterterpenes	5	C_{25}
triterpenes	6	C_{30}

Isoprene itself, a C_5H_8 gaseous hydrocarbon, is emitted by the leaves of various plants as a natural byproduct of plant metabolism. Next to methane it is the most common volatile organic compound found in the atmosphere. Examples of C10 and higher terpenes, representing the

four most common classes are shown in the following diagrams. Most terpenes may be structurally dissected into isopentane segments. How this is done can be seen in the diagram directly below.

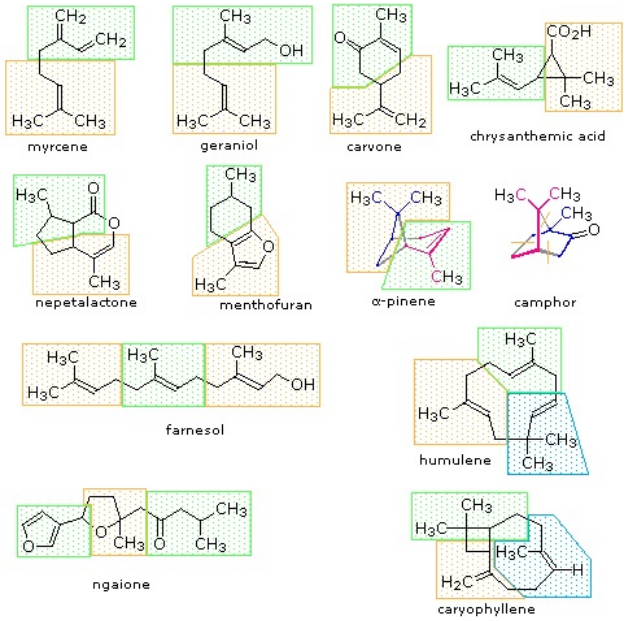


Figure 27.5.1: Monoterpenes and sesquiterpenes

The isopentane units in most of these terpenes are easy to discern, and are defined by the shaded areas. In the case of the monoterpene camphor, the units overlap to such a degree it is easier to distinguish them by coloring the carbon chains. This is also done for alpha-pinene. In the case of the triterpene lanosterol we see an interesting deviation from the isoprene rule. This thirty carbon compound is clearly a terpene, and four of the six isopentane units can be identified. However, the ten carbons in center of the molecule cannot be dissected in this manner. Evidence exists that the two methyl groups circled in magenta and light blue have moved from their original isoprenoid locations (marked by small circles of the same color) to their present location. This rearrangement is described in the biosynthesis section. Similar alkyl group rearrangements account for other terpenes that do not strictly follow the isoprene rule.

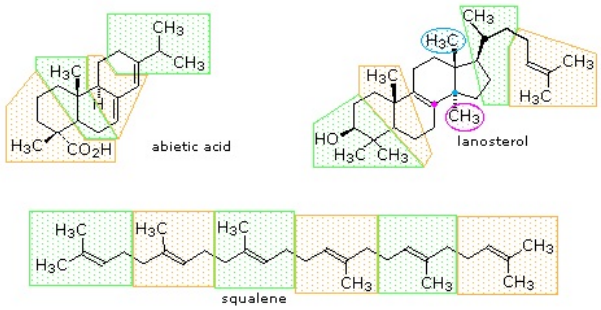
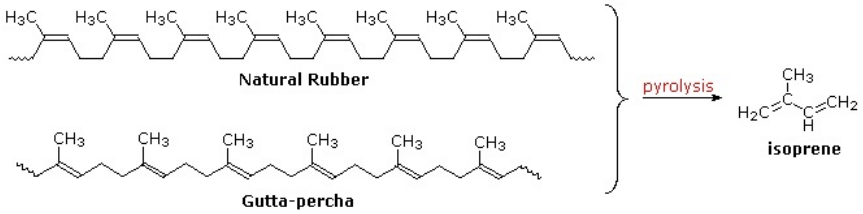


Figure 27.5.2: Triterpenes

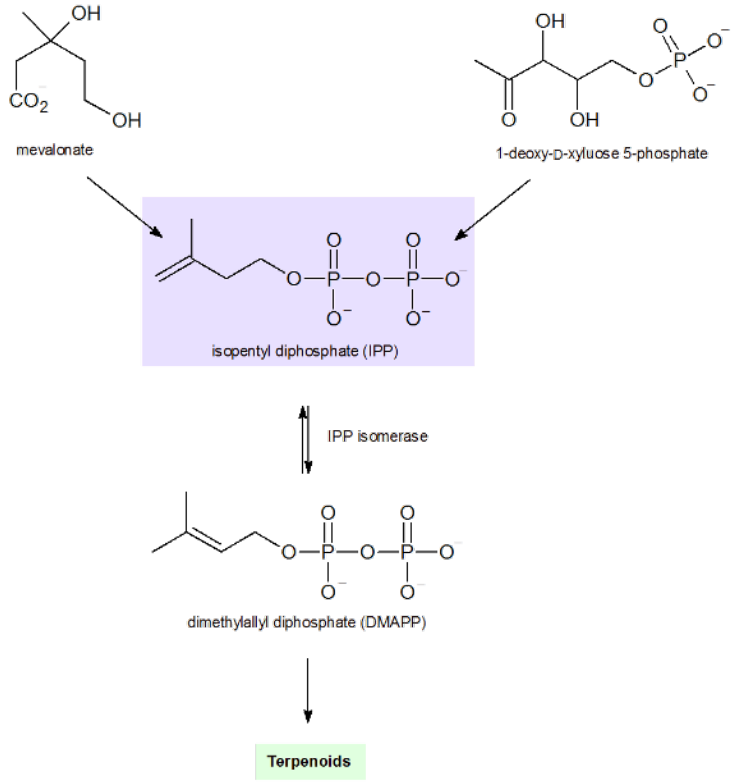
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, and exhibits all the expected reactions of the C=C function. Bromine, hydrogen chloride and hydrogen all add with a stoichiometry of one molar equivalent per isoprene unit. Ozonolysis of rubber generates a mixture of levulinic acid ($CH_3COCH_2CH_2CO_2H$) and the corresponding aldehyde. Pyrolysis of rubber produces the diene isoprene along with other products.



The double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation. This is reflected in the physical properties of rubber. Despite its high molecular weight (about one million), crude latex rubber is a soft, sticky, elastic substance. Chemical modification of this material is normal for commercial applications. Gutta-percha (structure above) is a naturally occurring E-isomer of rubber. Here the hydrocarbon chains adopt a uniform zig-zag or rod like conformation, which produces a more rigid and tough substance. Uses of gutta-percha include electrical insulation and the covering of golf balls.

TERPENOID BIOSYNTHESIS

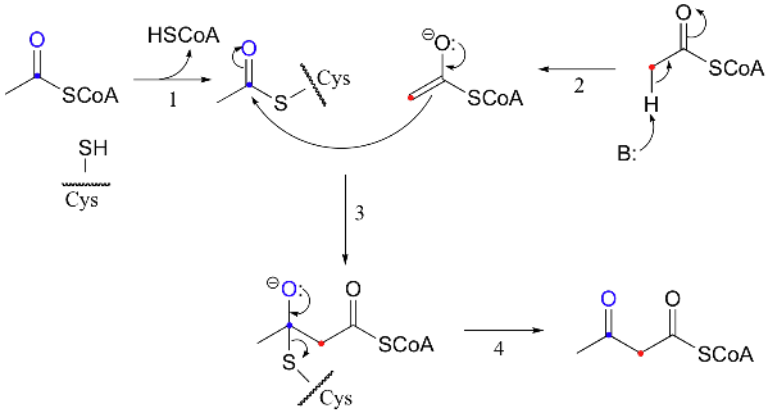
While we can identify isoprene units within a terpenoid structure and use that in its classification, the building block for terpenoid synthesis in nature is isopentenyl diphosphate (formerly called isopentenyl pyrophosphate and abbreviated IPP). There are two major routes to the synthesis of IPP; namely (1) the mevalonate pathway and (2) the 1-deoxyxylulose pathway.



MEVALONATE PATHWAY

Step 1 - Claisen Condensation

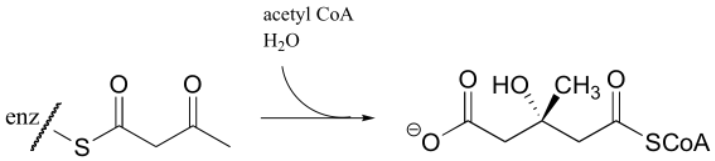
An early step in the biosynthesis of cholesterol and other 'isoprenoid' compounds is a Claisen condensation between two acetyl CoA molecules. An initial trans-thioesterase process transfers the acetyl group of the first acetyl CoA to an enzymatic cysteine (Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl CoA is deprotonated, forming an enolate (Reaction 2).



The enolate carbon attacks the electrophilic thioester carbon, forming a tetrahedral intermediate (Reaction 3) which quickly collapses to expel the cysteine thiol (Reaction 4) and produce acetoacetyl CoA.

Step 2 - Aldol Condensation

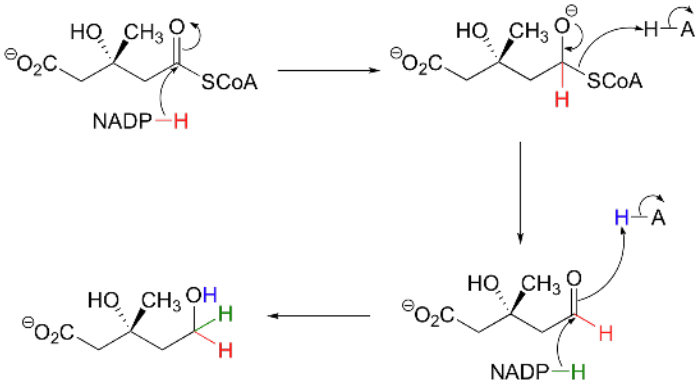
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

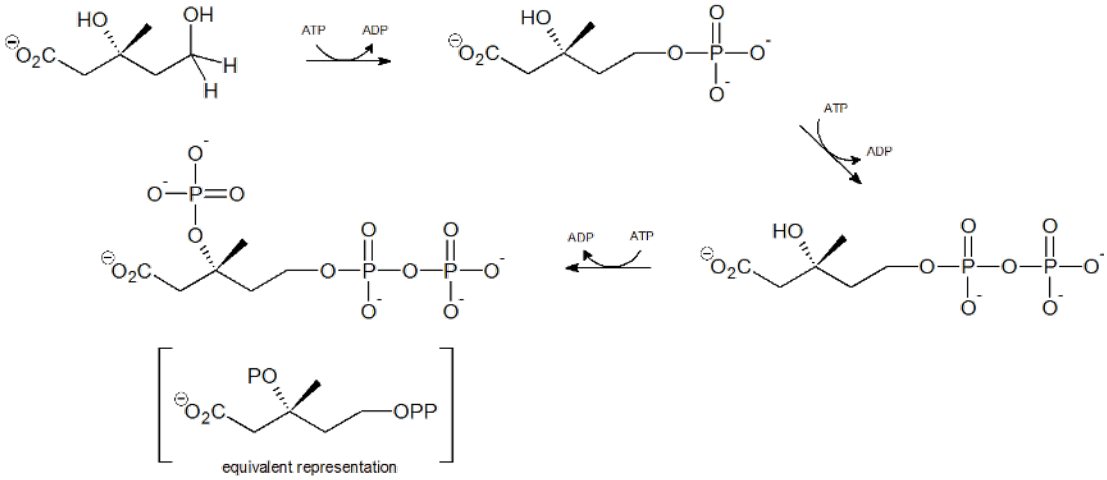
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

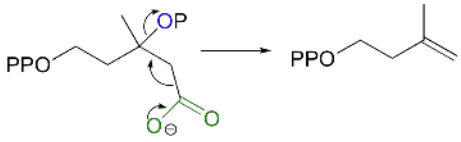
Step 4 - Mevalonate Phosphorylation

Two phsophorylations by adenosine triphosphate (ATP) occur at the terminal hydroxyl/phosphorus group through nucleophilic substitution, followed by a third ATP phosphorylation of the tertiary hydroxyl group.



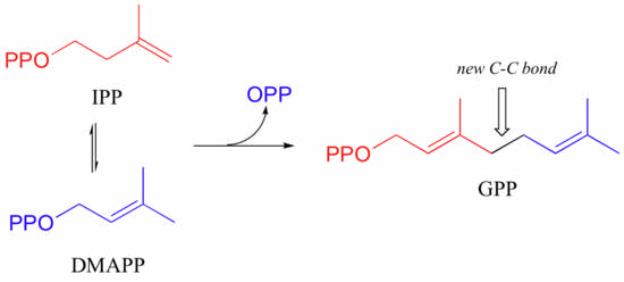
Step 5 - Decarboxylation

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

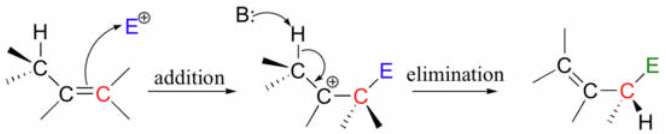


CONVERSION OF IPP TO TERPENOIDS

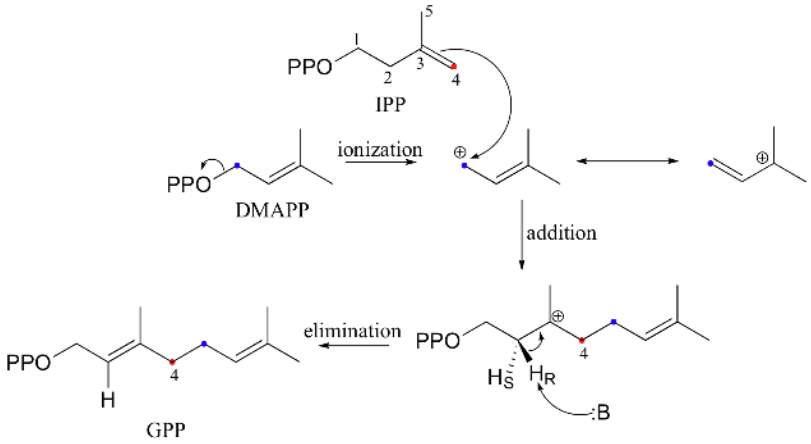
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

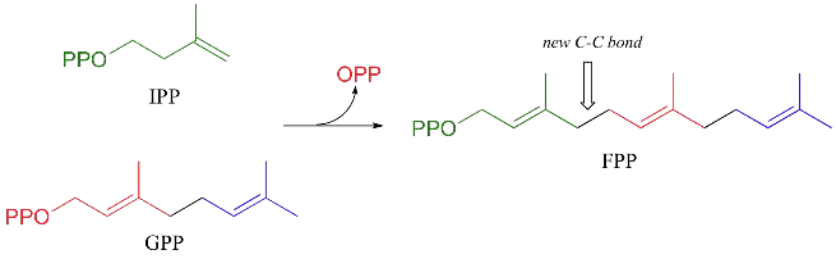


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

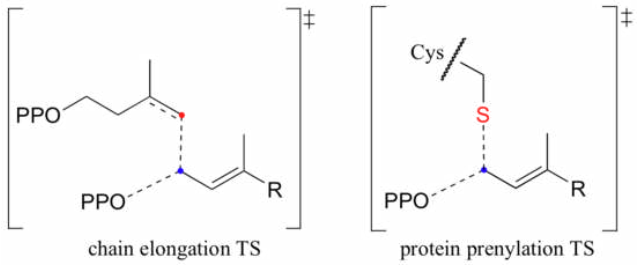


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double bond in the GPP product. Notice that the enzyme specifically takes the *pro-R* proton in this step.

To continue the chain elongation process, another IPP molecule can then condense, in a very similar reaction, with C_1 of geranyl diphosphate to form a 15-carbon product called farnesyl diphosphate (FPP).

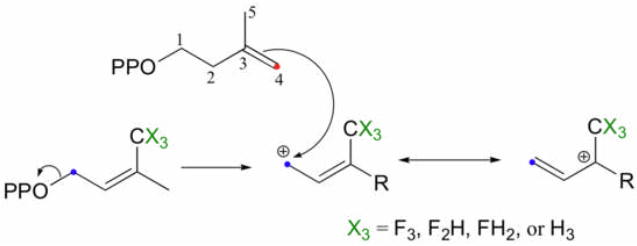


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere in between, like the protein prenyltransferase reaction. The protein prenyltransferase reaction and the isoprenoid chain elongation reactions are very similar: the electrophile is the same, but in the former the nucleophile is a thiolate, while in the latter the nucleophile is a pi bond.



This difference in the identity of the nucleophilic species would lead one to predict that the chain elongation reaction has more S_N1-like character than the protein prenylation reaction. A thiolate is a very powerful nucleophile, and thus is able to *push* the pyrophosphate leaving group off, implying some degree of S_N2 character. The electrons in a pi bond, in contrast, are only weakly nucleophilic, and thus need to be *pulled* in by a powerful electrophile - *ie*. a carbocation.

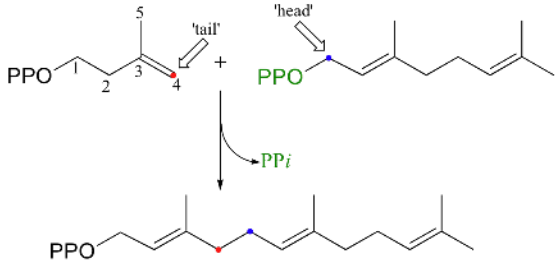
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



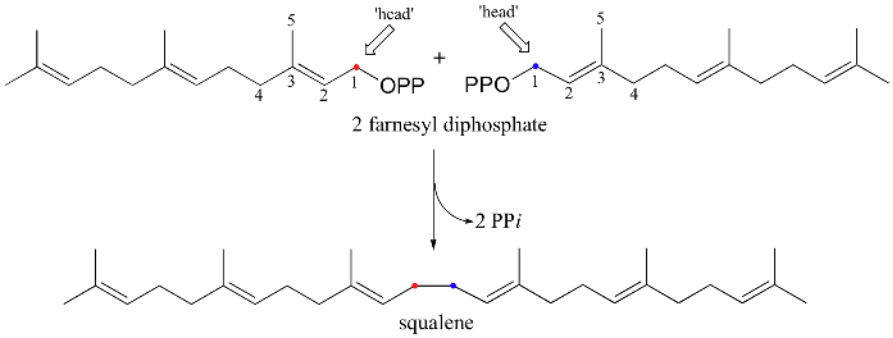
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would not be formed. When this experiment was performed with FPP synthase, the results were dramatic: the presence of a single fluorine slowed down the rate of the reaction by a factor of about 60, while two and three fluorines resulted in a reaction that was 500,000 and 3 million times slower, respectively (*J. Am. Chem. Soc*. **1981**, *103*, 3926.) These results strongly suggest indicate the formation of a carbocation intermediate in an S_N1-like displacement.

In this section, we will briefly examine the reaction catalyzed by an enzyme called squalene synthase, an important enzymatic transformation that involves some very interesting and unusual electrophilic additions, rearrangements, and reactive intermediates. This particular enzyme is also of interest because it represents a potential new target for cholesterol-lowering drugs.

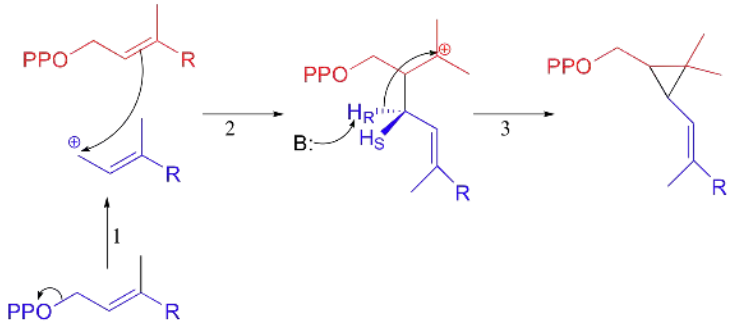
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, or 'head to tail' electrophilic condensation of isoprenoid chains:



The condensation of two molecules of FPP to form squalene, however, is something different: this is a 'head to head' condensation, where C_1 of the first molecule forms a bond to C_1 of the second. The chemistry involved is quite a bit more complicated.

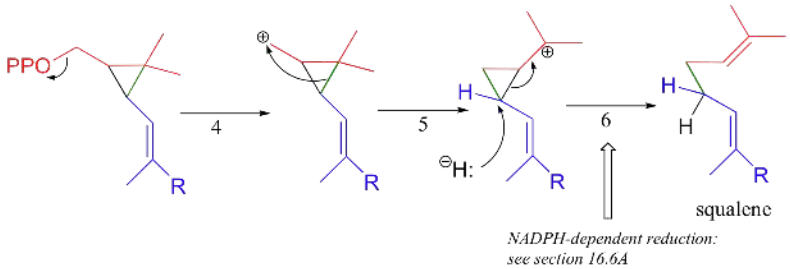


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).



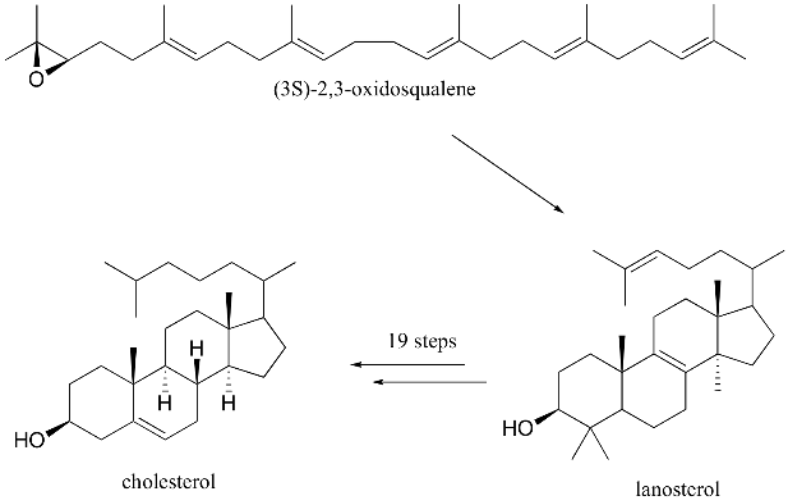
This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl intermediate.

In the second stage of squalene synthesis, the second pyrophosphate group leaves, generating a cyclopropylcarbinyl cation (step 4). Because this is a primary carbocation, you probably are wondering about how stable it could be (and thus how likely an intermediate). As it turns out, such carbocations are remarkably stable, due to favorable interactions between the empty orbital and orbitals on the three-membered ring (the level of bonding theory needed to really understand this idea is beyond the scope of this text, but you may learn about it if you take a class in advanced organic chemistry). What occurs next is an alkyl shift leading to a tertiary carbocation (step 5).



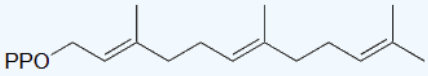
Discussion of the final step (step 6) will need to be put off - this is a reduction with a hydride nucleophile derived from a coenzyme called NADPH. Although this may seem like an extremely convoluted (and perhaps unlikely!) mechanism, there is much experimental evidence to

back it up.



EXERCISE 27.5.1

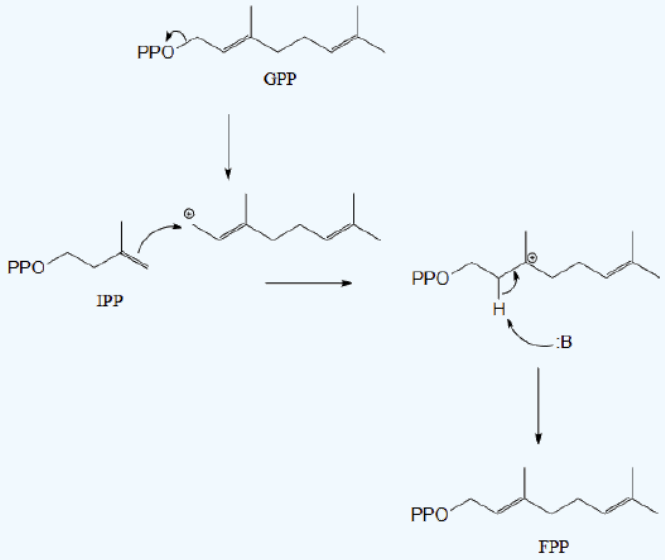
Farnesyl diphosphate (FPP) is synthesized by adding another five-carbon building block to geranyl diphosphate. What is this building block - IPP or DMAPP? Draw a mechanism for the formation of FPP.



farnesyl diphosphate

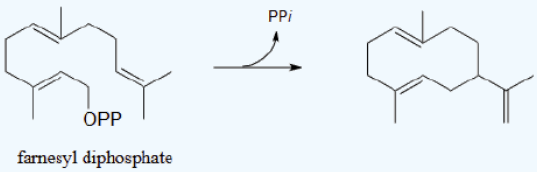
Answer

IPP is the five-carbon species added to geranyl diphosphate to make the 15-carbon farnesyl diphosphate.



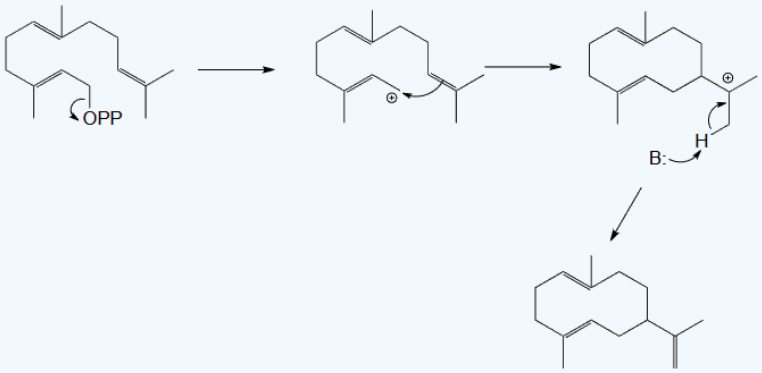
EXERCISE 27.5.2

Propose a likely mechanism for the following transformation, which is the first stage in a somewhat complex reaction in the synthesis of an isoprenoid compound in plants. (Science 1997, 277, 1815)



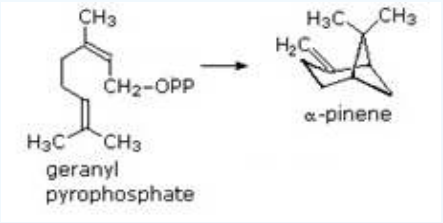
farnesyl diphosphate

Answer

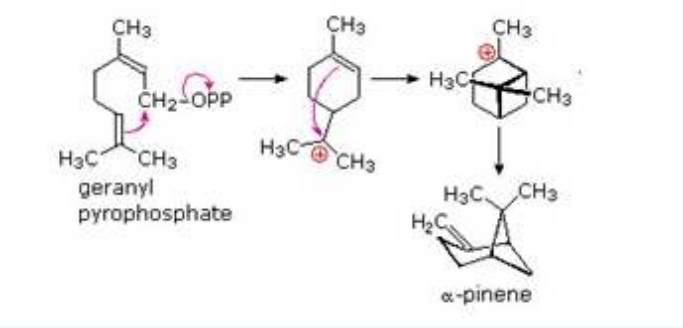


EXERCISE 27.5.3

Propose a likely mechanism for the following transformation.



Answers



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27.6: STEROIDS

OBJECTIVES

After completing this section, you should be able to

1. draw the tetracyclic ring system on which the structure of all steroids is based.
2. identify the occurrence and biological roles of at least two common steroids.
3. sketch the stereochemical conformation of a steroid, given an adequate wedge and dash structure, and determine whether the ring substituents in such a compound occupy axial or equatorial positions.
4. construct a molecular model of a steroid, given a suitable written description or a wedge and dash structure from which to work.

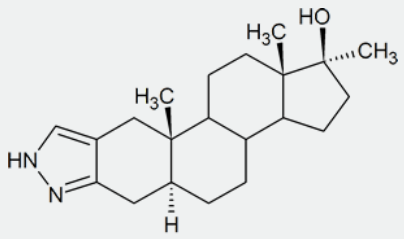
KEY TERMS

Make certain that you can define, and use in context, the key term below.

- steroid

STUDY NOTES

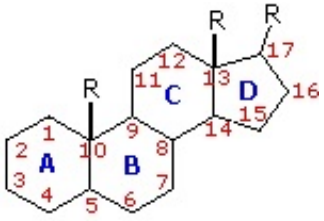
Since the 1988 Olympic Games in Seoul, even individuals who have no interest in chemistry or sport have heard the word “steroid” and are aware that some athletes use these substances to enhance their athletic abilities. Stanozolol, the substance which Canadian sprinter, Ben Johnson, was found to have used, has the structure shown below:



stanozolol

GENERAL STEROID STRUCTURE

The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram below. The four rings are designated A, B, C & D as noted, and the peculiar numbering of the ring carbon atoms (shown in red) is the result of an earlier misassignment of the structure. The substituents designated by R are often alkyl groups, but may also have functionality. The R group at the A:B ring fusion is most commonly methyl or hydrogen, that at the C:D fusion is usually methyl. The substituent at C-17 varies considerably, and is usually larger than methyl. The most common locations of functional groups are C-3, C-4, C-7, C-11, C-12 & C-17. Ring A is sometimes aromatic. Since a number of tetracyclic triterpenes also have this tetracyclic structure, it cannot be considered a unique identifier.

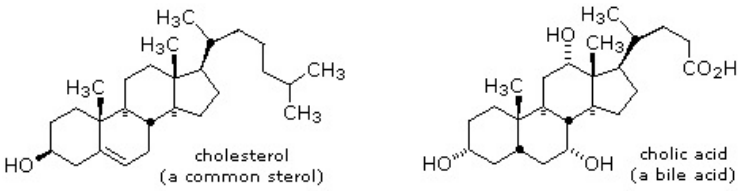


The Steroid Carbon Skeleton

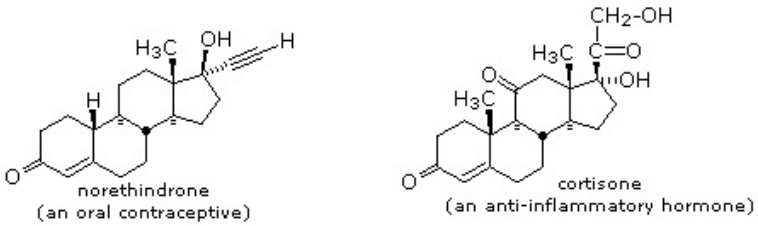
COMMON STEROIDS

Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally.

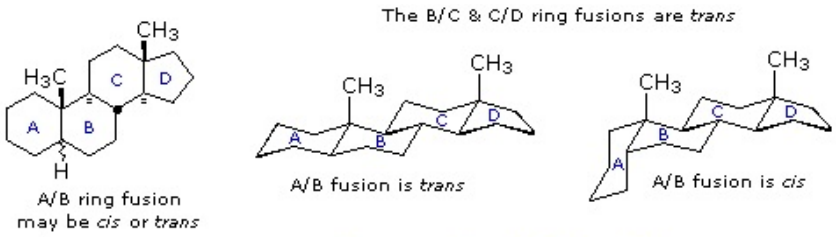
The generic steroid structure drawn above has seven chiral stereocenters (carbons 5, 8, 9, 10, 13, 14 & 17), which means that it may have as many as 128 stereoisomers. With the exception of C-5, natural steroids generally have a single common configuration.



Typical Animal Steroids



Medicinally Useful Steroids

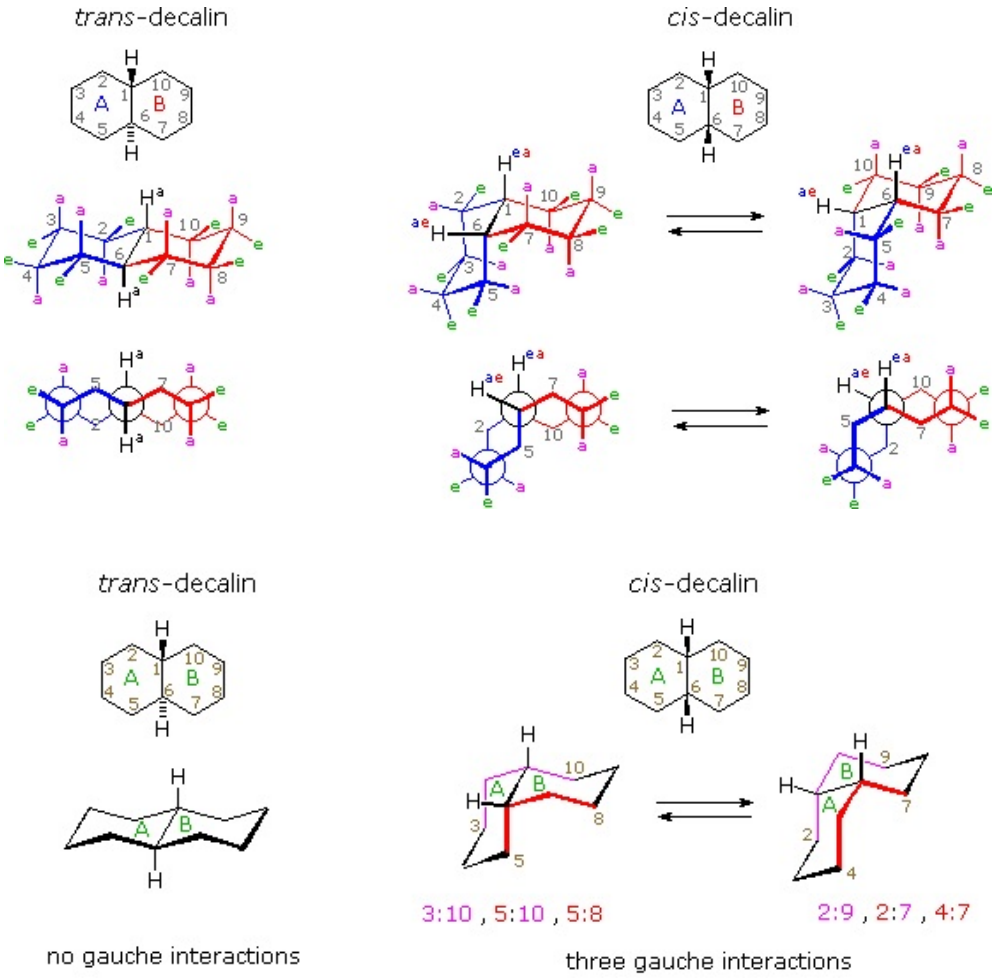


Common Steroid Conformations

Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of the trans-fused rings. This fixed orientation influences chemical reactivity, largely due to the greater steric hindrance of axial groups versus their equatorial isomers. Thus an equatorial hydroxyl group is esterified more rapidly than its axial isomer.

DECALIN AS A MODEL SYSTEM

It is instructive to examine a simple bicyclic system as a model for the fused rings of the steroid molecule. Decalin, short for decahydronaphthalene, exists as cis and trans isomers at the ring fusion carbon atoms. Planar representations of these isomers are drawn at the top of the following diagram, with corresponding conformational formulas displayed underneath. The numbering shown for the ring carbons follows IUPAC rules, and is different from the unusual numbering used for steroids. For purposes of discussion, the left ring is labeled A (colored blue) and the right ring B (colored red). In the conformational drawings the ring fusion and the angular hydrogens are black.



The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above the plane of the two rings alternate from axial to equatorial and back if we proceed around the rings from C-1 to C-10 in numerical order. The bonds directed below the rings also alternate in a complementary fashion.

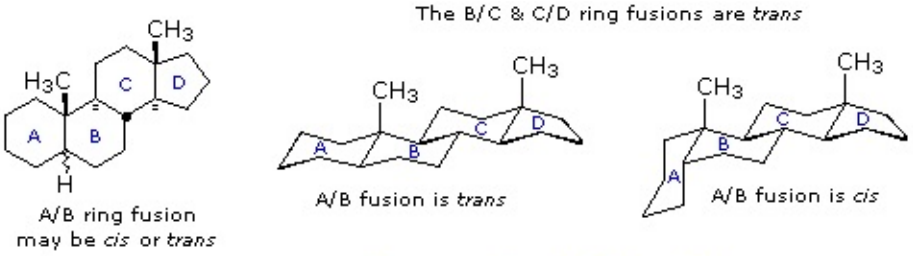
Conformational descriptions of cis- decalin are complicated by the fact that two energetically equivalent fusions of chair cyclohexanes are possible, and are in rapid equilibrium as the rings flip from one chair conformation to the other. In each of these all chair conformations the rings are fused by one axial and one equatorial bond, and the overall structure is bent at the ring fusion. In the conformer on the left, the red ring (B) is attached to the blue ring (A) by an axial bond to C-1 and an equatorial bond to C-6 (these terms refer to ring A substituents). In the conformer on the right, the carbon bond to C-1 is equatorial and the bond to C-6 is axial. Each of the angular hydrogens (Hae or Hea) is oriented axial to one of the rings and equatorial to the other. This relationship reverses when double ring flipping converts one cis-conformer into the other.

Cis-decalin is less stable than trans-decalin by about 2.7 kcal/mol (from heats of combustion and heats of isomerization data). This is due to steric crowding (hindrance) of the axial hydrogens in the concave region of both cis-conformers, as may be seen in the model display activated by the following button. This difference is roughly three times the energy of a gauche butane conformer relative to its anti conformer. Indeed three gauche butane interactions may be identified in each of the cis-decalin conformations, as will be displayed by clicking on the above conformational diagram. These gauche interactions are also shown in the model.

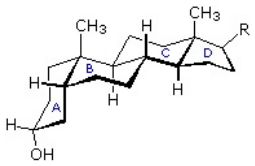
STEROID CONFORMATIONS

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the same conformational mobility exhibited by cis-decalin. The fusion of ring C to ring B in a trans configuration prevents ring B from undergoing a conformational flip to another chair form. If this were to occur, ring C would have to be attached to ring B by two adjacent axial bonds directed 180º apart. This is too great a

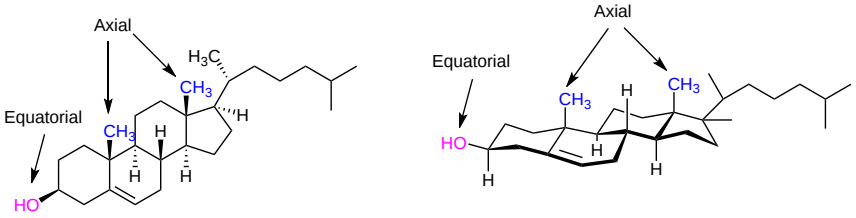
distance to be bridged by the four carbon atoms making up ring C. Consequently, the steroid molecule is locked in the all chair conformation shown here. Of course, all these steroids and decalins may have one or more six-membered rings in a boat conformation. However the high energy of boat conformers relative to chairs would make such structures minor components in the overall ensemble of conformations available to these molecules.



Common Steroid Conformations



Much like cyclohexanes substituents (Section 4-7) on a steroid ring system can be either an axial or equatorial position. Fused rings makes steroids ridge and unable to undergo cyclohexane ring-flips Because of sterics, substituents in the equatorial posltion tend to be more energetically favorable. The -OH group present in cholesterol is in the more stable equatorial position while the two -CH_3 groups on the steroid ring are both in an axial position.

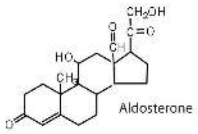
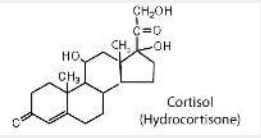
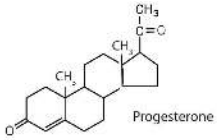
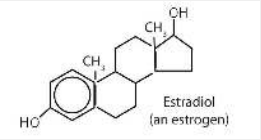
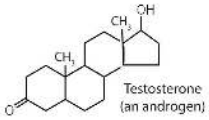


STEROID HORMONES

Hormones are chemical messengers that are released in one tissue and transported through the circulatory system to one or more other tissues. One group of hormones is known as steroid hormones because these hormones are synthesized from cholesterol, which is also a steroid. There are two main groups of steroid hormones: adrenocortical hormones and sex hormones.

The adrenocortical hormones, such as aldosterone and cortisol (Table 27.6.1), are produced by the adrenal gland, which is located adjacent to each kidney. Aldosterone acts on most cells in the body, but it is particularly effective at enhancing the rate of reabsorption of sodium ions in the kidney tubules and increasing the secretion of potassium ions and/or hydrogen ions by the tubules. Because the concentration of sodium ions is the major factor influencing water retention in tissues, aldosterone promotes water retention and reduces urine output. Cortisol regulates several key metabolic reactions (for example, increasing glucose production and mobilizing fatty acids and amino acids). It also inhibits the inflammatory response of tissue to injury or stress. Cortisol and its analogs are therefore used pharmacologically as immunosuppressants after transplant operations and in the treatment of severe skin allergies and autoimmune diseases, such as rheumatoid arthritis.

Table 27.6.1 Representative Steroid Hormones and Their Physiological Effects

Hormone	Effect
 Aldosterone	regulates salt metabolism; stimulates kidneys to retain sodium and excrete potassium
 Cortisol (Hydrocortisone)	stimulates the conversion of proteins to carbohydrates
 Progesterone	regulates the menstrual cycle; maintains pregnancy
 Estradiol (an estrogen)	stimulates female sex characteristics; regulates changes during the menstrual cycle
 Testosterone (an androgen)	stimulates and maintains male sex characteristics

The sex hormones are a class of steroid hormones secreted by the gonads (ovaries or testes), the placenta, and the adrenal glands. Testosterone and androstenedione are the primary male sex hormones, or *androgens*, controlling the primary sexual characteristics of males, or the development of the male genital organs and the continuous production of sperm. Androgens are also responsible for the development of secondary male characteristics, such as facial hair, deep voice, and muscle strength. Two kinds of sex hormones are of particular importance in females: progesterone, which prepares the uterus for pregnancy and prevents the further release of eggs from the ovaries during pregnancy, and the estrogens, which are mainly responsible for the development of female secondary sexual characteristics, such as breast development and increased deposition of fat tissue in the breasts, the buttocks, and the thighs. Both males and females produce androgens and estrogens, differing in the amounts of secreted hormones rather than in the presence or absence of one or the other.

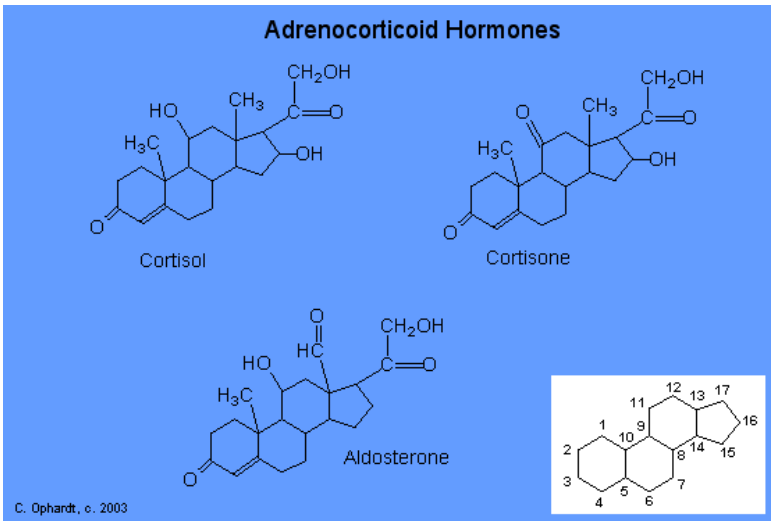
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment option for prostate cancer because they block the release and activity of testosterone. Testosterone enhances prostate cancer growth. Sex hormones are also administered in preparation for sex-change operations, to promote the development of the proper secondary sexual characteristics. Oral contraceptives are synthetic derivatives of the female sex hormones; they work by preventing ovulation.

ADRENOCORTICOID HORMONES

The adrenocorticoid hormones are products of the adrenal glands ("adrenal" means adjacent to the renal (kidney). The most important adrenocorticoid is **aldosterone**, which regulates the reabsorption of sodium and chloride ions in the kidney tubules and increases the loss of potassium ions. Aldosterone is secreted when blood sodium ion levels are too low to cause the kidney to retain sodium ions. If sodium levels are elevated, aldosterone is not secreted, so that some sodium will be lost in the urine. Aldosterone also controls swelling in the tissues.

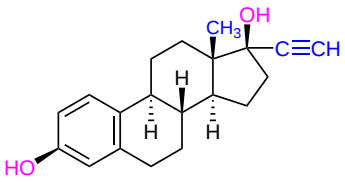
Cortisol, the most important glucocortinoid, has the function of increasing glucose and glycogen concentrations in the body. These reactions are completed in the liver by taking fatty acids from lipid storage cells and amino acids from body proteins to make glucose and glycogen.

In addition, cortisol and its ketone derivative, **cortisone**, have the ability to inflammatory effects. Cortisone or similar synthetic derivatives such as prednisolone are used to treat inflammatory diseases, rheumatoid arthritis, and bronchial asthma. There are many side effects with the use of cortisone drugs, so there use must be monitored carefully.

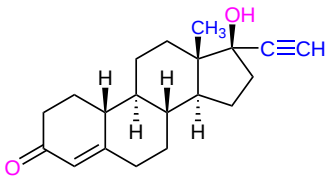


SYNTHETIC STEROIDS

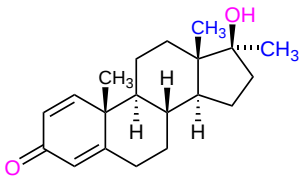
In the hope of producing new drugs, thousands of steroid derivatives have been synthesized and test by pharmaceutical companies. The two classes of synthetic steroids most commonly know by the public are oral contraceptives and anabolic steroids. Oral contraceptives contain synthetic versions of the hormones estrogen (ethynylestradiol) and progestin (norethindrone). They prevent pregnancy by interfering with ovulation, fertilization, and/or implantation of the fertilized egg. Anabolic steroids (methandrostenolone) mimic the effects of natural testosterone.



Ethynylestradiol
(A synthetic estrogen)



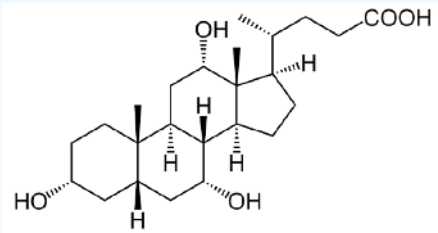
Norethindrone
(A synthetic progestin)



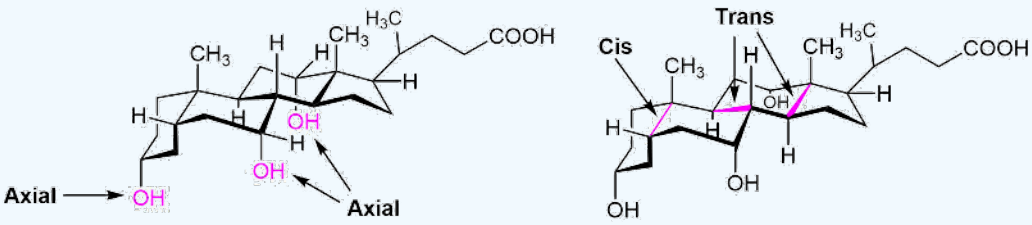
Methandrostenolone
(A synthetic androgen)

? EXERCISE 27.6.1

The following molecule is cholic acid. Draw it showing the chair conformations. Determine if the three fused bonds have a *cis* or *trans* configuration. Determine if the OH groups are axial or equatorial.



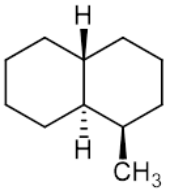
Answer



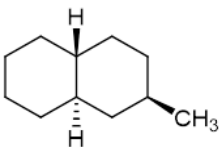
EXERCISE 27.6.2

Draw the following decalin molecules in chair conformations. Determine if the -CH_3 groups are axial or equatorial.

a)

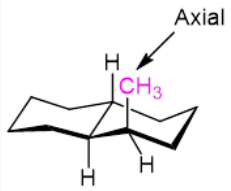


b)

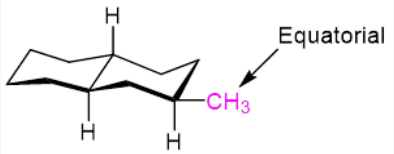


Answer

a)



b)



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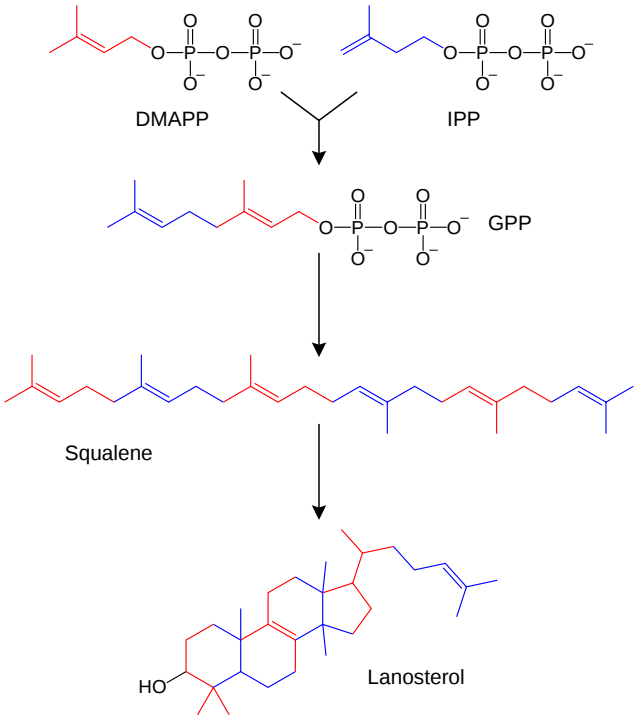
27.7: BIOSYNTHESIS OF STEROIDS

OBJECTIVES

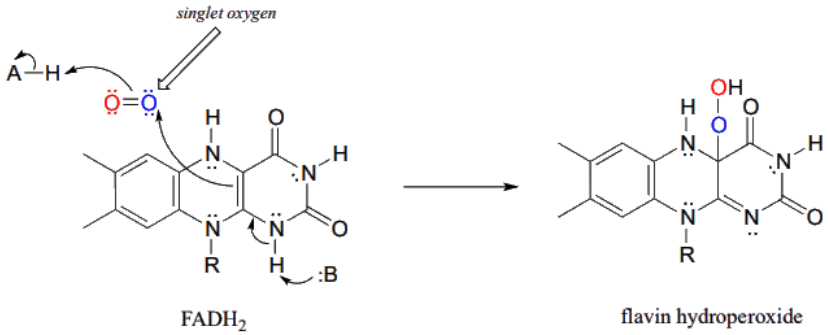
After completing this section, you should be able to

- give an overview of how steroids are synthsized.
- describe changes to molecules through the biosynthesis of steroids.

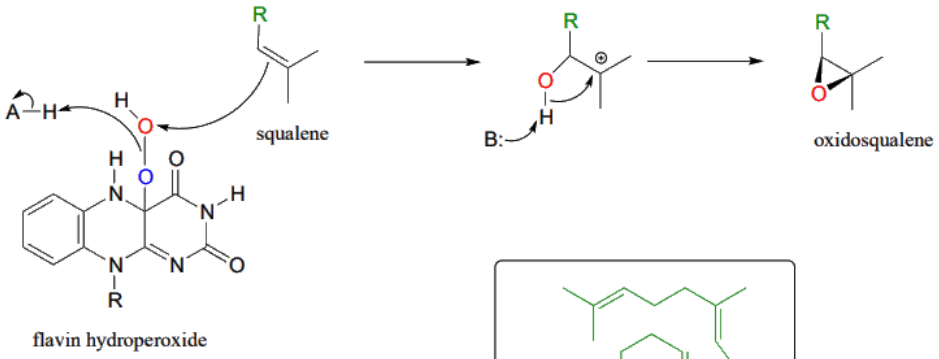
Steroid biosynthesis is an anabolic metabolic pathway that produces steroids from simple precursors. A unique biosynthetic pathway is followed in animals compared to many other organisms, making the pathway a common target for antibiotics and other anti-infective drugs. In humans and other animals, the biosynthesis of steroids follows the **mevalonate pathway** that uses acetyl-CoA as building blocks to form dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP). These two compounds are coupled to form geranyl pyrophosphate (GPP) which is then converted to the hydrocarbon polyene squalene. After an oxidation and multiple rearrangements, lanosterol the first steroid in the pathway is formed. Further conversions can yield different steroids.

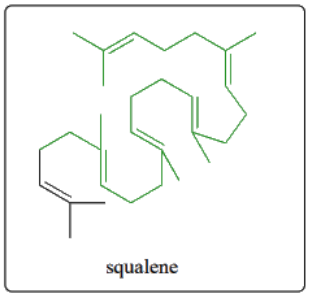


The key step in the biosynthesis of lanosterol is the regioselective epoxidation of squalene to give (3*S*)-2,3-oxidosqualene. This reaction is catalyzed by the monooxygenase enzyme squalene epoxidase. In this step, flavin hydroperoxide serves as the direct oxidizing agent. In flavin hydroperoxide, the peroxide group is linked to one of the carbons of the reactive triple-ring system of the coenzyme. A possible mechanism for the formation of flavin peroxide from $FADH_2$ and molecular oxygen is shown below.

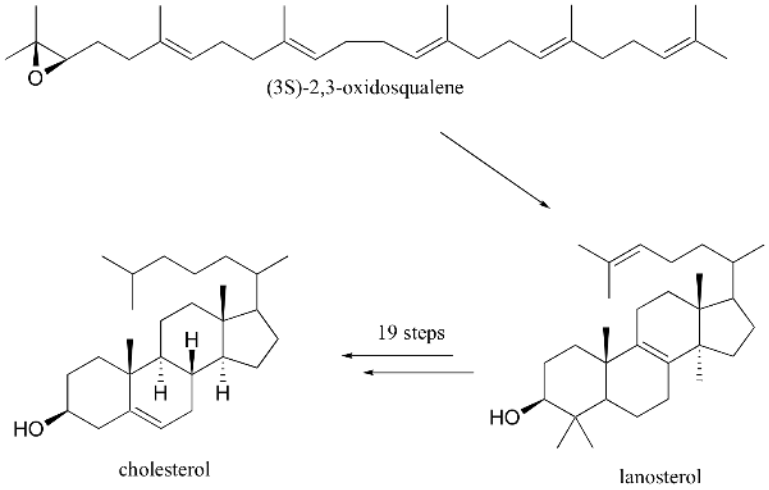


The mechanism for the flavin-hydroperoxide-dependent epoxidation of squalene is initiated by the nucleophilic attack of the pi electrons of a squalene double bond on the electrophilic terminal hydroperoxide oxygen.

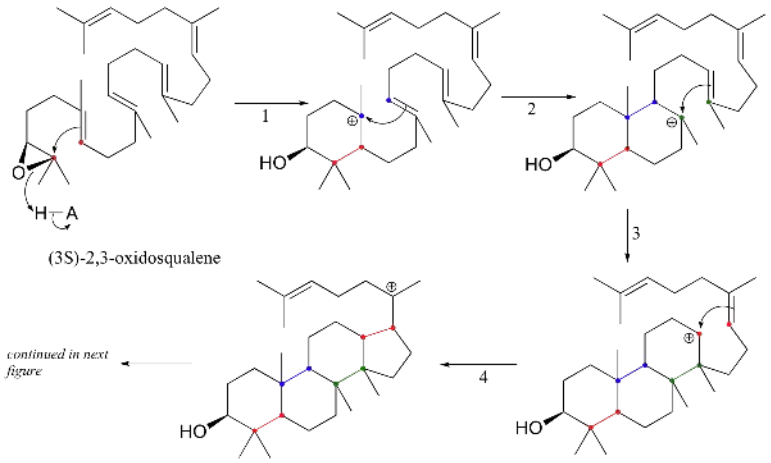




Oxidosqualene goes on to cyclize to lanosterol in a complex and fascinating electrophilic reaction which catalyzed by oxidosqualene-lanosterol cyclase. This reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise. After lanosterol is formed the pathway continued to form cholesterol which is the precursor that all other steroids are derived.

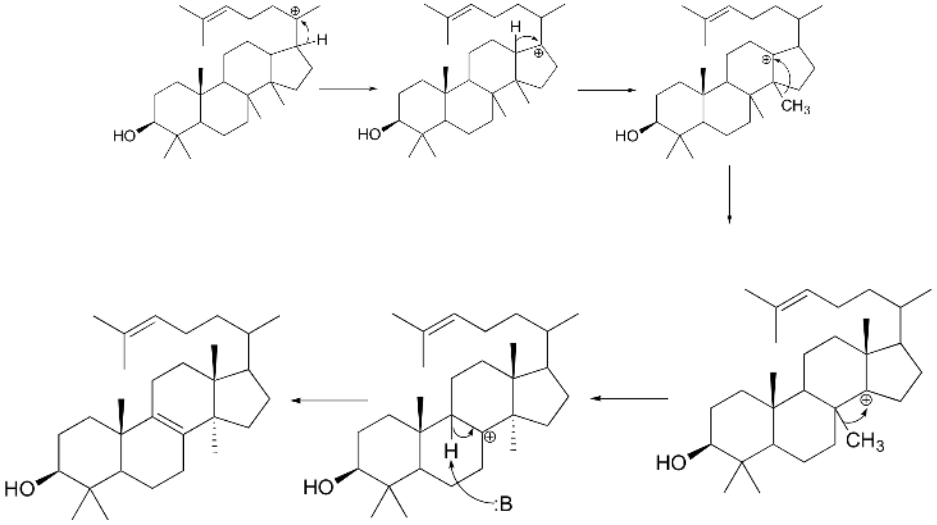


The cyclization phase begins with attack by pi electrons on an epoxide electrophile. The epoxide ring opens to form an alcohol after protonation. A relatively stable tertiary carbocation is also formed. Steps 2, 3, and 4 are simply successive attacks by pi electrons on the carbocation generated by the previous attack. The overall result of this electrophilic cascade is the opening of the epoxide ring, and closure of three six-membered and one five-membered ring.



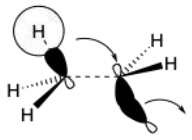
(3S)-2,3-oxidosqualene

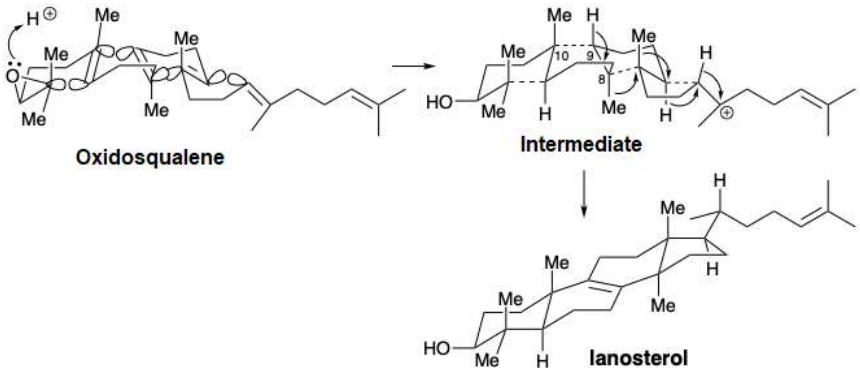
Next comes the rearrangement phase of the reaction in which a series of two 1,2-hydride and two 1,2-methyl shifts to give lanosterol after proton loss from the 9 position.



lanosterol

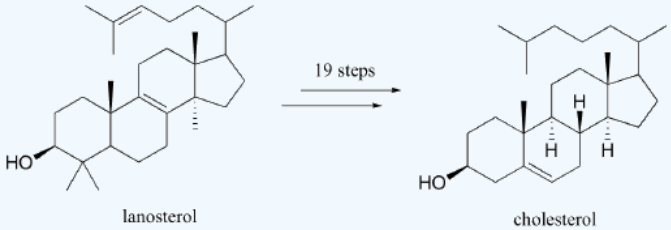
Especially interesting are the stereochemical details of the polyene cyclization and subsequent rearrangement. The polyene cyclization involves stereospecific **anti-periplanar** addition across three C=C bonds in oxidosqualene (see below). The folded conformation of oxidosqualene, required for cyclization is probably imposed by the enzyme involved since appreciable steric congestion is present in both oxidosqualene and the intermediate. Relief of steric strain provides a large driving force for the rearrangements to lanosterol that involves stereospecific inversion of configuration at each stereocenter during 1,2-hydrogen or methyl shifts. Thus, each 1,2-hydride or 1,2-methyl shift occurs to the backside of the orbital connected to the leaving group in what can be viewed as a series of nucleophilic substitution reactions – where σ-bonding electron pairs serve as the nucleophiles.





EXERCISE 27.7.1

What changes must be made to the structure of lanosterol to convert it to cholesterol?



Answer

Three methyl groups and a double bond are removed. Another double bond is moved to the other side of a six-membered ring.

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27.S: BIOMOLECULES - LIPIDS (SUMMARY)

CONCEPTS & VOCABULARY

- fulfill all of the detailed objectives listed under each individual section.
- define, and use in context, any of the key terms introduced in this chapter.

25.1 Introduction

- Carbohydrates are composed of carbon, hydrog

25.2 Classification of Carbohydrates

- Carbohydrates originate as products from photosynt

25.3 Fischer Projections

- The Fischer projection is a type of notation often used when multip

25.4 D,L Sugars

- To determine absolute configuration for carbohydrates, Emil Fischer started with an arb

25.5 Configurations of Aldoses

- The aldos

25.6 Anomers

- The preferred structural form of mon

25.7 Reactions of Monosaccharides

- The -OH groups on a monosacc

25.8 The Eight Essential Monosaccharides

- The eight essential monos

25.9 Disaccharides

- Disaccharides are sugars com

25.10 Polysaccharides and Their Synthesis

- Polysaccharides are very large polymers co

25.11 Other Important Carbohydrates

- The backbone of DNA is based on a repeated

25.12 Cell-Surface Carbohydrates and Influenza Viruses

- Carbohydrates a

SKILLS TO MASTER

- Skill 25.1 Determine which molecules can be classified as carbohydr
-

SUMMARY OF REACTIONS

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CHAPTER OVERVIEW

28: BIOMOLECULES - NUCLEIC ACIDS

LEARNING OBJECTIVES

When you have completed Chapter 28, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the structure of a given nucleotide.
3. discuss the structure of DNA and RNA.
4. describe the processes involved in DNA replication, transcription, translation, and protein synthesis.
5. define, and use in context, the key terms introduced in this chapter.

Two types of nucleic acids are found in cells—deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). These highly complex substances are built up from a number of simpler units, called nucleotides. Each nucleotide consists of three parts: a phosphoric acid residue, a sugar and a nitrogen-containing heterocyclic base. Thus, in order to understand the biochemistry of the nucleic acids, you must first study the chemistry of the sugars (see Chapter 25) and simple heterocyclic systems. We have already discussed certain aspects of the structure of heterocyclic ring systems during our study of aromaticity (Sections 15.5–15.6). You may find it helpful to review this chapter.

Chapter 28 examines the structure and replication of DNA and then describes the structure and synthesis of RNA. The chapter closes with a brief study of the role played by RNA in the biosynthesis of proteins.

28.0: Chapter Objectives
28.1: Nucleotides and Nucleic Acids
28.2: Base Pairing in DNA - The Watson-Crick Model
28.3: Replication of DNA
28.4: Transcription of DNA
28.5: Translation of RNA - Protein Biosynthesis
28.6: DNA Sequencing
28.7: DNA Synthesis
28.8: The Polymerase Chain Reaction

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28.0: Chapter Objectives

Learning Objectives

- Understand the components and chemical structure of nucleotides, and their role in forming DNA and RNA molecules.
- Analyze the principles of base pairing and hydrogen bonding in nucleic acids, and how they contribute to the stability and specificity of DNA and RNA structures.
- Examine the chemical mechanisms involved in nucleic acid synthesis (polymerization) and degradation (hydrolysis), and the enzymatic processes of DNA replication, RNA transcription, and repair.
- Explore the different conformations of nucleic acids, including their impact on function and interactions with other molecules.
- Learn about analytical techniques used to study nucleic acids, and how they provide insights into structure, function, and interactions.

Nucleic acids are biopolymers found in all living organisms, serving as the essential molecules for the storage, transmission, and expression of genetic information. These complex macromolecules are composed of repeating units called nucleotides, which consist of three main components: a nitrogenous base, a five-carbon sugar (ribose or deoxyribose), and a phosphate group.

There are two primary types of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA is the genetic blueprint of an organism, encoding the instructions for the synthesis of proteins and the regulation of cellular activities. It exists in the form of a double helix, with two complementary strands held together by hydrogen bonds between the nitrogenous bases adenine (A) and thymine (T), and guanine (G) and cytosine (C).

RNA, on the other hand, plays diverse roles in gene expression, including messenger RNA (mRNA) which carries genetic information from DNA to the ribosomes for protein synthesis, transfer RNA (tRNA) which brings amino acids to the ribosomes during protein synthesis, and ribosomal RNA (rRNA) which forms the structural and catalytic core of ribosomes.

The structure and function of nucleic acids are intricately linked. The sequence of nitrogenous bases along the nucleic acid chain determines the genetic code, with each triplet of bases (codon) encoding a specific amino acid or serving as a signal for regulatory functions. The ability of nucleic acids to undergo replication, transcription, and translation enables the faithful transmission and expression of genetic information from one generation to the next.

Beyond their role in genetics, nucleic acids also participate in various cellular processes, including DNA repair, RNA processing, and gene regulation. Moreover, advances in biotechnology have led to the manipulation and engineering of nucleic acids for applications such as genetic engineering, molecular diagnostics, and gene therapy.

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28.1: NUCLEOTIDES AND NUCLEIC ACIDS

OBJECTIVES

After completing this section, you should be able to

- outline the relationship between nucleic acids, nucleotides and nucleosides.
- identify, in general terms, the enzymatic hydrolysis products of nucleosides.
- explain the structural difference between the sugar components of DNA and RNA.
- identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
- identify by name the four heterocyclic amine bases found in ribonucleotides.
- draw the general structure of a nucleotide and a nucleoside.
- indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
- sketch a section of nucleic acid to show how the nucleotide units are joined together.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- deoxyribonucleic acid (DNA)
- nucleosides nucleotides
- ribonucleic acid (RNA)

STUDY NOTES

The five bases that are found in nucleotides are often represented by their initial letter: adenine, A; guanine, G; cytosine, C; thymine, T; and uracil, U. Note that A, G, C and T occur in DNA; A, G, C and U occur in RNA. You are not required to memorize the structures of these bases, but you must know how each one bonds to the sugar unit in a nucleotide.

To fulfill Objective 6, you should be able to reproduce the figure below.

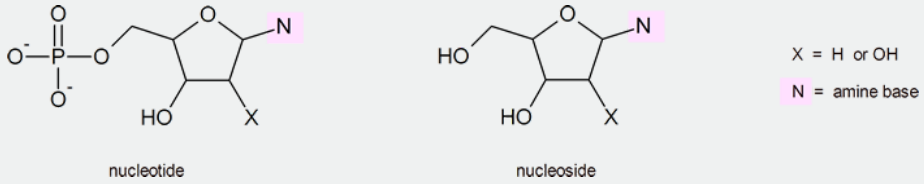


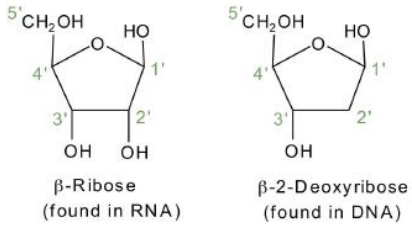
Figure **28.1.0** The Pyrimidine and Purine Nucleotides below.

The Learning Objective of this Module is to identify the different molecules that combine to form nucleotides.

The repeating, or monomer, units that are linked together to form **nucleic acids** are known as **nucleotides**. The deoxyribonucleic acid (DNA) of a typical mammalian cell contains about 3×10^9 nucleotides. Nucleotides can be further broken down to a phosphate group (PO_4^{-3}) and a nucleoside which is composed of a aldopentose sugar (a sugar with five carbon atoms), and a heterocyclic purine or pyrimidine base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleosides are used in ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleoside are used in deoxyribonucleic acid (DNA). The prefix -deoxy implies that there is an oxygen missing from the 2' position of ribose.



The nitrogenous bases found in nucleotides are classified as pyrimidines or purines. Pyrimidines are heterocyclic amines with two nitrogen atoms in a six-member ring and include uracil, thymine, and cytosine. Purines are heterocyclic amines consisting of a pyrimidine ring fused to a five-member ring with two nitrogen atoms. Adenine and guanine are the major purines found in nucleic acids (Figure **28.1.1**). The numbering convention is that primed numbers designate the atoms of the pentose ring, and unprimed numbers designate the atoms of the purine or pyrimidine ring.

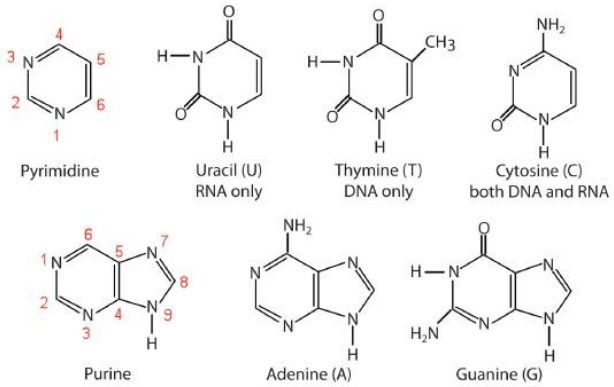
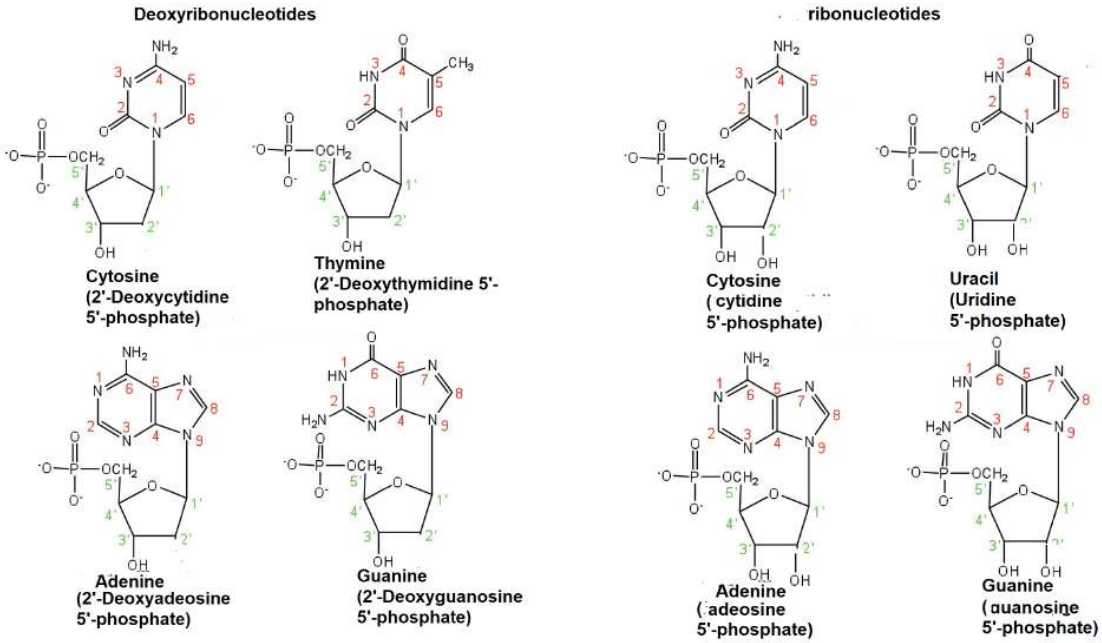


Figure **28.1.1**: The Nitrogenous Bases Found in DNA and RNA

Nucleosides are formed by a bond between the anomeric C1′ of the pentose sugar and N1 position of the pyrimidine base or the N9 position of the purine base. The addition of a phospate groups at the 5' position of a nucleoside creates a corresponding nucleotide. DNA is made from four deoxyribonucleotides (Cytosine, Thymine, Adenine, Guanine) and RNA is made from four ribonucleotides Cytosine, Uracil, Adenine, Guanine. The names and structures of the major ribonucleotides and deoxyribonucleotides are given in Figure **28.1.2**.



Apart from being the monomer units of DNA and RNA, the nucleotides and some of their derivatives have other functions as well. Adenosine diphosphate (ADP) and adenosine triphosphate (ATP), shown in Figure **28.1.3**, have a role in cell metabolism. Moreover, a

number of coenzymes, including flavin adenine dinucleotide (FAD), nicotinamide adenine dinucleotide (NAD^+), and coenzyme A, contain adenine nucleotides as structural components.

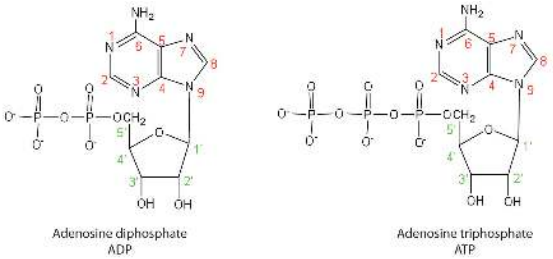


Figure **28.1.3**: Structures of Two Important Adenine-Containing Nucleotides

PRIMARY STRUCTURE OF NUCLEIC ACIDS

Nucleotides are joined together through the phosphate group of one nucleotide connecting in an ester linkage to the OH group on the 3' carbon atom of the sugar unit of a second nucleotide. This unit joins to a third nucleotide, and the process is repeated to produce a long nucleic acid chain (Figure 28.1.4). The backbone of the chain consists of alternating phosphate and sugar units (2-deoxyribose in DNA and ribose in RNA). The purine and pyrimidine bases branch off this backbone.

Like proteins, nucleic acids have a primary structure that is defined as the sequence of their nucleotides. Unlike proteins, which have 20 different kinds of amino acids, there are only 4 different kinds of nucleotides in nucleic acids. For amino acid sequences in proteins, the convention is to write the amino acids in order starting with the N-terminal amino acid. In writing nucleotide sequences for nucleic acids, the convention is to write the nucleotides (usually using the one-letter abbreviations for the bases, shown in Figure 28.1.4) starting with the nucleotide having a free phosphate group, which is known as the 5′ end, and indicate the nucleotides in order. For DNA, a lowercase *d* is often written in front of the sequence to indicate that the monomers are deoxyribonucleotides. The final nucleotide has a free OH group on the 3′ carbon atom and is called the *3′ end*. The sequence of nucleotides in the DNA segment shown in Figure 28.1.4 would be written 5′-dG-dT-dA-dC-3′, which is often further abbreviated to dGTAC or just GTAC.

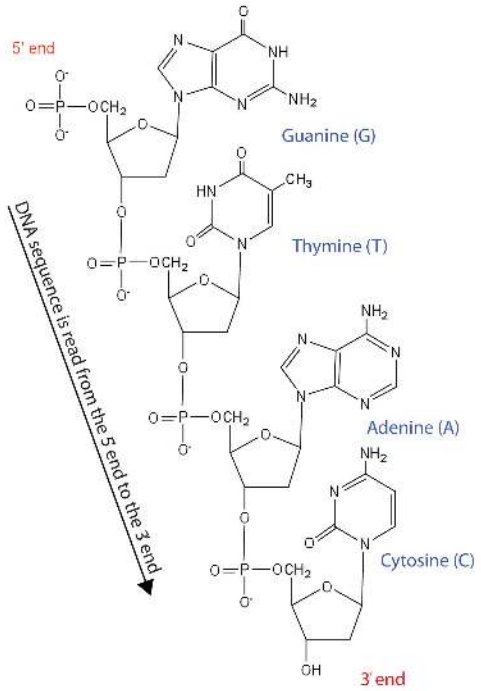


Figure **28.1.4**: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

NOTE

Each phosphate group has one acidic hydrogen atom that is ionized at physiological pH. This is why these compounds are known as nucleic acids.

EXERCISE 28.1.1

Classify each compound as a pentose sugar, a purine, or a pyrimidine.

a. adenine
b. guanine
c. deoxyribose
d. thymine
e. ribose
f. cytosine

Answer

a. purine
b. purine
c. pentose sugar
d. pyrimidine
e. pentose sugar
f. pyrimidine

EXERCISE 28.1.2

Identify the three molecules needed to form the nucleotides in each nucleic acid.

a. DNA
b. RNA

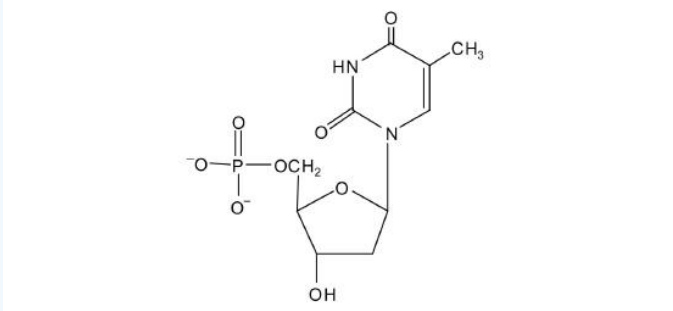
Answer

a. nitrogenous base (adenine, guanine, cytosine, and thymine), 2-deoxyribose, and H_3PO_4
b. nitrogenous base (adenine, guanine, cytosine, and uracil), ribose, and H_3PO_4

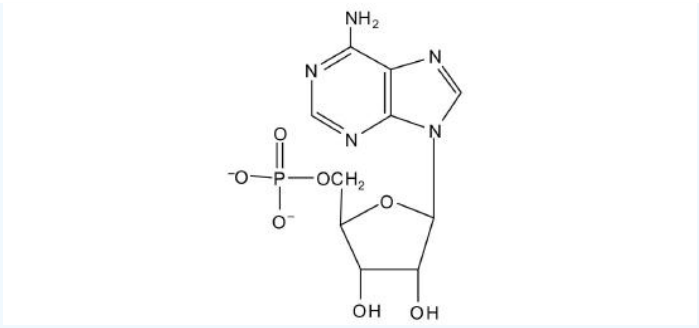
EXERCISE 28.1.3

For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

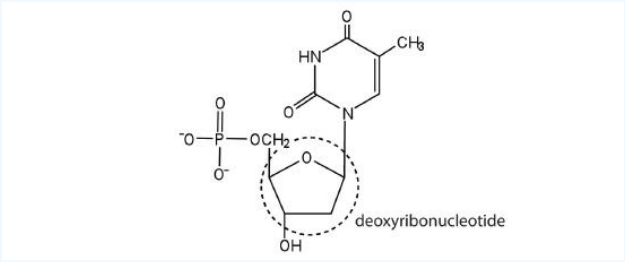
a.

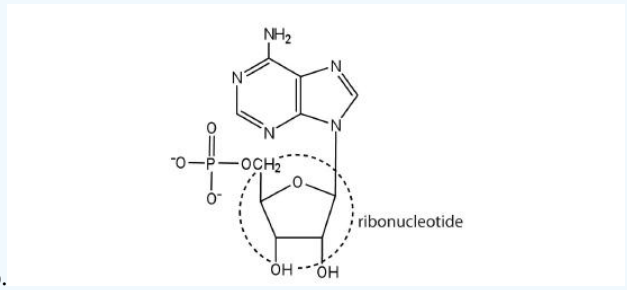


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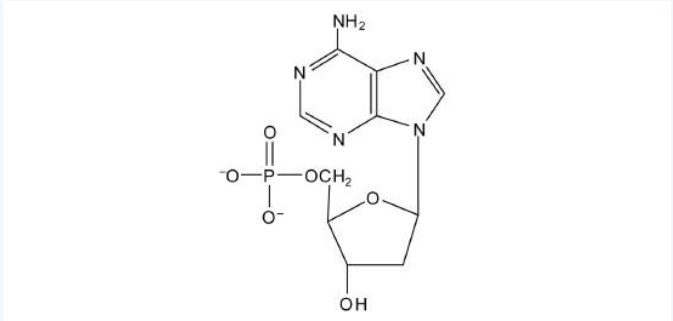
Answer

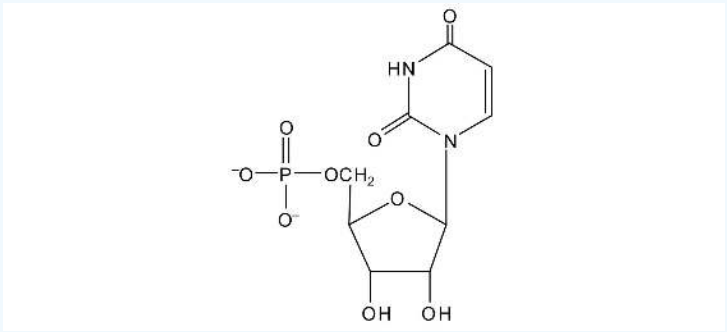
a. 

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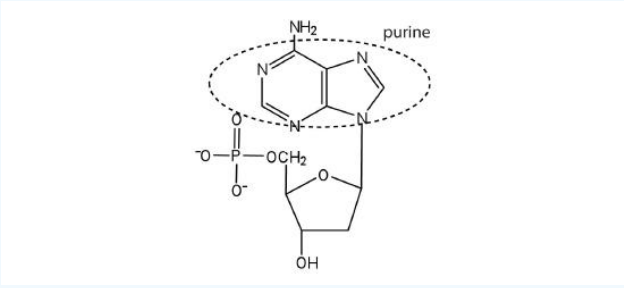
EXERCISE 28.1.4

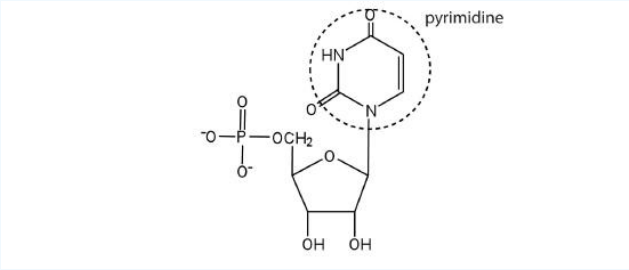
For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 



Answer

a. 

b. 

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28.2: BASE PAIRING IN DNA - THE WATSON-CRICK MODEL

OBJECTIVES

After completing this section, you should be able, given the necessary Kekulé structures, to show how hydrogen bonding can occur between thymine and adenine, and between guanine and cytosine; and to explain the significance of such interactions to the primary and secondary structures of DNA.

STUDY NOTES

Watson and Crick received the Nobel Prize in 1962 for elucidating the structure of DNA and proposing the mechanism for gene reproduction. Their work rested heavily on X-ray crystallographic work done on RNA and DNA by Franklin and Wilkins. Wilkins shared the Nobel Prize with Watson and Crick, but Franklin had been dead four years at the time of the award (you cannot be awarded the Nobel Prize posthumously).

The history of Watson and Crick's proposed DNA model is controversial and a travesty of scientific ethics. Rosalind Franklin was deeply involved in the determination of the structure of DNA, and had collected numerous diffraction patterns. Watson attended a departmental colloquium at King's College given by Franklin, and came into possession of an internal progress report she had written. Both departmental colloquia and progress reports are merely methods of discussion between colleagues; works presented in these fora are not considered by scientists to be "published" works, and therefore are not in the public domain. Watson and Crick not only were aware of Franklin's work, but used her unpublished data, presented in confidence within her own college.

The final blow came about a year after the colloquium. Watson visited Wilkins at King's College, and Wilkins inexplicably handed over Franklin's diffraction photographs without her consent. Had Franklin's work not been secretly taken from her, she might quite possibly have solved the DNA structure before Watson and Crick, who at the time did not yet have their own photographs. This is truly one of the sadder episodes of questionable scientific ethics and discovery that I have ever encountered.

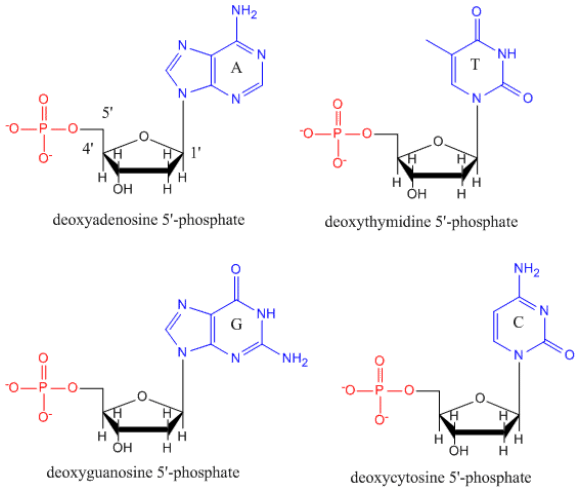
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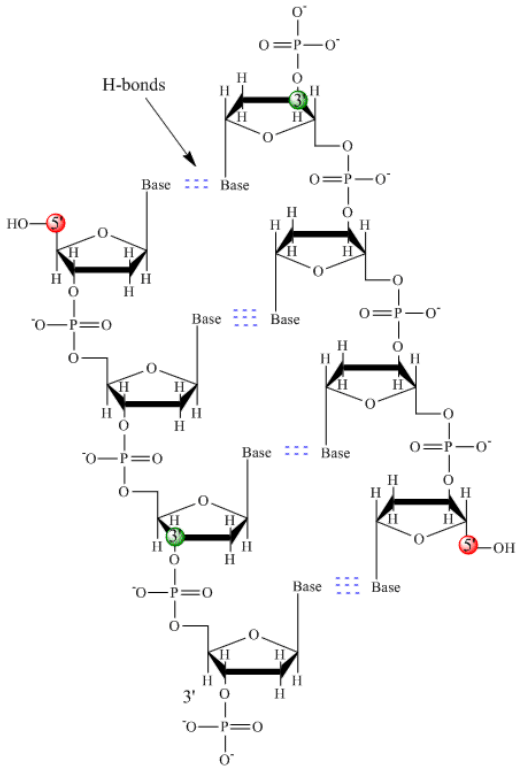
INTERMOLECULAR FORCES IN NUCLEIC ACIDS

The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (double-stranded helices) and tertiary structures in a fashion similar to proteins. The complex 3D structures formed by RNA allow it to perform functions other than simple genetic information storage, such as catalysis. Hence most scientists believe that RNA preceded both DNA and proteins in evolution as it can both store genetic information and catalyze chemical reactions.

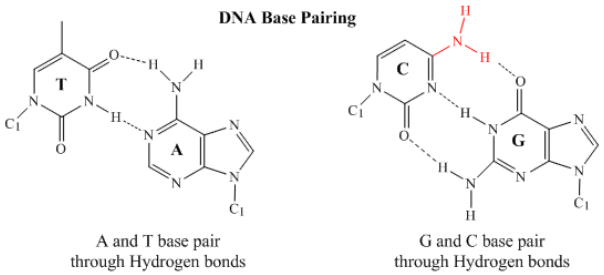


DNA

DNA is a polymer, consisting of monomers call deoxynucleotides. The monomer contains a simple sugar (deoxyribose, shown in black above), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid. Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with one base attached to each sugar molecule. As with proteins, the DNA backbone is polar but also charged. It is a polyanion. The bases, analogous to the side chains of amino acids, are predominately polar. Given the charged nature of the backbone, you might expect that DNA does not fold to a compact globular (spherical) shape, even if positively charged cations like Mg bind to and stabilize the charge on the polymer. Instead, DNA exists usually as a double-stranded (ds) structure with the sugar-phosphate backbones of the two different strands running in opposite directions (5'-3' and the other 3'-5'). The strands are held together by hydrogen bonds between bases on complementary strands. Hence like proteins, DNA has secondary structure but in this case, the hydrogen bonds are not within the backbone but between the "side chain" bases on opposing strands. It is actually a misnomer to call dsDNA a molecule, since it really consists of two different, complementary strands held together by hydrogen bonds. A structure of ds-DNA showing the opposite polarity of the strands is shown below.

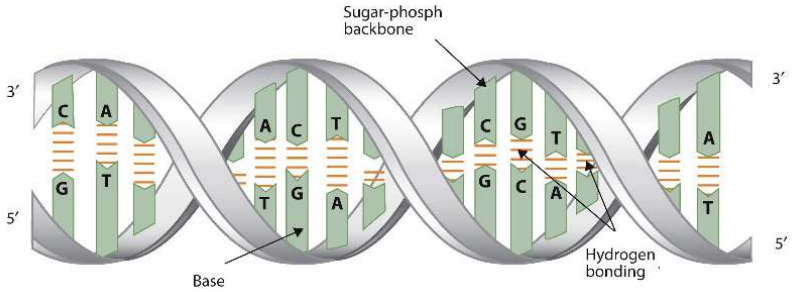


In 1950, Erwin Chargaff of Columbia University showed that the molar amount of adenine (A) in DNA was always equal to that of thymine (T). Similarly, he showed that the molar amount of guanine (G) was the same as that of cytosine (C). Chargaff's findings clearly indicate that some type of heterocyclic amine base pairing exists in the DNA structure. In double stranded DNA, the guanine (G) base on one strand can form three H-bonds with a cytosine (C) base on another strand (this is called a GC base pair). The thymine (T) base on one strand can form two H-bonds with an adenine (A) base on the other strand (this is called an AT base pair). Double-stranded DNA has a regular geometric structure with a fixed distance between the two backbones. This requires the bases pairs to consists of one base with a two-ring (bicyclic) structure (these bases are called purines) and one with a single ring structure (these bases are called pyrimidines). Hence a G and A or a T and C are not possible base pair partners.

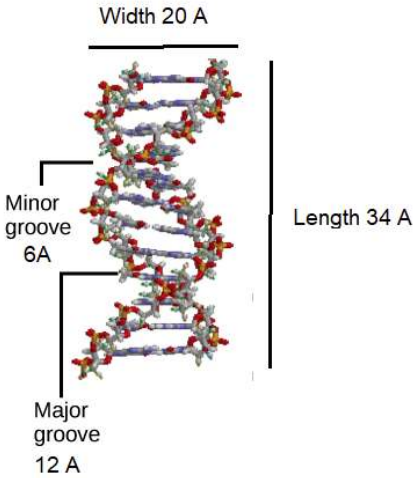


SECONDARY STRUCTURE OF DNA

The three-dimensional structure of DNA was the subject of an intensive research effort in the late 1940s to early 1950s. DNA exists as a double-stranded molecule that twists around its axis to form a helical structure,stabilized through Watson-Crick hydrogen bonding between purines and pyrimidines, and through pi-pi stacking interactions among the bases arranged in structure. helical column. Each strand is a complement to the other; the nucleotides on one strand hydrogen-bond with complementary nucleotides on the opposite strand—that is, side-by-side with the 5′ end of one chain next to the 3′ end of the other. The purine and pyrimidine bases face the inside of the helix, with guanine always opposite cytosine and adenine always opposite thymine. The double helical "twist" occurs because of the angular geometry of each bonded nucleotide.



Initial work revealed the DNA polymer had a regular repeating pattern X-ray diffraction data shows that a repeating helical pattern is 20 Angstrom units wide and occurs every 34 Angstrom units with 10 nucleotide subunits per turn. Each subunit occupies 3.4 Angstrom units which is the same amount of space occupied by a single nucleotide unit. The helix is Under most conditions, the two strands are slightly offset, which creates a 12 Angstrom major groove on one face of the double helix, and a 6 Angstrom minor groove on the other. The overall DNA polymer varies in length (number of sugar-phosphate units connected), base composition (how many of each set of bases) and sequence (the order of the bases in the backbone).



What do we mean when we say information is encoded in the DNA molecule? An organism’s DNA can be compared to a book containing directions for assembling a model airplane or for knitting a sweater. Letters of the alphabet are arranged into words, and these words direct the individual to perform certain operations with specific materials. If all the directions are followed correctly, a model airplane or sweater is produced.

In DNA, the particular sequences of nucleotides along the chains encode the directions for building an organism. Just as *saw* means one thing in English and *was* means another, the sequence of bases CGT means one thing, and TGC means something different. Although there are only four letters—the four nucleotides—in the genetic code of DNA, their sequencing along the DNA strands can vary so widely that information storage is essentially unlimited.

Deoxyribonucleic acid (DNA) stores genetic information, while ribonucleic acid (RNA) is responsible for transmitting or expressing genetic information by directing the synthesis of thousands of proteins found in living organisms. But how do the nucleic acids perform these functions?

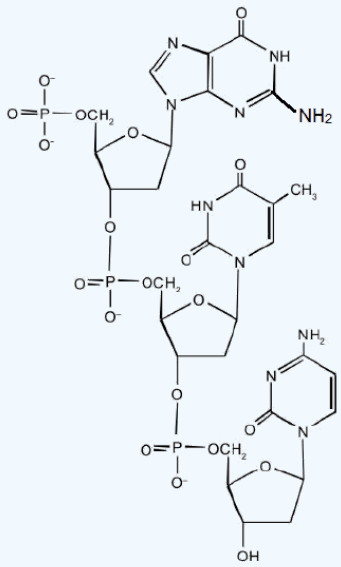
Three processes are required:

1. ***Replication***, in which new copies of DNA are made.
2. ***Transcription***, in which a segment of DNA is used to produce RNA.
3. ***Translation***, in which the information in RNA is translated into a protein sequence.

? EXERCISE 28.2.1

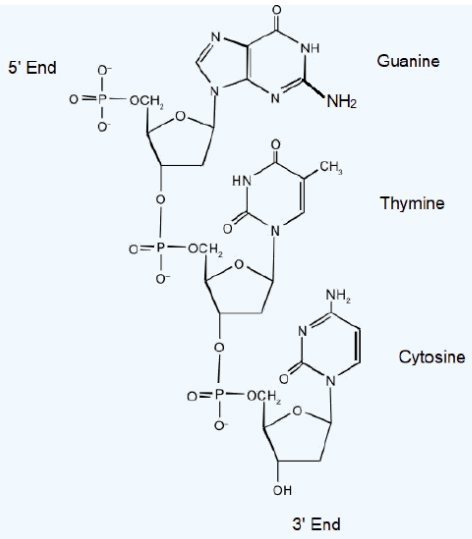
For this short DNA segment,

a. Identify the 5′ end and the 3′ end of the molecule.
b. Circle the atoms that comprise the backbone of the nucleic acid chain.
c. Write the nucleotide sequence of this DNA segment.



Answer

https://chem.libretexts.org/@go/page/36494



EXERCISE 28.2.2

Which nitrogenous base in DNA pairs with each listed nitrogenous base?

a. Cytosine
b. Adenine
c. Guanine
d. Thymine

Answer

a. Guanine
b. Thymine
c. Cytosine
d. Adenine

EXERCISE 28.2.3

How many hydrogen bonds can form between the two strands in the short DNA segment shown below?

5′ ATGCGACTA 3′ 3′ TACGCTGAT 5′

Answer

22 (2 between each AT base pair and 3 between each GC base pair).

EXERCISE 28.2.4

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Answer

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

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28.3: REPLICATION OF DNA

OBJECTIVES

After completing this section, you should be able to describe, very briefly, the replication of DNA.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- replication
- semiconservative replication

STUDY NOTES

Notice that the objective for this section requires only that you be able to describe the replication process briefly.

According to the central dogma of molecular genetics, DNA is the genetically active component of the chromosomes of a cell. That is, DNA in the cell nucleus contains all the information necessary to control synthesis of the proteins, enzymes, and other molecules which are needed as that cell grows, carries on metabolism, and eventually reproduces. Thus when a cell divides, its DNA must pass on genetic information to both daughter cells. It must somehow be able to divide into duplicate copies. This process is called **replication**. Given the complementary double strands of DNA, it is relatively easy to see how DNA as a molecule is well structured for replication, as is show in Figure 28.3.1. Each strand serves as a template for a new strand. Thus, after DNA is replicated, each new DNA double helix will have one strand from the original DNA molecule, and one newly synthesized molecule. This is referred to as **semiconservative replication**.

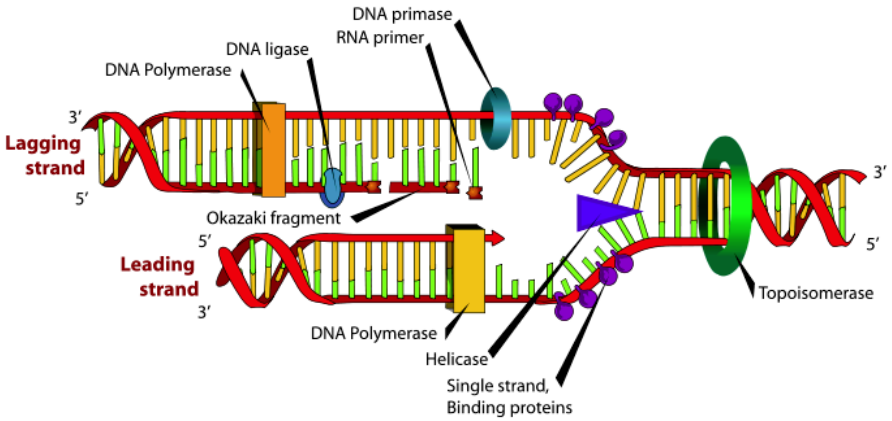


Figure 28.3.1: The replication of DNA. Replication occurs by means of partial unwinding of the two strands accompanied by synthesis of a new strand complementary to each of the originals. (CC BY 4.0; Aida Khakimova, Oleg Zolotarev, and Igor Zatsman via the Open Public Health Journal)

A rather complex mechanism exists for DNA replication, involving many different enzymes and protein factors. Let us consider some of the more important aspects of DNA replication. First, the double strand needs to be opened up to replicate each template strand. To do this, a set of proteins and enzymes bind to and open up the double helix at an origin point in the molecule. This forms **replication forks**, points where double stranded DNA opens up, allowing replication to occur. A helicase enzyme binds at the replication forks, with the function of further unwinding the DNA and allowing the replication fork to move along the double strand as DNA is replicated. Another enzyme, DNA gyrase, is also required to relieve stress on the duplex caused by unwinding the double strand. Further, single strand binding proteins are needed to prevent the single strands from reforming a double strand. Another essential enzyme in this initiation phase is primase, which creates an RNA primer on each single strand of DNA to begin replication from.

All of these initial functions are necessary to prepare the DNA for the main enzyme which builds then new strands, DNA polymerase. Multiple polymerase enzymes exist, but for the moment we will DNA polymerase III, the main DNA polymerase in *E. coli*. DNA polymerase III catalyzes the reaction by which a new nucleotide is added to a growing DNA strand. That reaction is seen in Figure 28.3.2. The DNA polymerase enzymes need a free 3' OH group in order to begin synthesizing a new strand, which explains the necessity of the RNA primer, which gives a 3'OH group for DNA polymerase III to start from.

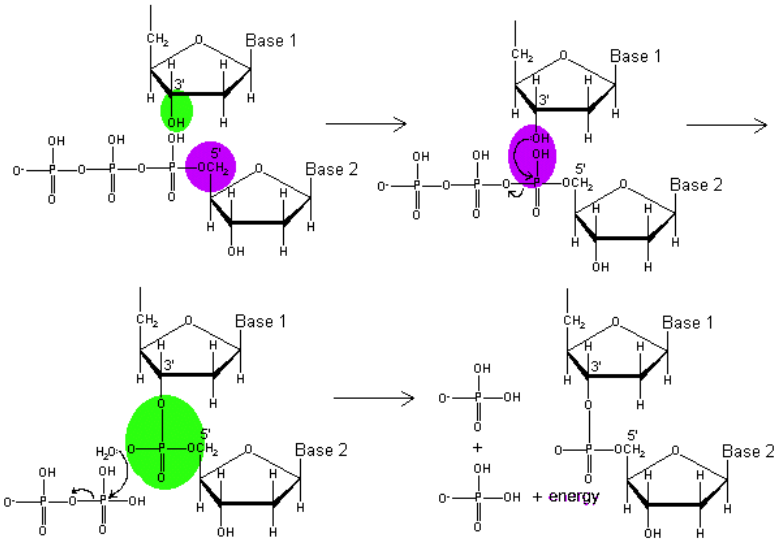


Figure **28.3.3**: The polymerization of DNA nucleotides. The 3' hydroxyl group attacks the triphosphate group on the incoming nucleotide. A new phosphodiester bond is formed, and a pyrophosphate group leaves. This leaves two phosphates, the energy released from breaking down a the high energy phosphate group, and a elongated strand of DNA with a new 3' hydroxyl group to which another nucleotide may be added.
(Copyright; author via source)

This leads to another constraint on DNA polymerase III. One strand, the **leading strand** can be polymerized continuously since the new strand being created goes 5' to 3' from the replication fork, but since the original strands are anti-parallel, the other strand, the **lagging strand** is going in the wrong direction for polymerization. In this case, the polymerization reaction starts away from the replication fork and works back toward it. This means that the lagging strand is synthesized in disconnected segments, known as **Okazaki fragments**, instead of continuously. Later, another DNA polymerase, in the case of *E. coli*, DNA polymerase I, removes RNA primers and fills in the missing discontinuities. Then, *another* enzyme, DNA ligase, connects breaks between 3'OH groups and 5' phosphate groups in the newly synthesized strands that exist due to these discontinuities. While the enzymes of this process differ in eukaryotes, they fulfill similar mechanisms. Even with this complexity of this process, DNA polymerase III is able to add new nucleotides at a rate of 250-1,000 nucleotides per second.[3]

A number of advantages of the double-stranded structure held together by hydrogen bonds is evident in the process of replication. Complementary base pairing, A to T and G to C, insures that the two new DNA molecules will be the same as the original. The large number of hydrogen bonds, each of which is relatively weak, makes complete separation of the two strands unlikely, but one hydrogen bond, or even a few, can be broken rather easily. The helicase portion of the replication complex can therefore separate the two strands in much the same way that a zipper operates. Like the teeth of a zipper, hydrogen bonds provide great strength when all work together, but the proper tool can separate them one at a time.

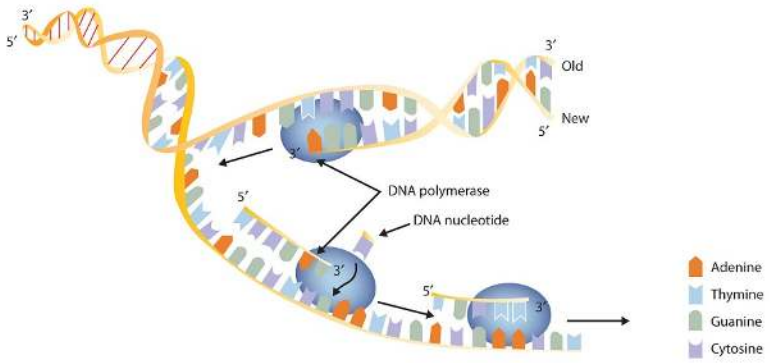


Figure **28.3.4**: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix.

THE SCOPE OF THE PROBLEM OF DNA REPLICATION

The 46 chromosomes of the human genome consists of roughly 6.5 billion base pairs of DNA if one considers the full diploid genome (i.e. if you count the DNA inherited from both parents). Considering that this DNA can be copied in just a few hours shows that the rate of DNA

replication is staggering.

Although DNA replication is typically a highly accurate process and proofreading DNA polymerases help to keep the error rate low (about one per 10 billion bases), mistakes still occur. In addition to errors of replication, environmental damage may also occur to the DNA. Such uncorrected errors of replication or environmental DNA damage may lead to serious consequences. Therefore, Nature has evolved several mechanisms for detecting and repairing damaged or incorrectly synthesized DNA.

EXAMPLE 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

Solution

Knowing that the two strands are antiparallel and that T base pairs with A, while C base pairs with G, the sequence of the complementary strand will be 3′-AGGTACTCAACT-5′ (can also be written as TCAACTCATGGA).

EXERCISE 28.3.1

A segment of one strand from a DNA molecule has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the opposite, or complementary, DNA chain?

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28.4: TRANSCRIPTION OF DNA

OBJECTIVES

After completing this section, you should be able to

- describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
- identify the important structural differences between DNA and DNA.
- given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
- identify the base sequence in RNA that would be complementary to a given base sequence in DNA.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- messenger RNA
- RNA polymerase
- ribosomal RNA
- transcription
- transfer RNA

STUDY NOTES

"Messenger RNA" (mRNA) carries the genetic information from the DNA in the nucleus to the cytoplasm where protein synthesis occurs. The code carried by mRNA is read by "transfer RNA" (tRNA) in a process called translation (see Section 28.5).

"Ribosomal RNA" (rRNA) is the term used to describe the RNA molecules which, together with proteins, make up the ribosomes on which proteins are synthesized.

Three types of RNA are formed during transcription: *messenger RNA* (mRNA), *ribosomal RNA* (rRNA), and *transfer RNA* (tRNA). These three types of RNA differ in function, size, and percentage of the total cell RNA (Table **28.4.1**). mRNA makes up only a small percent of the total amount of RNA within the cell, primarily because each molecule of mRNA exists for a relatively short time; it is continuously being degraded and resynthesized. The molecular dimensions of the mRNA molecule vary according to the amount of genetic information a given molecule contains. After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Elsewhere, we shall see how mRNA directly determines the sequence of amino acids during protein synthesis.

Table **28.4.1**: Properties of Cellular RNA in Escherichia coli

Type	Function	Approximate Number of Nucleotides	Percentage of Total Cell RNA
mRNA	codes for proteins	100–6,000	~3
rRNA	component of ribosomes	120–2900	83
tRNA	adapter molecule that brings the amino acid to the ribosome	75–90	14

For the hereditary information in DNA to be useful, it must be "expressed," that is, used to direct the growth and functioning of an organism. The flow of genetic information in cells goes from DNA to mRNA to protein, by genes which specify the sequences of mRNAs, which in turn specify the sequences of proteins.

The first step in the processes that constitute DNA expression is the synthesis of RNA, by a template mechanism that is in many ways analogous to DNA replication. Because the RNA that is synthesized is a complementary copy of information contained in DNA, RNA synthesis is referred to as transcription. Transcription requires the DNA double helix to partially unwind in the region of mRNA synthesis. The region of unwinding is called a **transcription bubble**. The DNA sequence has patterns which indicate where RNA polymerase should start and end transcription. A DNA sequence at which the RNA polymerase binds to start transcription is called a **promoter**. The DNA sequence that indicates the endpoint of transcription, where the RNA polymerase should stop adding nucleotides and dissociate from the template is known as a **terminator** sequence. The promoter and terminator, thus, bracket the region of the DNA that is to be transcribed.

In bacteria, the promotor sequence contains two 6 bp region called **consensus** sequences. One sequence is centered about 10 bp upstream from the transcription start site. The second sequence at about 35 basepairs upstream from the start of transcription. The consensus

sequences at -10 and -35 are necessary for recognition of the promoter region by RNA polymerase.

The DNA sequence that is transcribed to make RNA is called the antisense strand (also called template, anticoding, or transcribed strand), while the complementary sequence on the other DNA strand is called the sense strand (also called the coding or informational strand). To initiate RNA synthesis, the two DNA strands unwind at specific sites along the DNA molecule. Ribonucleotides are attracted to the uncoiling region of the DNA molecule, beginning at the 3′ end of the template strand, according to the rules of base pairing. Thymine in DNA calls for adenine in RNA, cytosine specifies guanine, guanine calls for cytosine, and adenine requires uracil. RNA polymerase—an enzyme—binds the complementary ribonucleotide and catalyzes the formation of the ester linkage between ribonucleotides, a reaction very similar to that catalyzed by DNA polymerase (Figure **28.4.1**). Synthesis of the RNA strand takes place in the 5′ to 3′ direction, antiparallel to the template strand. Only a short segment of the RNA molecule is hydrogen-bonded to the template strand at any time during transcription. When transcription is completed, the RNA is released, and the DNA helix reforms. The nucleotide sequence of the RNA strand formed during transcription is identical to that of the corresponding coding strand of the DNA, except that U replaces T.

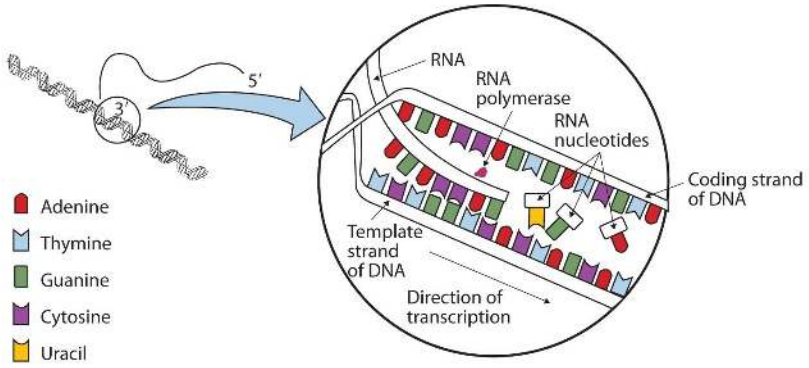


Figure **28.4.1**: A Schematic Diagram of RNA Transcription from a DNA Template. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time. (CC BY-SA-NC 3.0; Anonymous via LibreTexts)

The genes of eukaryotes (animals and plants) usually done have continuous segments of coding DNA. Rather they have intervening sequences of DNA (introns) within a given gene that separate coding fragments of DNA (exons). In a process called **splicing**, a primary transcript is made from the DNA, and then splicesomes cut out the introns and join the exons to form a contiguous stretch to form messenger RNA, mRNA. Once formed the mRNA leaves the nucleus is to be translated into a protein sequence..

New findings make it even more complicated to define a gene, especially if the transcripts of a "gene region" are studied. Cheng et al studied all transcripts from 10 different human chromosomes and 8 different cell lines. They found a large number of different transcripts, many of which overlapped. Splicing often occur between nonadjacent introns. Transcripts were found from both strands and were from regions containing introns and exons. Other studies found up to 5% of transcripts continued through the end of "gene" into other genes. 63% of the entire mouse genome, which is comprised of only 2% exons, is transcribed.

? EXERCISE 28.4.1

A portion of the template strand of a gene has the sequence 5′-TCCATGAGTTGA-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

Answer

Four things must be remembered in answering this question: (1) the DNA strand and the RNA strand being synthesized are antiparallel; (2) RNA is synthesized in a 5′ to 3′ direction, so transcription begins at the 3′ end of the template strand; (3) ribonucleotides are used in place of deoxyribonucleotides; and (4) thymine (T) base pairs with adenine (A), A base pairs with uracil (U; in RNA), and cytosine (C) base pairs with guanine (G). The sequence is determined to be 3′-AGGUACUCAACU-5′ (can also be written as 5′-UCAACUCAUGGA-3′).

? EXERCISE 28.4.2

What would be the DNA base sequence of the coding strand required to transcribe the following RNA sequence?

5′-AUGAGCGACUUUGCGGGAUUA-3′

Answer

5′-ATGAGCGACTTTGCGGGATTA-3′.

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28.5: TRANSLATION OF RNA - PROTEIN BIOSYNTHESIS

OBJECTIVES

After completing this section, you should be able to describe, very briefly, the roles of messenger RNA and transfer RNA in the biosynthesis of proteins.

KEY TERMS

Make certain that you can define, and use in context, the key terms below.

- anticodon
- codon
- translation

STUDY NOTES

As in the preceding section, you should not be too concerned about trying to memorize details. The objective requires you to have a general understanding of the roles played by mRNA and tRNA in the biosynthesis of proteins, and that you be able to describe this process.

After transcription, which takes place in the nucleus, the mRNA passes into the cytoplasm, carrying the genetic message from DNA to the ribosomes, the sites of protein synthesis. Ribosomes are cellular substructures where proteins are synthesized. They contain about 65% rRNA and 35% protein, held together by numerous noncovalent interactions, such as hydrogen bonding, in an overall structure consisting of two globular particles of unequal size. We turn now to the question of how the sequence of nucleotides in a molecule of ribonucleic acid (RNA) is translated into an amino acid sequence.

How can a molecule containing just 4 different nucleotides specify the sequence of the 20 amino acids that occur in proteins? If each nucleotide coded for 1 amino acid, then obviously the nucleic acids could code for only 4 amino acids. What if amino acids were coded for by groups of 2 nucleotides? There are 4^2, or 16, different combinations of 2 nucleotides (AA, AU, AC, AG, UU, and so on). Such a code is more extensive but still not adequate to code for 20 amino acids. However, if the nucleotides are arranged in groups of 3, the number of different possible combinations is 4^3, or 64. Here we have a code that is extensive enough to direct the synthesis of the primary structure of a protein molecule.

The **genetic code** can therefore be described as the identification of each group of three nucleotides and its particular amino acid. The sequence of these triplet groups in the mRNA dictates the sequence of the amino acids in the protein. Each individual three-nucleotide coding unit, as we have seen, is called a **codon**.

First base	Second base: U	C	A	G	Third base
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	Stop	Stop	A
	Leu	Ser	Stop	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Figure **28.5.1**: The Genetic Code

Early experimenters were faced with the task of determining which of the 64 possible codons stood for each of the 20 amino acids. The cracking of the genetic code was the joint accomplishment of several well-known geneticists—notably Har Khorana, Marshall Nirenberg, Philip Leder, and Severo Ochoa—from 1961 to 1964. The genetic dictionary they compiled, summarized in Figure **28.5.3**, shows that 61 codons code for amino acids, and 3 codons serve as signals for the termination of polypeptide synthesis (much like the period at the end of a sentence). Notice that only methionine (AUG) and tryptophan (UGG) have single codons. All other amino acids have two or more codons.

Protein synthesis is accomplished by orderly interactions between mRNA and the other ribonucleic acids (transfer RNA [tRNA] and ribosomal RNA [rRNA]), the ribosome, and more than 100 enzymes. The mRNA formed in the nucleus during transcription is transported across the nuclear membrane into the cytoplasm to the ribosomes—carrying with it the genetic instructions. The process in which the information encoded in the mRNA is used to direct the sequencing of amino acids and thus ultimately to synthesize a protein is referred to as *translation*.

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. The carboxylic acid group of the amino acid forms an ester linkage with with the 3' hydroxyl group on the riboses bonded at the 3' end of the tRNA. This crucial process requires an enzyme known as aminoacyl-tRNA synthetase (Figure **28.5.1**). There is a specific aminoacyl-tRNA synthetase for each amino acid. This high degree of specificity is vital to the incorporation of the correct amino acid into a protein. After the amino acid molecule has been bound to its tRNA carrier, protein synthesis can take place.

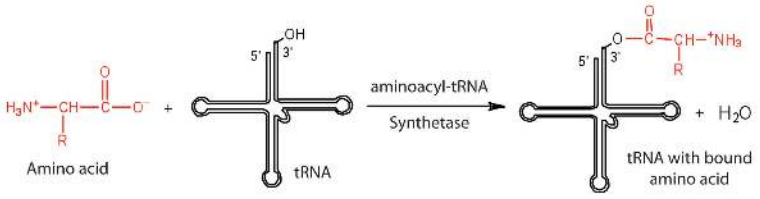


Figure **28.5.2** Binding of an Amino Acid to Its tRNA

The two-dimensional structure of a tRNA molecule is reminiscent of a cloverleaf. At one end of the tRNA molecule is the acceptor stem, where the amino acid is attached. The tRNA Molecule has three distinctive loops. One of these is called the anticodon loop which holds a sequence of three nucleotides called the **anticodon**. Each anticodon corresponds to the amino acid each is tRNA molecule is specifically designed to carry. For example, the amino acid lysine has the codon AAG, so the anticodon is UUC. Therefore, lysine would be carried by a tRNA molecule with the anticodon UUC. Each of the 20 amino acids found in proteins has at least one corresponding kind of tRNA, and most amino acids have more than one.

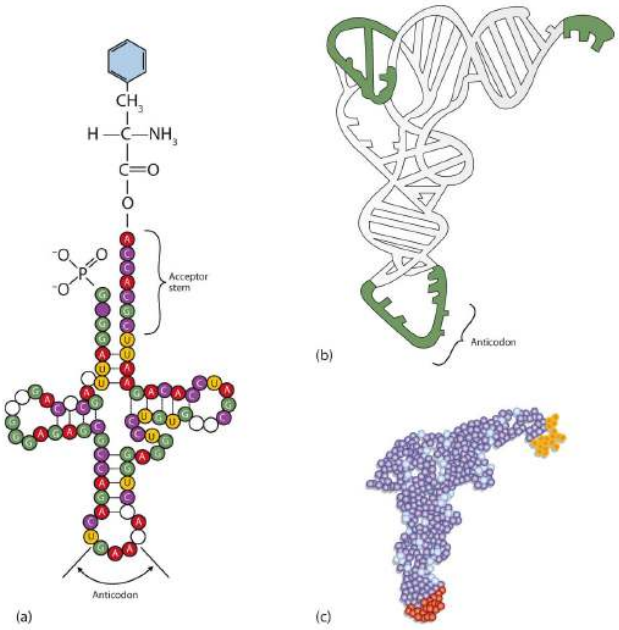
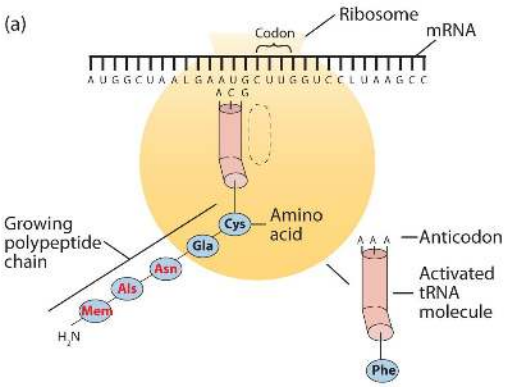
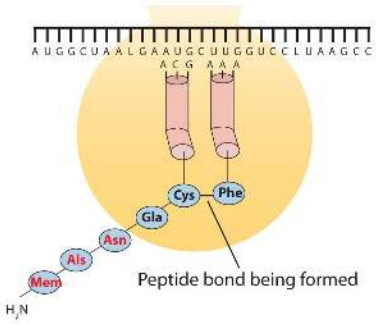


Figure **28.5.3**: Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common ribonucleotides A, U, C, and G.) (b) In the three-dimensional structure of yeast phenylalanine tRNA, note that the anticodon loop is at the bottom and the acceptor stem is at the top right. (c) This shows a space-filling model of the tRNA.

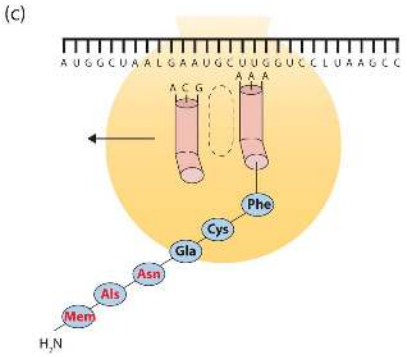
During protein synthesis the codon on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. Wherever the codon AAG appears in mRNA, a UUC anticodon on a tRNA temporarily binds to the codon ect. As each different tRNA brings an amino acid into position an enzyme adds it to the growing protein chain. The protein is released from the ribosome once it is completed. Figure **28.5.2** depicts a schematic stepwise representation of this all-important process.



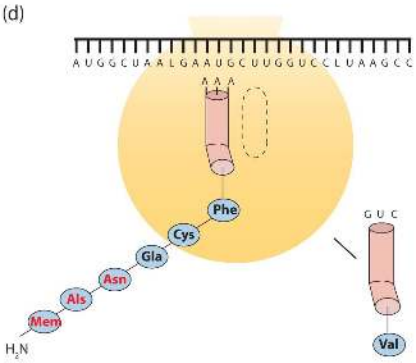
(a) Protein synthesis is already in progress at the ribosome. The growing polypeptide chain is attached to the tRNA that brought in the previous amino acid (in this illustration, cys.)



(b) An activated tRNA, which has the anticodon AAA, binds to the ribosome next to the previous bound tRNA and interacts with the mRNA molecule though base-pairing of the codon and anticodon. The amino acid Phe is being incorporated into the polypeptide chain by the formation of a peptide linkage between the carboxyl group of Cys and the amino acid group of the Phe. This reaction is catalyzed by the enzyme peptidyl transferase, a component of the ribosome.



(c) The Cys-Phe linkage is now complete, and the growing polypeptide chain remains attached to the tRNA for Phe.



(d) The ribosome moves to the right along the mRNA strand. This shift brings the next codon, GUC, into its correct position on the surface of the ribosome. Note that an activated tRNA molecule, containing the next amino acid to be attached to the chain is moving to the ribosome. Steps (b)–(d) will be repeated until the ribosome reaches a stop codon.

Figure 28.5.4: The Elongation Steps in Protein Synthesis

? EXERCISE 28.5.1

What are the roles of mRNA and tRNA in protein synthesis?

Answer

mRNA provides the code that determines the order of amino acids in the protein; tRNA transports the amino acids to the ribosome to incorporate into the growing protein chain.

EXERCISE 28.5.2

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Answer

Use Figure **28.5.1** to determine what amino acid each set of three nucleotides (codon) codes for. Remember that the sequence is read starting from the 5′ end and that a protein is synthesized starting with the N-terminal amino acid. The sequence 5′-AUGCCACGAGUUGAC-3′ codes for met-pro-arg-val-asp.

EXERCISE 28.5.3

Write the anticodon on tRNA that would pair with each mRNA codon.

a. 5′-UUU-3′
b. 5′-CAU-3′
c. 5′-AGC-3′
d. 5′-CCG-3′

Answer

a. 3′-AAA-5′
b. 3′-GUA-5′
c. 3′-UCG-5′
d. 3′-GGC-5′

EXERCISE 28.5.4

The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?

Answer

27 nucleotides (3 nucleotides/codon)

EXERCISE 28.5.5

Determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.

Answer

met-ser-asp-phe-ala-gly-leu

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28.6: DNA SEQUENCING

OBJECTIVES

After completing this section, you should be able to

- Describe briefly how DNA sequencing is carried out.

DNA sequencing determines the order of nucleotide bases within a given fragment of DNA. This information can be used to infer the RNA or protein sequence encoded by the gene, from which further inferences may be made about the gene's function and its relationship to other genes and gene products. DNA sequence information is also useful in studying the regulation of gene expression. If DNA sequencing is applied to the study of many genes, or even a whole genome, it is considered an example of genomics.

While techniques to sequence proteins have been around since the 1950s, techniques to sequence DNA were not developed until the mid-1970s, when two distinct sequencing methods were developed almost simultaneously, one by Walter Gilbert's group at Harvard University, the other by Frederick Sanger's group at Cambridge University. However, until the 1990s, the sequencing of DNA was a relatively expensive and long process. Using radiolabeled nucleotides also compounded the problem through safety concerns. With currently-available technology and automated machines, the process is cheaper, safer, and can be completed in a matter of hours. The Sanger sequencing method was used for the human genome sequencing project, which was finished its sequencing phase in 2003, but today both it and the Gilbert method have been largely replaced by better methods.

RESTRICTION ENZYMES

To be able to sequence DNA, it is first necessary to cut it into smaller fragments. What is needed is a way to cleave the DNA molecule at a few precisely-located sites so that a small set of homogeneous fragments are produced. To cut DNA at known locations, researchers use **restriction endonucleases** enzymes that have been purified from various bacterial species, and which can be purchased from various commercial sources. REs occur naturally in bacteria, where they specifically recognize short stretches of nucleotides in DNA and catalyze double-strand breaks at or near the recognition site (also known as a restriction site). These enzymes are usually named after the bacterium from which they were first isolated. For example, ***EcoRI*** and *EcoRV* are both enzymes from *E. coli*.

Restriction enzymes like EcoRI are frequently called 6-cutters, because they recognize a 6-nucleotide sequence. Assuming a random distribution of A, C, G and Ts in DNA, probability predicts that a recognition site for a 6-cutter should occur about once for every 4096 bp (4^6) in DNA. Of course, the distribution of nucleotides in DNA is not random, so the actual sizes of DNA fragments produced by EcoRI range from hundreds to many thousands of base pairs, but the mean size is close to 4000 bp. DNA fragments of this length are useful in the lab, since they long enough to contain the coding sequence for proteins and are well-resolved on agarose gels.

EcoRI recognizes the sequence G A A T T C in double stranded DNA. This recognition sequence is a palindrome with a two-fold axis of symmetry, because reading from 5' to 3' on either strand of the helix gives the same sequence. The palindromic nature of the restriction site is more obvious in the figure below. The dot in the center of the restriction site denotes the axis of symmetry. EcoRI catalyzes the hydrolysis of the phosphodiester bonds between G and A on both DNA strands. The restriction fragments generated in the reaction have short single-stranded tails at the 5'-ends. These ends are often referred to as "sticky ends," because of their ability to form hydrogen bonds with complementary DNA sequences.



Figure **28.6.1**: The recognition sequence for EcoRI (blue) is cleaved by the enzyme (grey). This particular enzyme cuts DNA at a position offset from the center of the restriction site. This creates an overhanging, sticky-end. (Original-Deyholos-CC:AN)

READING DNA SEQUENCES

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. Sanger sequencing, also known as chain-termination sequencing, requires a single-stranded DNA template, a DNA primer, a DNA polymerase, normal deoxynucleotidetriphosphates (dNTPs), and modified nucleotides (dideoxyNTPs - ddNTP) that terminate DNA strand elongation. These chain-terminating nucleotides lack a 3′-OH group required for the formation of a phosphodiester bond between two nucleotides, causing DNA polymerase to cease extension of DNA when a ddNTP is incorporated.

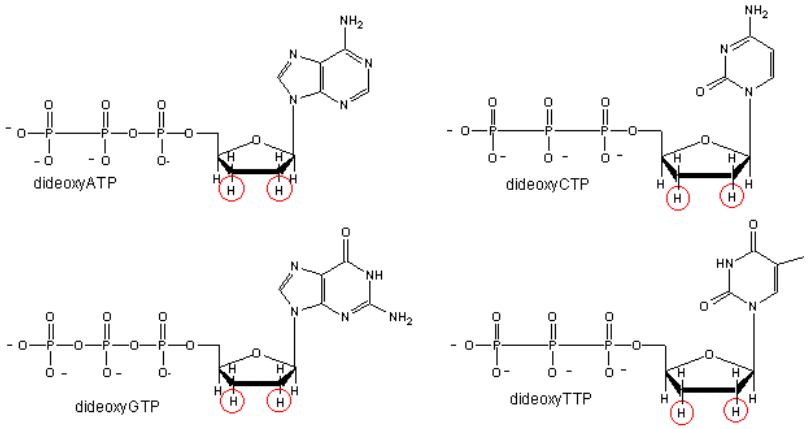


Figure **28.6.2**: Didexoynucleotides

Four reaction tubes are set up, each containing the template DNA to be sequenced, a *primer* of known sequence, all four of the standard deoxynucleotides (dATP, dGTP, dCTP and dTTP), and the DNA polymerase. To each reaction is added only one of the four dideoxynucleotides (ddATP, ddGTP, ddCTP, or ddTTP) which has been fluorescently labeled. Most of the time in a Sanger sequencing reaction, DNA Polymerase will add a proper dNTP to the growing strand it is synthesizing in vitro. But at random locations, it will instead add a ddNTP. When it does, that strand will be terminated at the ddNTP just added. If enough template DNAs are included in the reaction mix, each one will have the labeled ddNTP inserted at a different random location, and there will be at least one DNA terminated at each different nucleotide along its length for as long as the in vitro reaction can take place (about 900 nucleotides under optimal conditions.)

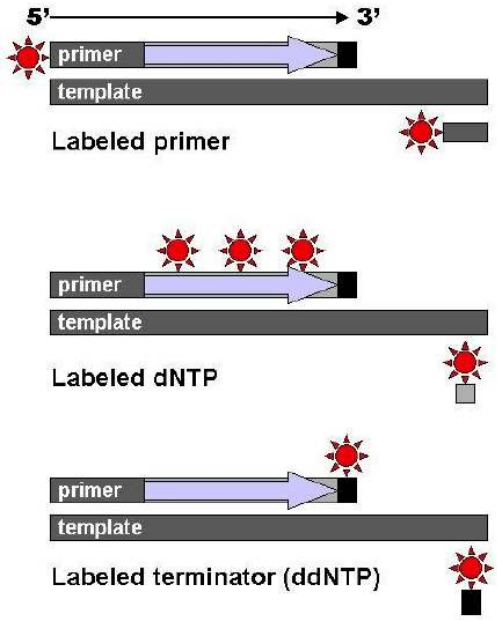


Figure **28.6.3**: Sanger sequencing: Different types of Sanger sequencing, all of which depend on the sequence being stopped by a terminating dideoxynucleotide (black bars).

After the reactions are over, the newly synthesized strands can be denatured from the template, and then separated by capillary electrophoresis or other equivalent methods. Since each band differs in length by one nucleotide, and the identity of that nucleotide is known from its fluorescence, the DNA sequence can be read simply from the order of the colors in successive bands.

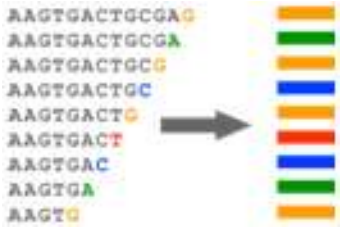


Figure **28.6.4**: Fluorescently labeled products can be separated electrophoretically based on their length. (Original-Deyholos-CC:AN)

As each differently-sized fragment exits the capillary column, a laser excites the florescent tag on its terminal nucleotide. From the color of the resulting florescence, a computer can keep track of which nucleotide was present as the terminating nucleotide. The computer also keeps track of the order in which the terminating nucleotides appeared, which is the sequence of the DNA used in the original reaction. In practice, the maximum length of sequence that can be read from a single sequencing reaction is about 700 bp.

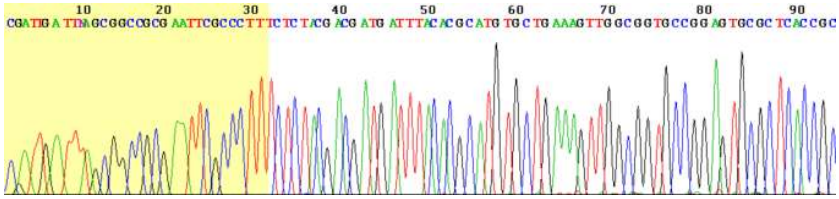


Figure **28.6.5**: Chromatograph: This is an example of the output of a Sanger sequencing read using fluorescently labeled dye-terminators. The four DNA bases are represented by different colors which are interpreted by the software to give the DNA sequence above.

Scientists now know the sequence of all the 3 billion DNA base pairs in the entire human genome. This knowledge was attained by the **Human Genome Project (HGP),** a $3 billion, international scientific research project that was formally launched in 1990. The project was completed in 2003, two years ahead of its 15-year projected deadline. Determining the sequence of the billions of base pairs that make up human DNA was the main goal of the HGP. Another goal was mapping the location and determining the function of all the genes in the human genome. There are only about 20,500 genes in human beings. If modern methods were used it might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.

EXAMPLE 28.6.1

You will pretend to sequence a single stranded piece of DNA as shown below. The new nucleotides are added by the enzyme DNA polymerase to the primer, GACT, in the 5' to 3' direction. You will set up 4 reaction tubes, Each tube contains all the dXTP's. In addition, add ddATP to tube 1, ddTTP to tube 2, ddCTP to tube 3, and ddGTP to tube 4. For each separate reaction mixture, determine all the possible sequences made by writing the possible sequences on one of the unfinished complementary sequences below. Cut the completed sequences from the page, determine the size of the polynucleotide sequences made, and place them as they would migrate (based on size) in the appropriate lane of a imaginary gel which you have drawn on a piece of paper. Lane 1 will contain the nucleotides made in tube 1, etc. Then draw lines under the positions of the cutout nucleotides to represent DNA bands in the gel. Read the sequence of the complementary DNA synthesized. Then write the sequence of the ssDNA that was to be sequenced.

- 5' T C A A C G A T C T G A 3' (STAND TO SEQUENCE)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)
- 3' G A C T 5' (primer)

Since the DNA fragments have no detectable color, they can not be directly visualized in the gel. Alternative methods are used. In the one described above, radiolabeled ddXTP's where used. Once the sequencing gel is run, it can be dried and the bands visualized by radioautography (also called autoradiography). A place of x-ray film is placed over the dried gel in a dark environment. The radiolabeled bands will emit radiation which will expose the x-ray film directly over the bands. The film can be developed to detect the bands. In a newer technique, the primer can be labeled with a flourescent dye. If a different dye is used for each reaction mixture, all the reaction mixtures can be run in one lane of a gel. (Actually only one reaction mix containing all the ddXTP's together need be performed.) The gel can then be scanned by a laser, which detects fluorescence from the dyes, each at a different wavelength.

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28.7: DNA SYNTHESIS

OBJECTIVES

After completing this section, you should be able to

- describe, briefly, the steps required for chemical synthesis of DNA segments.

DNA must be synthesized to study genes, the sequence of genomes, and many other studies. This occurs in two fashions, by polymerase chain reaction (PCR) and chemical synthesis. PCR is covered in Section 28.8. Here we will focus on chemical synthesis of short DNA segments, which which are called oligonucleotides. Oligonucleotide synthesis is the chemical synthesis of relatively short fragments of nucleic acids, both DNA and RNA with a defined chemical structure (sequence). The technique is extremely useful in current laboratory practice because it provides a rapid and inexpensive access to custom-made oligonucleotides of the desired sequence.

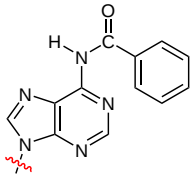
The synthesis of DNA is more difficult than peptide synthesis (Section 26-8) because of the complexity of nucleotide monomers. Commercial automated DNA synthesizers are available which allow for DNA segments to be made quickly and at a low cost. DNA synthesizers typically uses solid-phase techniques similar to the Merrifield solid-phase peptide synthesizer. Nucleotides are protected then covalently bonded to a solid support. Nucleotides are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, it is then deprotected, and collected. The occurrence of side reactions sets practical limits for the length of synthetic oligonucleotides (up to about 200 nucleotide residues) because the number of errors accumulates with the length of the oligonucleotide being synthesized. Products are often isolated by HPLC to obtain the desired oligonucleotides in high purity. Typically, synthetic oligonucleotides are single-stranded DNA or RNA molecules around 15–25 bases in length.

DNA CHEMICAL SYNTHESIS

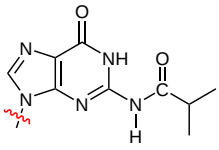
The synthesis of DNA involves five steps:

STEP 1

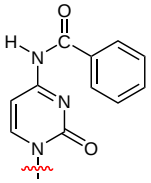
Nucleosides used for this synthesis are modified with a linking agent at the 3' hydroxyl group of deoxyribose. The 5' hydroxyl group of the nucleosides is protected with *p*-dimethoxytrityl (DMT) ether. The amine groups on the nucleoside's heterocyclic bases are also protected. The amines of adenine and cytosine bases are protected with benzoyl groups. Guanine's amine are protected by a isobutyryl group and thymine has no amine groups so protection is not required.



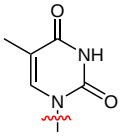
N-Protected Adenine



N-Protected Guanine

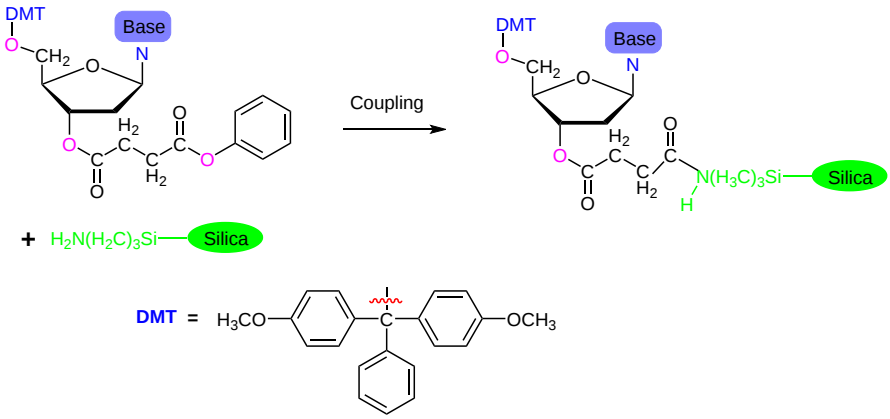


N-Protected Cytosine



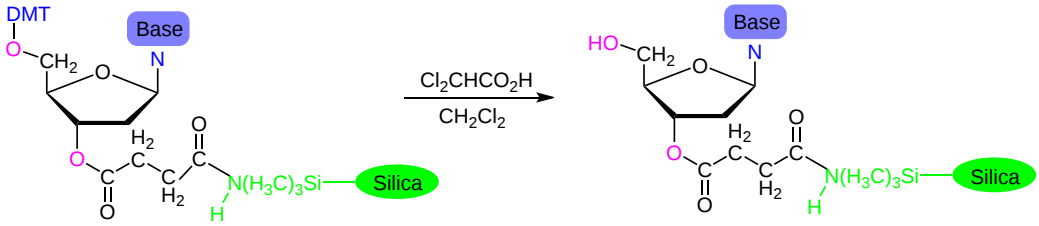
Thymine

The solid phase support used for DNA synthesis is commonly silica (SO_2) spheres which have been functionalized with (3-aminopropyl)triethoxysilane such that an amine group is available for reaction on the surface. A protected nucleoside is coupled to the solid phase support through an ester linkage with the 3' hydroxyl group of the nucleoside and an amide linkage with amine group from the silica surface.



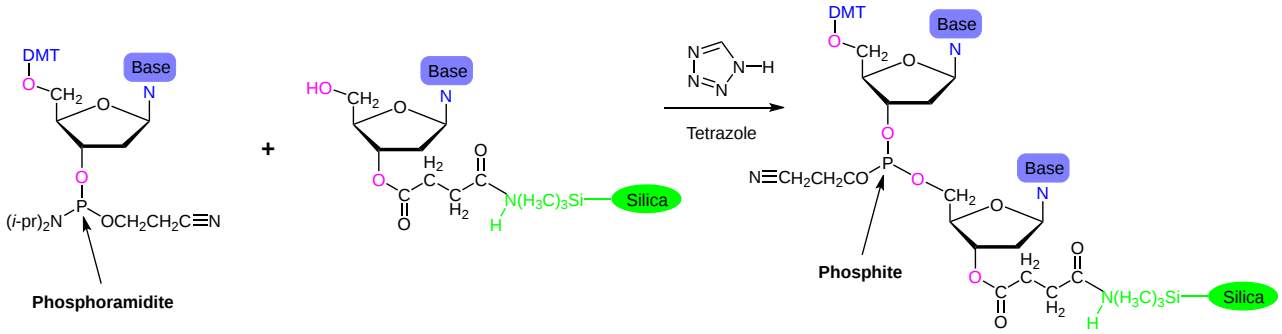
STEP 2

Reaction with with dichloroacetic acid removes the DMT protecting group from the 5' hydroxyl of the nucleoside attached to the silica surface. The *p*-dimethoxytrityl leaving group forms a relatively stable dimethoxytrityl cation which is both tertiary and benzylic. The reaction proceeds rapidly through a S_N1 mechanism.



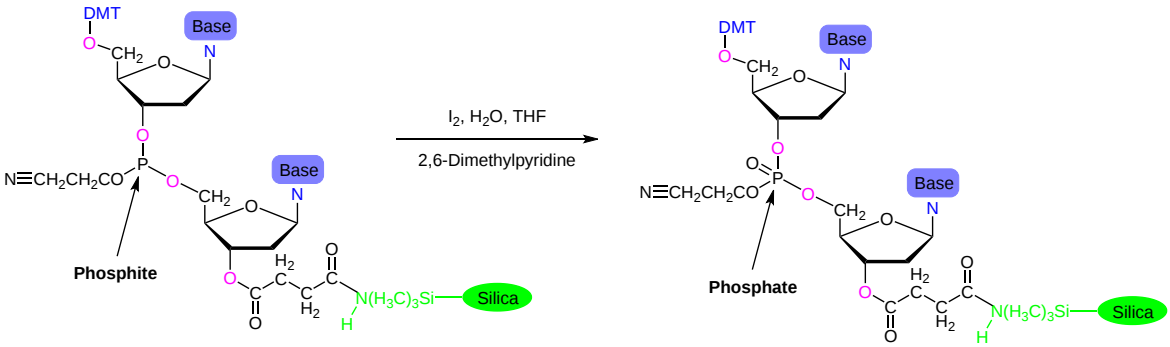
STEP 3

The nucleoside attached to the silica surface is then reacted with a protected nucleoside which has a **phosphoramidite** functional group [$R_2NP(OR)_2$] attached to the 3' hydroxyl group of its deoxyribose moiety. In addition, one of the phosphorus oxygen atoms of the phosphoramidite group is protected with a beta-cyanoethyl group (-OCH_2CH_2CN). The two nucleosides are coupled in a reaction which uses acetonitrile as a polar aprotic solvent, tetrazole as a heterocyclic amine catalyst, and produces a product with a phosphite functional group [$P(OR)_3$].



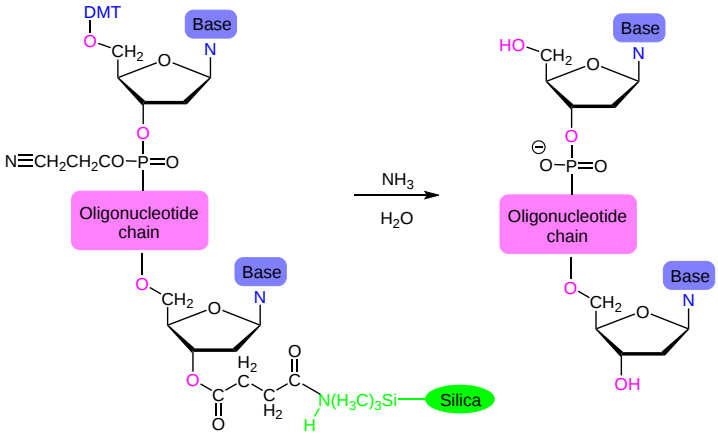
STEP 4

Next the phosphite product of the previous step is oxidized to a phosphate by reaction with iodine (I_2) along with 2,6-dimethylpyridine in aqueous tetrahydrofuran (THF). Additional nucleosides can now be added by repeating the **phosphoramidite oligodeoxynucleotide synthesis cycle** of (1) DMT deprotection, (2) phosphoramidite coupling, and (3) oxidation to a phosphite.



STEP 5

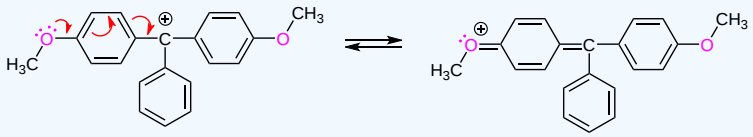
After the oligonucleotide chain of the desired sequence has been made, the final step is the removal of all the protecting groups and the linkage to silica by reaction with aqueous ammonia (NH_3).



? EXERCISE 28.7.1

Draw a mechanism which shows why dimethoxytrityl cation produced by the cleavage of a *p*-dimethoxytrityl protecting group is exceptionally stable.

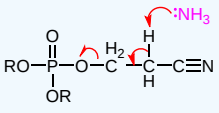
Answer



? EXERCISE 28.7.2

When the beta-cyanoethyl protecting group is cleaved with aqueous ammonia, Acrylonitrile, H_2CCHCN , is also produced as a by-product. Draw a mechanism for the reaction.

Answer



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28.8: THE POLYMERASE CHAIN REACTION

OBJECTIVES

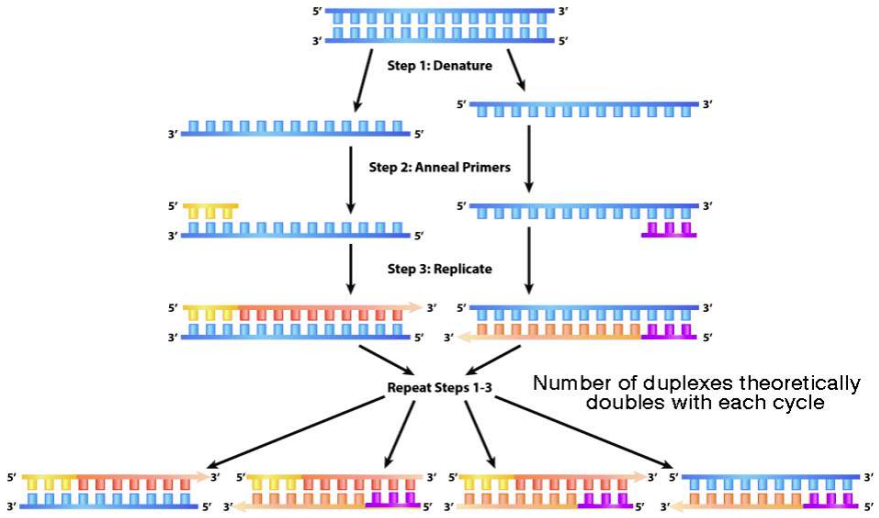
After completing this section, you should be able to

1. describe, briefly the three steps of PCR.

The polymerase chain reaction (PCR), allows one to use the power of DNA replication to amplify DNA enormously in a short period of time. As you know, cells replicate their DNA before they divide, and in doing so, double the amount of the cell's DNA. PCR essentially mimics cellular DNA replication in the test tube, repeatedly copying the target DNA over and over, to produce large quantities of the desired DNA. Kary B. Mullis was awarded a Nobel Prize in 1993 for his development of PCR, which is now the basis of innumerable research studies of gene structure, function and evolution as well as applications in criminal forensics, medical diagnostics and other commercial uses.

PCR requires a DNA fragment, some primers, which are short synthetic oligonucleotides whose sequence matches a region flanking the target sequence. All four deoxynucleotide triphosphates (dATP, dCTP, dGTP, dTTP), are added along with a heat stable DNA polymerase, **Taq**, from the organism *Thermophilus aquaticus* (which lives in hot springs).

PCR is run in a repeating cycle which involves three steps, template denaturing, primer annealing and primer extension.



TEMPLATE DENATURING

This step is the first regular cycling event and consists of heating the reaction to 94-98°C. It causes denaturing of the DNA template by disrupting the hydrogen bonds between complementary bases, yielding single-stranded DNA molecules. The Taq polymerase is heat-stable so it is not denatured by the high temperature needed to separate the DNA template strands.

PRIMER ANNEALING

Next, the solution is cooled to 50-65°C, a temperature that favors complementary DNA sequences finding each other and making base pairs, a process called **annealing**. Since the primers are present in great excess, the complementary sequences they target are readily found and base-paired to the primers. These primers direct the synthesis of DNA. Only where primer anneals to a DNA strand will replication occur, since DNA polymerases require a primer to begin synthesis of a new strand.

PRIMER EXTENSION

The temperature at this step depends on the DNA polymerase used; Taq polymerase has its optimum activity temperature at 75-80°C, and commonly a temperature of 72°C is used with this enzyme. At this step the DNA polymerase synthesizes a new DNA strand complementary to the DNA template strand by adding dNTPs that are complementary to the template in 5′ to 3′ direction, condensing the 5′-phosphate group of the dNTPs with the 3′-hydroxyl group at the end of the nascent (extending) DNA strand. On completion of this step there are two copies of the DNA template. The new DNA then be denatured to start the cycle again. Each cycle doubles the amount of DNA. Using

automated equipment, each cycle of replication can be completed in less than 5 minutes. After 30 cycles, what began as a single molecule of DNA has been amplified into more than a billion copies.

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CHAPTER OVERVIEW

29: ORBITALS AND ORGANIC CHEMISTRY - PERICYCLIC REACTIONS

Pericyclic reactions are of significant synthetic importance in organic chemistry due to their high stereo- and regioselectivity, mild reaction conditions, and the formation of multiple bonds in a single step. They find applications in the synthesis of complex organic molecules, natural product synthesis, and the construction of functional materials. Understanding the principles governing pericyclic reactions is essential for synthetic chemists to design and control reactions with precision.

29.0: Chapter Overview
29.1: Molecular Orbitals of Conjugated Pi Systems
29.2: Electrocyclic Reactions
29.3: Stereochemistry of Thermal Electrocyclic Reactions
29.4: Photochemical Electrocyclic Reactions
29.5: Cycloaddition Reactions
29.6: Stereochemistry of Cycloadditions
29.7: Sigmatropic Rearrangements
29.8: Some Examples of Sigmatropic Rearrangements
29.9: A Summary of Rules for Pericyclic Reactions

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29.0: Chapter Overview

Learning Objectives

- Define pericyclic reactions as concerted processes involving cyclic movement of electrons.
- Explain the Woodward-Hoffmann Rules for predicting outcomes based on molecular orbital symmetry.
- Outline subclasses like cycloadditions, electrocyclic reactions, and sigmatropic rearrangements.
- Describe how pericyclic reactions proceed through cyclic transition states and molecular orbitals.
- Provide key examples like Diels-Alder, electrocyclic ring closures, and Claisen rearrangements.
- Discuss how pericyclic reactions are used in synthesis of complex molecules and materials.

Pericyclic reactions represent a fascinating class of organic reactions characterized by the concerted movement of electrons around a cyclic array of atoms. These reactions involve a cyclic transition state where bonding changes occur with the involvement of π electrons. The term "pericyclic" stems from the Greek roots "peri," meaning around, and "cyclo," referring to cycle or ring, encapsulating the cyclic nature of these reactions.

Key features of pericyclic reactions include their stereospecificity, concertedness, and often high regio- and stereochemical control. They are governed by orbital symmetry rules, primarily the Woodward-Hoffmann rules, which provide a theoretical framework for predicting the outcome of these reactions based on the symmetry properties of the molecular orbitals involved.

Pericyclic reactions encompass several important subclasses, including:

1. **Cycloadditions**: In cycloaddition reactions, two or more unsaturated molecules combine to form a cyclic product. Diels-Alder reaction is a classic example, where a conjugated diene reacts with a dienophile to form a cyclohexene ring.
2. **Electrocyclic Reactions**: These reactions involve the reorganization of π electrons in a conjugated system to form a cyclic compound. Examples include the ring-opening and ring-closing reactions of cyclobutene and cyclohexadiene systems.
3. **Sigmatropic Rearrangements**: Sigmatropic rearrangements involve the migration of a σ-bond (a single bond) along a conjugated system. The Claisen rearrangement and the Cope rearrangement are prominent examples of sigmatropic shifts.
4. **[2+2] Cycloadditions**: These reactions involve the formation of a four-membered ring from two unsaturated reactants.

Pericyclic reactions find wide applications in organic synthesis due to their efficiency, selectivity, and the ability to form multiple bonds stereospecifically in a single step. Moreover, their predictable nature based on orbital symmetry principles makes them valuable tools for designing complex molecular architectures. Understanding and mastering pericyclic reactions are essential for synthetic chemists aiming to construct intricate organic molecules efficiently and with precision.

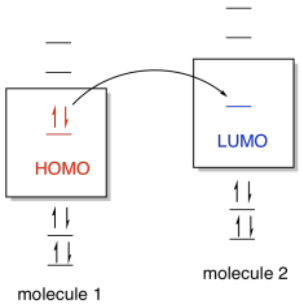
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29.1: MOLECULAR ORBITALS OF CONJUGATED PI SYSTEMS

FRONTIER MOLECULAR ORBITAL THEORY

Prior to 1965, pericyclic reactions were known as "no mechanism reactions" since no one could adequately explain why reaction outcomes changed depending on whether reactants were exposed to heat or light. In 1965 Robert Burns Woodward and Roald Hoffmann used **Frontier Molecular Orbital Theory**, initially proposed by Kenichi Fukui, to develop their **Theory of Conservation of Orbital Symmetry** where outcomes of pericyclic reactions are explained by examining the **Highest Occupied Molecular Orbital (HOMO)** or **Lowest Unoccupied Molecular Orbital (LUMO)** of the reacting system. Their analysis of cycloadditions, electrocyclic reactions, and sigmatropic rearrangements is commonly referred to as the Woodward-Hoffmann Rules. A detailed analysis of three reaction types is provided in the subsequent sections of this chapter.

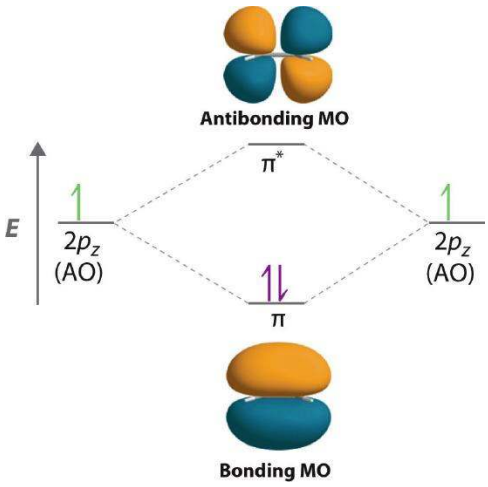
HOMO and LUMO are often referred to as **frontier orbitals** and their energy difference is termed the **HOMO–LUMO gap**. One common way of thinking about reactions in this way is through the concept of frontier orbitals. This idea says that if one species is going to donate electrons to another in order to form a new bond, then the donated electrons are most likely going to come from the highest occupied energy level. In this level, called the highest occupied molecular orbital (HOMO), the electrons are further from the nucleus and therefore less tightly held by the protons in the nucleus. The electrons would be donated, in turn, to the lowest empty energy level on the other species, called the lowest unoccupied molecular orbital (LUMO).



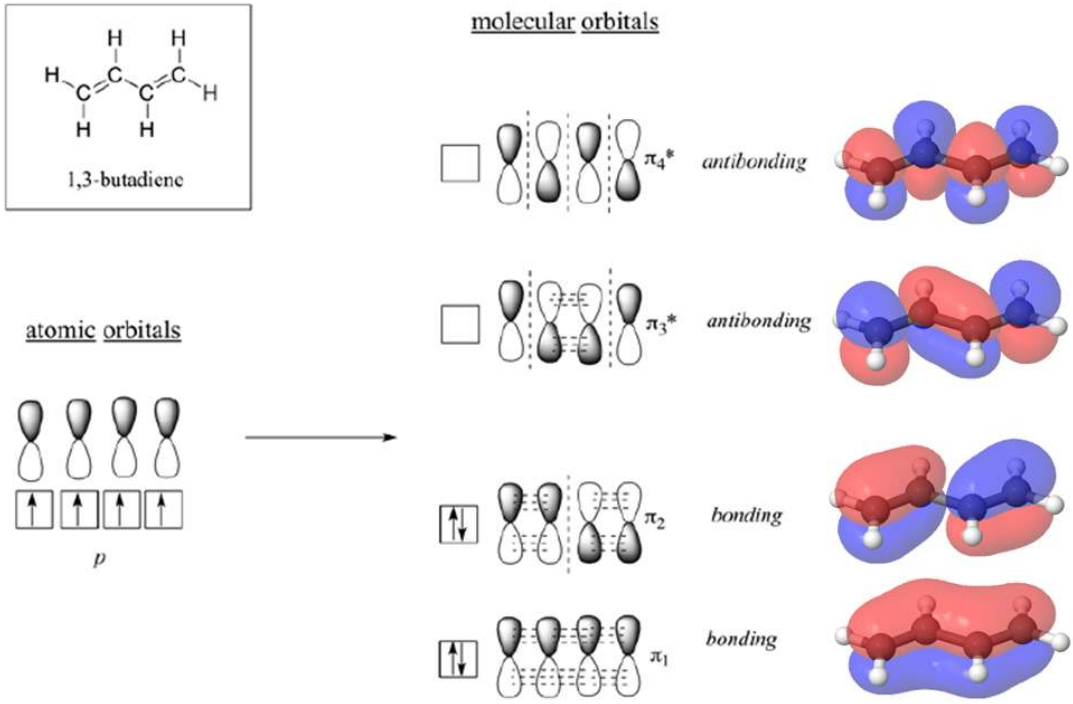
Molecular orbital interaction between frontier orbitals.

MOLECULAR ORBITALS

According to MO theory discussed in **Section 1-11**, when a double bond is non-conjugated, the two atomic $2p_z$ orbitals combine to form two **pi (π) molecular orbitals**, one a low-energy π bonding orbital and one a high-energy **π-star (π*) anti-bonding molecular orbital**. These are sometimes denoted, in MO diagrams like the one below, with the Greek letter psi (Ψ) instead of π. In the bonding Ψ_1 orbital, the two (+) lobes of the $2p_z$ orbitals interact constructively with each other, as do the two (-) lobes. Therefore, there is increased electron density between the nuclei in the molecular orbital – this is why it is a bonding orbital. In the higher-energy anti-bonding Ψ_2* orbital, the (+) lobes of one $2p_z$ orbital interacts destructively with the (-) lobe of the second $2p_z$ orbital, leading to a node between the two nuclei and overall repulsion. By the *aufbau* principle, the two electrons from the two atomic orbitals will be paired in the lower-energy $\Psi_1$orbital when the molecule is in the ground state.

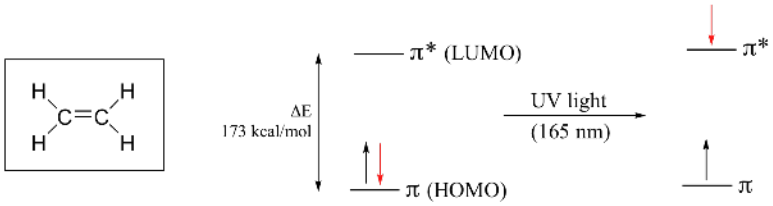


With a conjugated diene, such as 1,3-butadiene, the four *2p* atomic orbitals combine to form four pi molecular orbitals of increasing energy. Two bonding pi orbitals and two antibonding pi* orbitals. The combination of four pi molecular orbitals allow for the formation of a bonding molecular orbital that is lower in energy than those created by an unconjugated alkene. The 4 pi electrons of 1,3-butadiene completely fill the bonding molecular orbitals giving is the additional stability associated with conjugated double bonds.

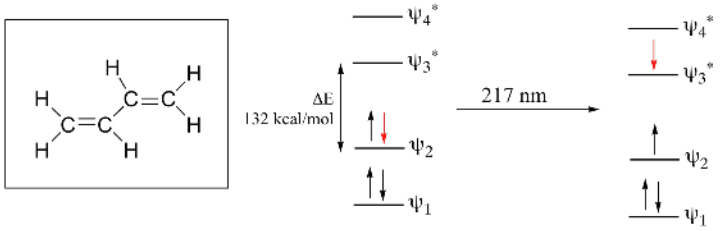


ELECTRONIC TRANSITIONS

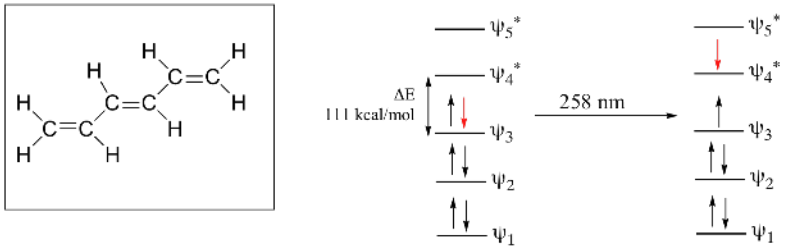
When a double-bonded molecule such as ethene (common name ethylene) absorbs 165 nm light, it undergoes a **π - π* transition**. An electron is moved from the HOMO of ethene to the LUMO placing the molecule in an **excited state**.



Where electronic transition becomes useful to most organic and biological chemists is in the study of molecules with conjugated pi systems. In these groups, the HOMO–LUMO gap energy gap for π -π* transitions is smaller than for isolated double bonds, and thus the wavelength absorbed is longer. The MO diagram for 1,3-butadiene, the simplest conjugated system. Recall that we can draw a diagram showing the four pi MO's that result from combining the four $2p_z$ atomic orbitals. The lower two orbitals are pi bonding, while the upper two are pi antibonding. Comparing this MO picture to that of ethene, our isolated pi-bond example the HOMO would be psi 2 and the LUMO would be psi 3. The HOMO-LUMO energy gap is smaller for the conjugated 1,3-butadiene system which absorbs UV light with a wavelength of 217 nm.



As conjugated pi systems become larger, the HOMO–LUMO gap energy gap for a π - π* transition becomes increasingly narrow, and the wavelength of light absorbed correspondingly becomes longer. The absorbance due to the π - π* transition in 1,3,5-hexatriene, for example, occurs at 258 nm.



WOODWARD-HOFFMANN RULES

Much of what we have said about the electronic factors controlling pericyclic reaction was formulated in the mid 1960's by the American chemists R. B. Woodward and R. Hoffmann, in terms of what came to be called the **orbital symmetry** principles, or the **Woodward-Hoffmann rules**. This is a particularly simple approach says that many details of pericyclic reactions can explained by "conservation of orbital symmetry." This requires the symmetries of the molecular orbitals of reactants to be the same as the molecular orbitals of the products for a reaction to proceed.

The original approach of Woodward and Hoffmann involved construction of an "orbital correlation diagram" to see if the lobes of the reactant molecular orbitals match phases and allow for overlap required for bonding to occur. The symmetries of the appropriate reactant and product orbitals were matched to determine whether the transformation could proceed without a symmetry imposed conversion of bonding reactant orbitals to antibonding product orbitals. If the correlation diagram indicated that the reaction could occur without encountering such a **symmetry-imposed barrier**, it was termed **symmetry allowed**. If a symmetry barrier was present, the reaction was designated **symmetry-forbidden**.

? EXERCISE 29.1.1

Using the molecular orbital diagram for 1,3,5-hexatriene determine the HOMO and LUMO for both the ground and excited state.

Answer

For the ground state the HOMO is psi 3 and LUMO is psi 4.

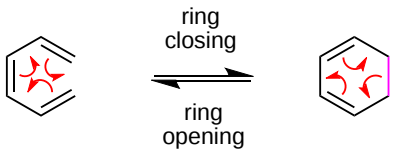
For the excited state the HOMO is psi 4 and LUMO is psi 5.

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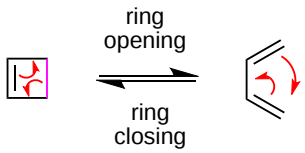
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29.2: ELECTROCYCLIC REACTIONS

An electrocyclic reaction is the concerted cyclization of a conjugated π-electron system by converting one π-bond to a ring forming σ-bond. The key sigma bond must be formed at the terminus of a pi system. These reactions classified by the number of pi electrons involved. Thus, 4 pi reactions form 4 membered rings, as in a conjugated diene can being converted into a cyclobutene. Also, 6 pi reactions form 6 membered rings as in a conjugated triene can be converted into a cyclohexadiene. These reactions are often reversible with the reverse reaction may be called *electrocyclic ring opening*. Although more more pi electrons can be used, the 4 pi and 6 pi variants are by far the most common and are illustrated below with the key sigma bond highlighted in magenta.

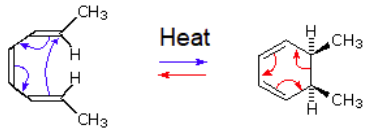


6 pi Electrocyclic Reaction



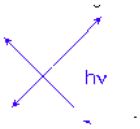
4 pi Electrocyclic Reaction

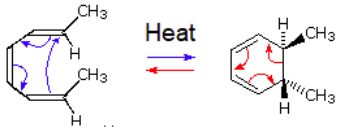
A striking feature of electrocyclic reactions that proceed by concerted mechanisms is their high degree of stereospecificity. For example, 2-*trans*, *4-cis*, *6-trans*-2,4,6-octatriene undergoes ring closure to *cis*-5,6-dimethyl-1,3-cyclohexadiene under thermal conditions i.e. when heated. Similarly the isomeric 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene *produces trans*-5,6-dimethyl-1,3-cyclohexadiene, as noted below. However these results are completely reversed if the reaction is run under photochemical conditions (Irradiation with ultraviolet light). For example if 2-*trans*, *4-cis*, *6-cis*-2,4,6-octatriene is irradiated with UV light *cis*-5,6-dimethyl-1,3-cyclohexadiene would be produced.



2-trans, 4-cis, 6-trans-2,4,6-octatriene

cis-5,6-dimethyl-1,3-cyclohexadiene

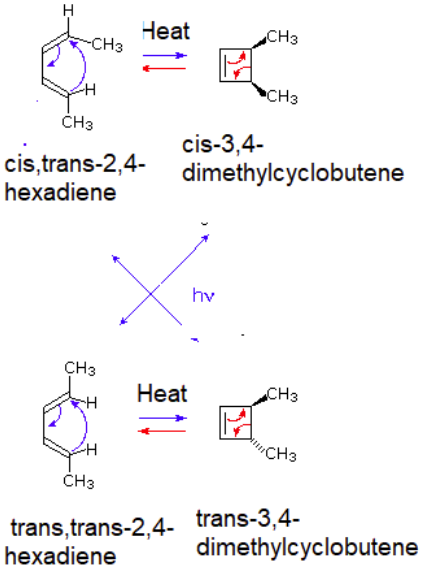




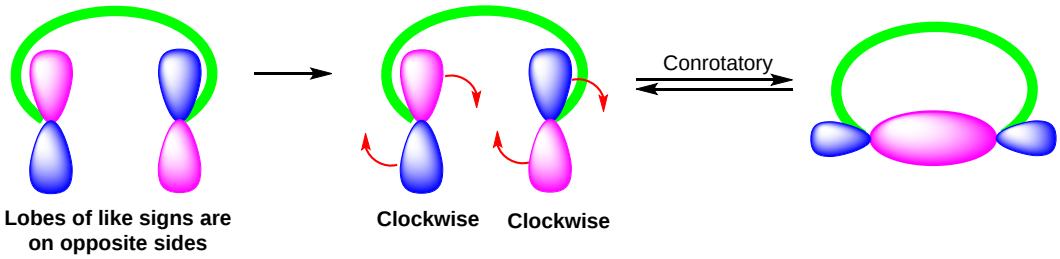
2-trans, 4-cis, 6-cis-2,4,6-octatriene

trans-5,6-dimethyl-1,3-cyclohexadiene

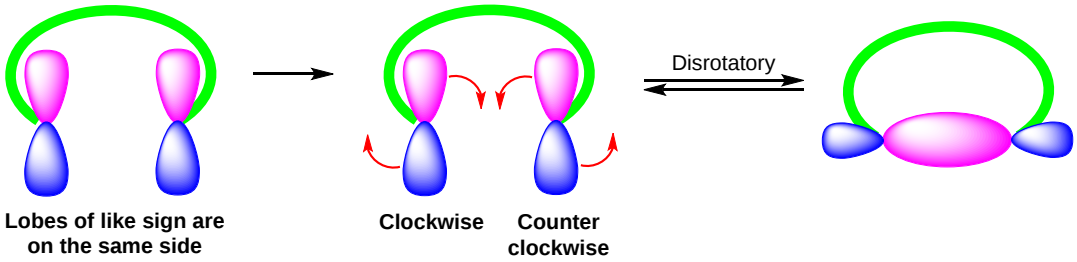
Similar results are seen with the 4 pi electrocyclic reaction of *cis*,*trans*-2,4-hexadiene being heated to exclusively form *cis*-3,4-dimethylcyclobutene and being irradiated with UV light to exclusively form *trans*-3,4-dimethylcyclobutene. Likewise, *trans*,*trans*-2,4-hexadiene forms *trans*-3,4-dimethylcyclobutene when heated and *cis*-3,4-dimethylcyclobutene when being irradiated with UV light.



The stereospecificity of electrocyclic reaction can be explained by considering the terminal lobes of the molecular orbital fo the conjugated π-electron system. For electrocyclic reactions of occur, molecular orbital lobes with the same sign from the HOMO of the molecule must rotate to form/break the key ring sigma bond. If the orbital lobes involved both rotate in the same direction (both counterclockwise or both clockwise), the process is called conrotatory. This typically occurs when orbital lobes of the same sign are on opposite sides of the molecule.



If the orbitals involved rotate in opposite directions (one clockwise and one counterclockwise), the process is called disrotatory. These differences in rotation are critically important when stereocenters are formed or broken. This typically occurs when orbital lobes of the same sign are on the same side of the molecule.

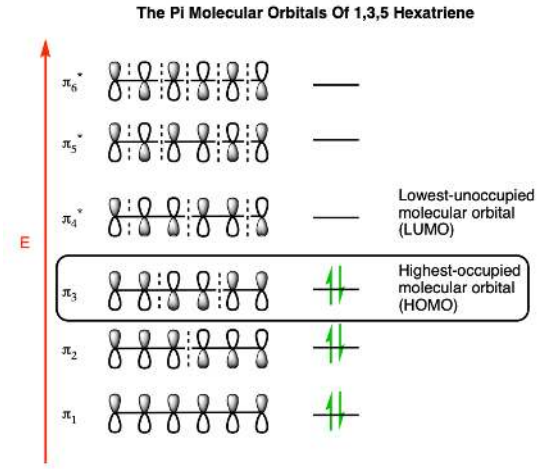


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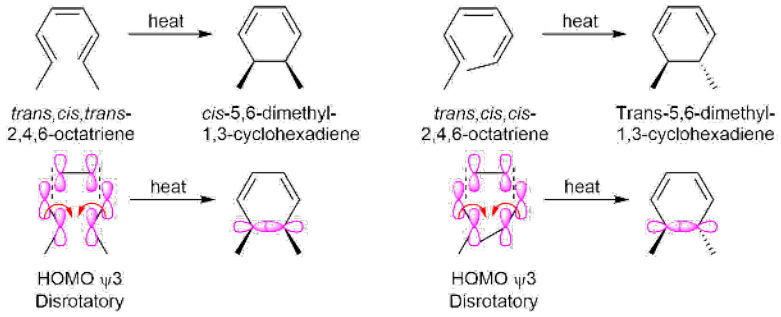
29.3: STEREOCHEMISTRY OF THERMAL ELECTROCYCLIC REACTIONS

Frontier orbital theory can be used to predict the stereochemistry of electrocyclic reactions. Electrons in the HOMO are the highest energy and therefore the most easily moved during a reaction. A molecular orbital diagram can be used to determine the orbital symmetry of a conjugated polyene's HOMO. Thermal reactions utilize the HOMO from the ground-state electron configuration of the molecular orbital diagram while photochemical reactions utilize the HOMO in the excited-state electron configuration.

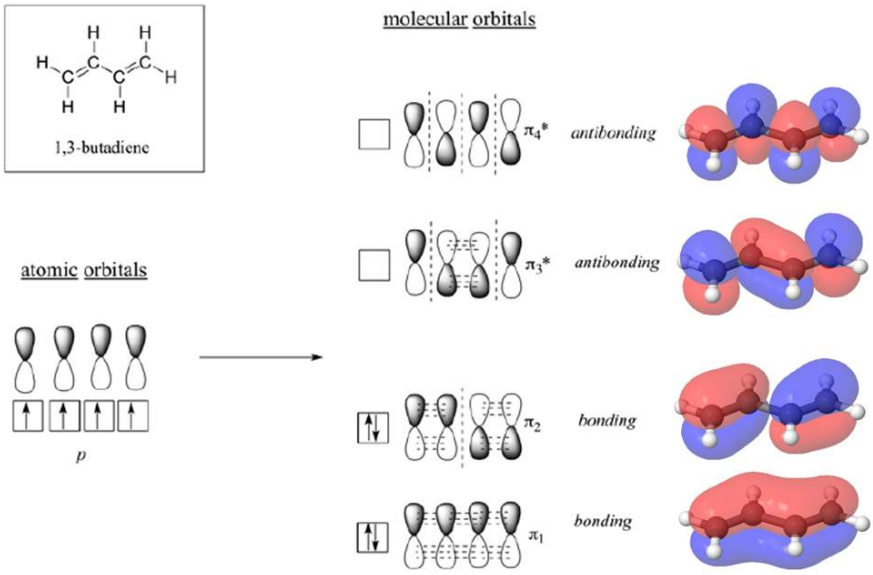
The molecular orbital of 1,3,5-hexatriene in its ground state electron configuration has psi three as its HOMO. The terminal molecular orbital lobes of the HOMO with the same sign are on the same side which predicts disrotatory ring closure under thermal conditions.



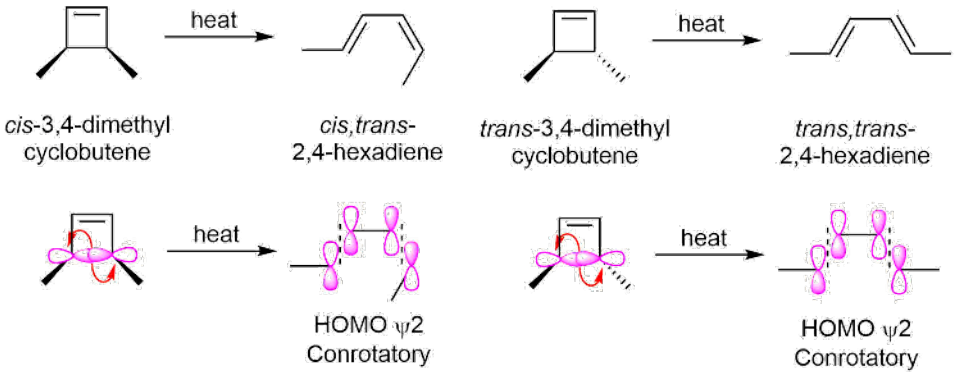
Disrotatory cyclization is observed during the electrocyclic reaction of 2,4,6-octatriene. The *trans*,*cis*,*cis*-2,4,6-octatriene isomer produces *cis*-5,6-dimethyl-1,3-cyclohexadiene as the product of thermal cyclization while the *trans*,*cis*,*cis*-2,4,6-octatriene isomer produces *trans*-5,6-dimethyl-1,3-cyclohexadiene.



The molecular orbital of a conjugated diene, such as 1,3-butadiene has psi two as the HOMO in its ground state electron configuration. The terminal molecular orbital lobes of the HOMO with the same sign are on opposite sides which predicts conrotatory ring closure under thermal conditions. However, the equilibrium of the electrocyclic reaction only allows for the ring opening to be observed.



Thus heating *cis*-3,4-dimethylcyclobutene causes the conrotatory ring opening to form *cis*,*trans*-2,4-hexadiene. Likewise, *trans*-3,4-dimethylcyclobutene forms *trans*,*trans*-2,4-hexadiene when heated.



A pattern begins to form revealing a relationship between the number of double bonds in the conjugated polyene and the rotation during electrocyclic reactions. For thermal electrocyclic reactions, polyenes with an odd number of double bonds undergo disrotation and those with an even number of double bond undergo conrotation.

? EXERCISE 29.3.1

1) The thermal electrocyclic ring opening of *trans*-3,4-dimethylcyclobutene could form *trans*,*trans*-2,4-hexadiene or *cis*,*cis*-2,4-hexadiene. However, the *trans*,*trans*-2,4-hexadiene is the isomer obtained from the reaction. Explain how it is possible to get both products and why the *trans*,*trans*-2,4-hexadiene is preferred.

2) If a conjugated tetraene were to undergo a thermal electrocylic reaction would the orbital nodes undergo con or disrotation?

Answer

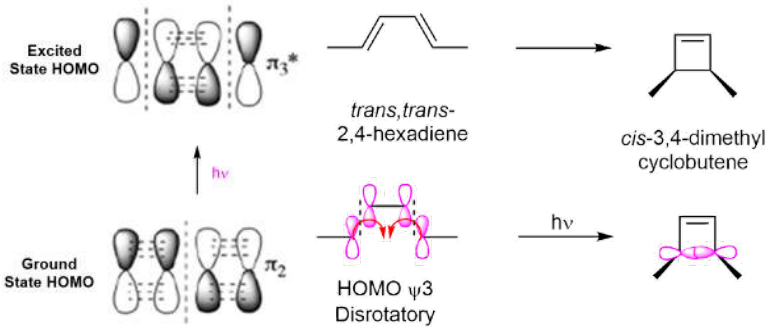
1) Dienes undergo conrotation during thermal electrocyclic ring opening. Conrotation means the orbital nodes both rotate in the same direction either both clock with or both counter clockwise. If the nodes both rotate counter clockwise the *trans*,*trans*-2,4-hexadiene isomers forms. If they both rotate clockwise the *cis*,*cis*-2,4-hexadiene isomer is formed. Trans double bonds are more stable than cis due to steric strain. The *trans*,*trans*-2,4-hexadiene is perferably formed because it is more stable.

2) A tetraene has an even number of double bonds so it would be expected to undergo conrotation.

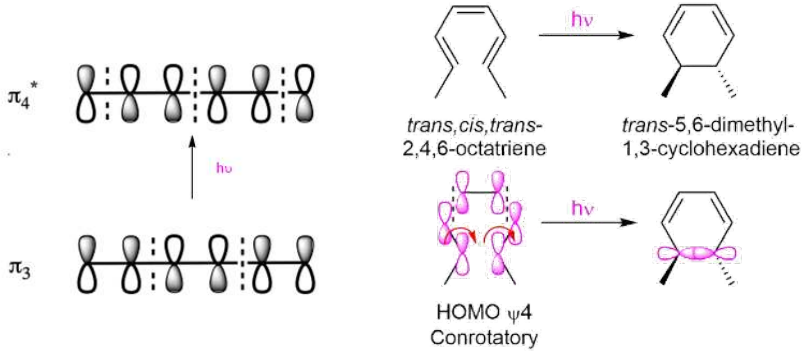
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29.4: PHOTOCHEMICAL ELECTROCYCLIC REACTIONS

As discussed in **Section 30.1**, irradiation of a conjugated polyene with ultraviolet light causes an electron from the groude-state HOMO to be excited to the ground state LUMO. This creates a new higher energy HOMO in an electron configuration called the excited state. Electron excitation changes the symmetry of the new HOMO which has a corresponding effect on the reaction stereochemistry. Under photochemical reaction conditions conjugated dienes undergo disrotatory cyclization whereas under thermal conditions they underwent conrotatory cyclization. Likewise, conjugated triene undergo conrotatory photochemical cyclization while undergoing disrotatory thermal cyclization. For example, trans,trans-2,4-hexadiene undergoes conrotatory photochemical cyclization to form *cis*-3,4-dimethylcyclobutene.



The conjugated tirene, *trans*,*cis*,*trans*-2,4,6-octatriene undergoes conrotation to form *trans*-5,6-dimethyl-1,3-cyclohexadiene during photochemical cyclization.



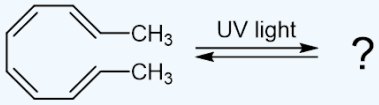
GENERALIZED STATEMENT OF WOODWARD-HOFFMANN RULES FOR ELECTROCYCLIC REACTIONS

Thermal and photochemical electrocyclic reactions always produce the opposite stereochemistry products due to the difference in symmetries in their HOMO frontier orbitals. This idea can be combined with the trend of even and odd polyenes to provide simple rules to predict the stereochemistry of electrocyclic reactions.

Number of Double Bonds	Thermal	Photochemical
Odd	Disrotatory	Conrotatory
Even	Conrotatory	Disrotatory

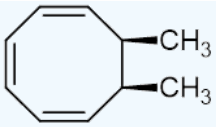
? EXERCISE 29.4.1

Would the following electrocyclic reaction be con or disrotatory? Please draw the expected product.



Answer

An even number of double bonds in photochemical conditions predicts a disrotatory reaction.

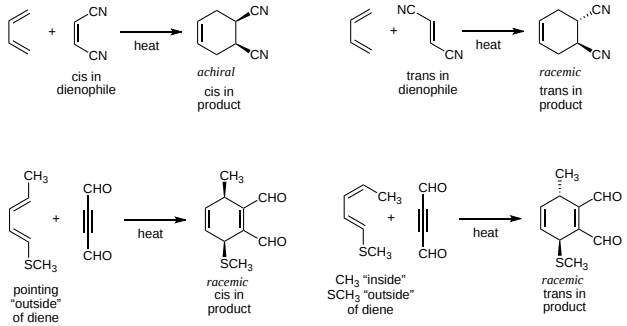


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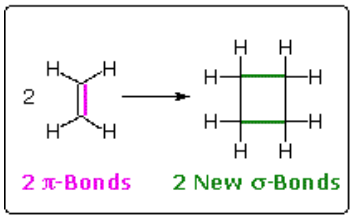
29.5: CYCLOADDITION REACTIONS

A concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds is called a **cycloaddition reaction**. The number of participating π-electrons in each component is given in brackets preceding the name of the reaction. The Diels-Alder reaction (**Section 14-4**) is the most useful cycloaddition reaction due to the ubiquity of 6-membered rings and its ability to reliably control stereochemistry in the product. In the Diels-Alder cycloaddition reaction, a conjugated diene, simply referred to as the **diene**, reacts with a double or triple bond coreactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder reaction is a [4+2] cycloaddition (4 pi electrons from the diene and 2 pi electrons from the dienophile) that yields a functionalized 6-membered ring product. During the Diels-Alder reaction, two pi-bonds are converted to two sigma-bonds.

Due to the concerted mechanism for cycloaddition reactions, the geometry of atoms on the dienophile or the diene maintain their orientation in the product. This is a critical point for the 4 atoms (both dienophile atoms and the terminal atoms of the diene) that become sp^3 hybridized and thus are potential stereocenters in the product. (As a reminder, when chiral products are formed, we obtain a racemic mixture of enantiomers.) As highlighted below, cis dienophiles yield cis substituents in the product, while trans dienophiles yield trans product substituents. Substituents on the terminal atoms of the diene also can become stereocenters and this analysis is a little less straightforward than for dienophile substituents. The way to think about the diene substituents is whether the are pointing "outside" or "inside" the diene. These orientations are illustrated below. When groups are both pointing "outside" or "inside", we can consider them to be cis and they will end up cis in the product. When one group is pointing "outside" and one "inside", we can consider them as trans and they will be trans in the product.



Another important reaction is the [2+2] cycloaddition of two alkene containing molecules to form a 4-membered cyclobutane ring. The [2 + 2] cycloaddition of two alkenes does not occur by simply heating but can only be achieved by *irradiation* with ultraviolet light.

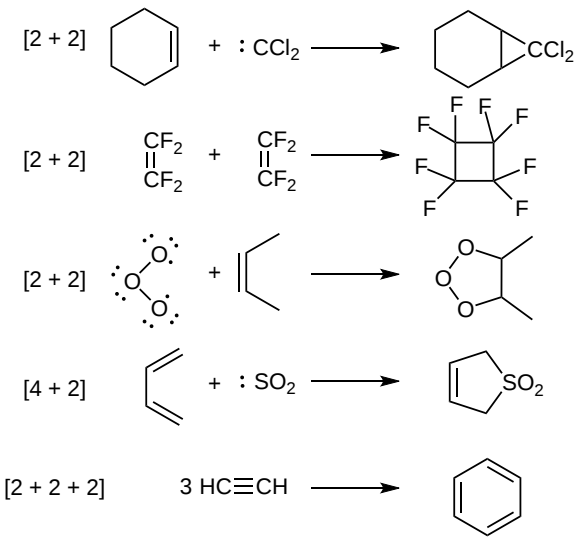


A [2+2] Cycloaddition

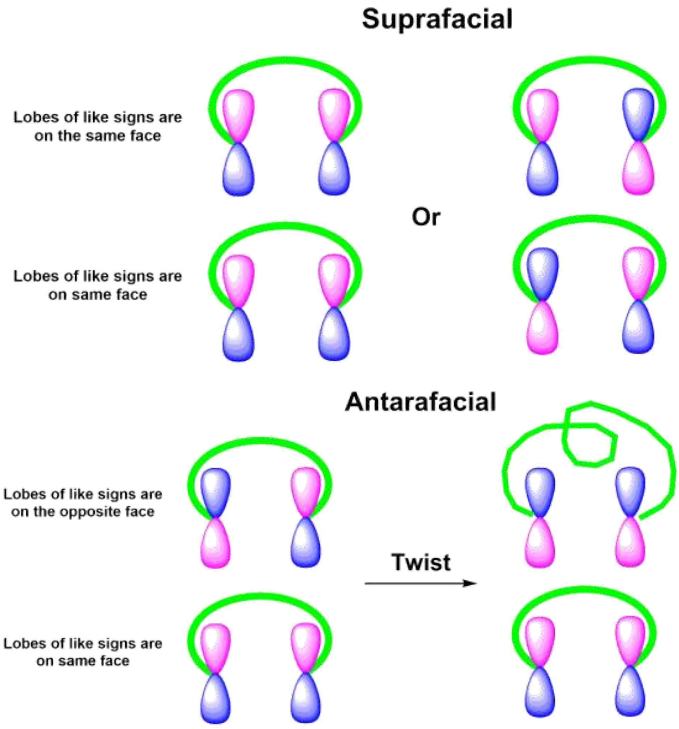


Photo [2+2] Cycloaddition

Many other cycloadditions are known, such as [2 + 2 + 2], and other types of [2 + 2], which give different size of rings. Some specific examples are shown below:



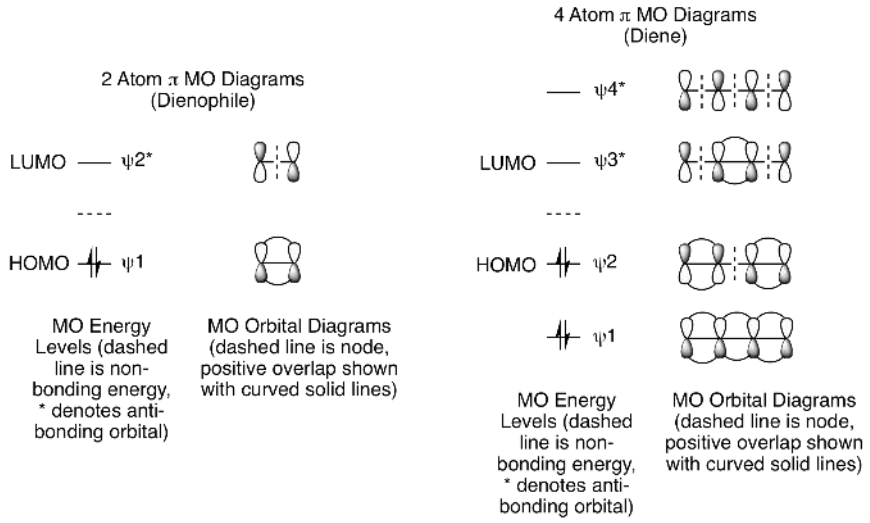
Like other pericyclic reactions, cycloadditions are determined by the orbital symmetry of the frontier orbitals of the reactants. For bonding to occur in a cycloaddition, the terminal lobes of the frontier orbitals of the two pi systems must have the correct symmetry. Correct symmetry can be obtained in two different ways. If the signs on the orbital lobes are the same on the faces of both reactants then the reaction undergoes a **suprafacial cycloaddition**. If the signs of the orbital lobes are the same on the face of one reactant but opposite on the other reactant then the reaction undergoes an **antarafacial cycloaddition**. Although both types are symmetry allowed, the fact that antarafacial cycloadditions require the twisting of a pi orbital system makes them more difficult to achieve.



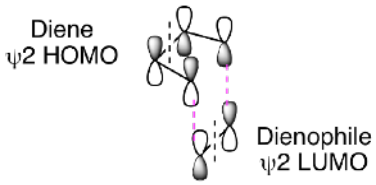
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29.6: STEREOCHEMISTRY OF CYCLOADDITIONS

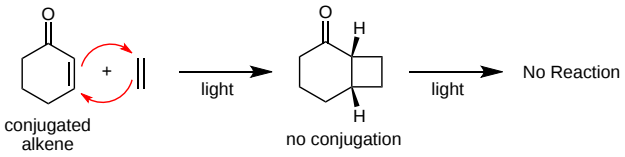
Frontier orbital theory can be used to predict if a given cycloaddition will occur with suprafacial or with antarafacial geometry. In a standard Diels-Alder reaction, bonding interactions are created when the electron containing HOMO of the diene donates electrons to the electron vacant LUMO of the other the dienophile. The dienophile has one pi bond, so it will use the pi MOs for a 2 atom system. The dienophile has 2 pi electrons which makes psi 2* its LUMO. The diene has two pi bonds, so it will use the pi MOs for a 4 atom system. The diene has has 4 pi electrons makes psi 2 its HOMO.



These MO diagrams show that the ground-state frontier orbitals of both reactants have terminal lobes with matching signs. The symmetry of these orbitals are such that bond formation will easily occur under thermal conditions with suprafacial geometry as shown below. (Note: The dashed black lines in the figure below represent nodes in the pi molecular orbitals of the diene and dienophile.) The two new sigma bonds, shown as dashed magenta lines below, are formed from constructive overlap of the terminal dienophile orbitals with the terminal orbitals of the diene.

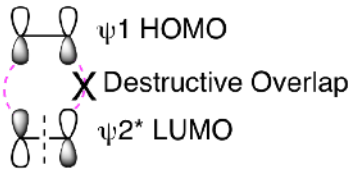


Photochemical [2+2] cycloadditions are excellent reactions for the synthesis of strained products containing 4-membered rings. One of the reaction partners must be conjugated so that it can absorb light and become an excited state molecule. These reactions produce strained 4-membered rings but are not reversible because the products lack conjugation and, thus, can't absorb light to facilitate a cycloreversion.



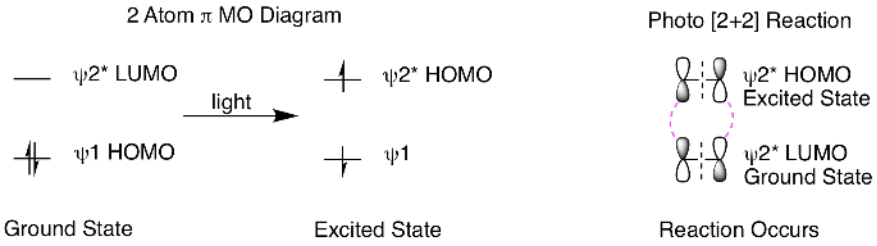
So, why won't this reaction happen thermally? How does our molecular orbital analysis help us understand the importance of this being a photochemical reaction? First, let's look at the orbital analysis if we tried to do a thermal [2+2] reaction. As shown below, we cannot get suprafacial overlap for both of the 2 pi reactants when trying to combine psi 1 HOMO with psi 2* LUMO. This means that it is not favorable to convert the two reactant pi bonds into two new product pi bonds.

Thermal [2+2] Reaction



No Reaction

What happens when we shine light on the reaction? Light creates an excited state molecule by promoting an electron in the HOMO to the LUMO, as shown below. This means the excited state HOMO is the ground state LUMO. We need to understand a few key points about photoreactions before doing our molecular orbital analysis. Excited state molecules are very short lived, relaxing back to the ground state very quickly. Therefore, it is practically impossible for two excited state molecules to find each other in a reaction. Instead, reactions occur between one excited state molecule and one ground state molecule. When only one molecule is conjugated, that is the molecule that will form the excited state. If both reactants are conjugated, either can form the excited state. The orbital analysis is shown below. First, we see the orbital picture when a ground state molecule absorbs light to form an excited state. Second, when we analyze the reaction, it is now psi 2* HOMO of the excited state molecule reacting with psi 2* LUMO of the ground state molecule. This gives suprafacial constructive overlap for both orbitals and the 2 reactant pi bonds can be converted into two product sigma bonds.



Cycloaddition reactions can be categorized based on the total number electrons involved in the rearrangement. The [4+2] Diels-Alder reaction involves 6 electrons and takes place using a suprafacial pathway under thermal conditions. The thermal [2+2] cycloaddtion of two alkenes involves 4 electrons and must take place by antarafacial pathway. However, the pathway is reversed for photochemical [2+2] cycloaddtions which take place by a supraficial pathway. These ideas can be generalized using the rules for cycloadditions below.

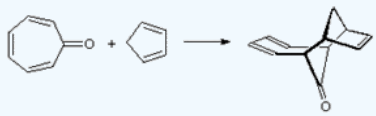
Generalized Statement of Woodward-Hoffmann Rules for Cycloadditions

Number of Electrons	Thermal	Photochemical
4n + 2	Suprafacial (Allowed)	Antarafacial (Forbidden)
4n	Antarafacial (Forbidden)	Suprafacial (Allowed)

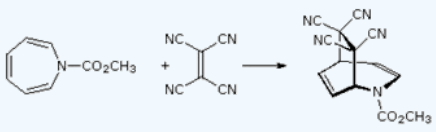
? EXERCISE 29.6.1

For the following reactions determine what type of cycloaddition is occurring, is the reaction supra or antarafacial, and would the reaction require thermal or photochemical conditions.

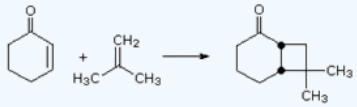
a)



b)



c)



Answer

a) [6+4], suprafacial, thermal

b) [4+2], suprafacial, thermal

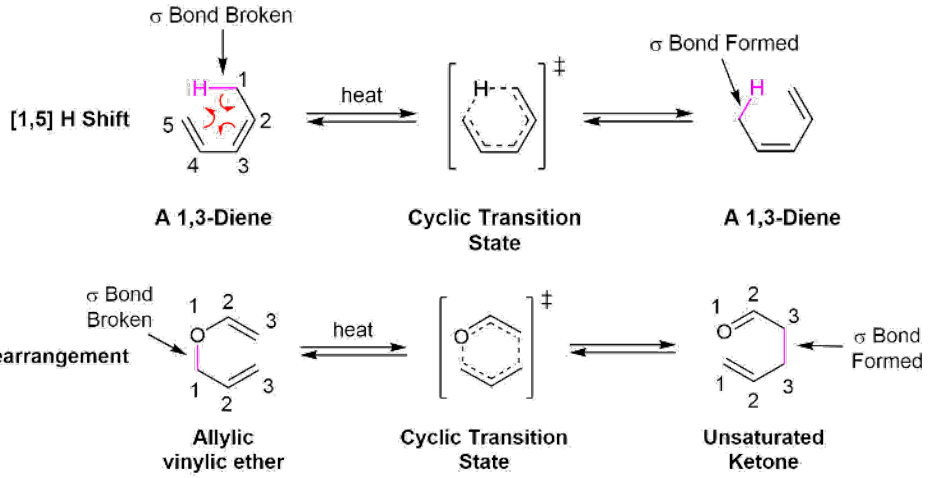
c) [2+2], antarafacial, photochemical

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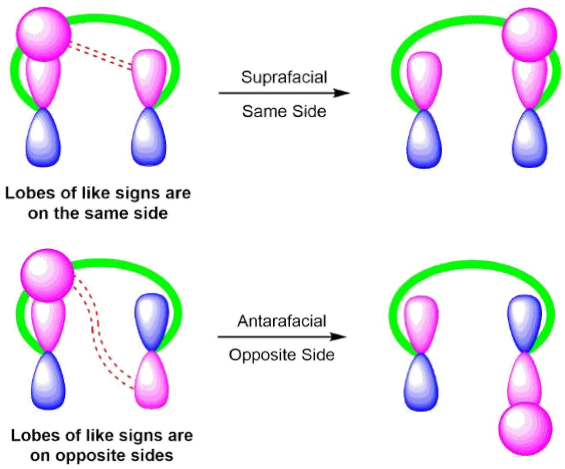
29.7: SIGMATROPIC REARRANGEMENTS

Molecular rearrangements in which a σ-bonded atom or group, flanked by one or more π-electron systems, shifts to a new location with a corresponding reorganization of the π-bonds are called **sigmatropic reactions**. The reactant and product have the same number and type of bonds, just different bond locations. These rearrangements are described by two numbers set in brackets, which refer to the position of the sigma bond in the reactant that is broken compared to the position of the sigma bond in the product that is formed. The most common examples include hydrogen shifts across a diene system (called a [1,5] H shift) and rearrangements of double allyl-type systems (called [3,3] rearrangements).

As shown in the examples below, the atoms on the sigma bond in the reactant that is broken (magenta bond) are both labeled "1", and the numbering of atoms on each side of that sigma bond continue until the atoms connected by the new sigma bond in the product (magenta) are reached. Thus, the H shift is [1,5] because the key sigma bond in both the reactant and product is to the H while the H moves from C-1 to C-5. For the [3,3] rearrangement, the broken sigma bond migrates across two allyl-type systems and forms between atoms "3" and "3" in the product. This particular example is a Claisen rearrangement since an allyl vinyl ether is transformed into a 1,4-carbonyl alkene.



The migration of a group during a sigmatropic rearrangement is controlled by the orbital symmetries of the alkenes involved. Sigmatropic rearrangements can occur on one face of the molecule (think top or bottom, like a syn addition to an alkene) which is called a **suprafacial** reaction or from one face to the other (think from top to bottom or vice versa, like an anti addition to an alkene) which is called **antarafacial**. We will explore this idea further in the next section.



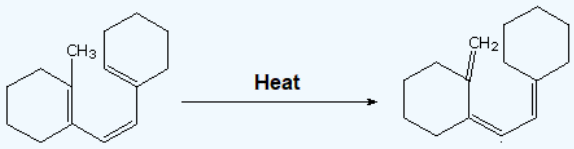
GENERALIZED STATEMENT OF WOODWARD-HOFFMANN RULES FOR SIGMATROPIC REARRANGEMENTS

Suprafacial and antarafacial sigmatropic rearrangements are considered symmetry-allowed by the Woodward-Hoffmann rules. However, suprafacial reactions are much more common. Note! These rules for sigmatropic rearrangements are the same as those given for cycloaddition reactions in **Section 30-3**.

Number of Double Bonds	Thermal	Photochemical
Odd	Suprafacial	Antarafacial
Even	Antarafacial	Suprafacial

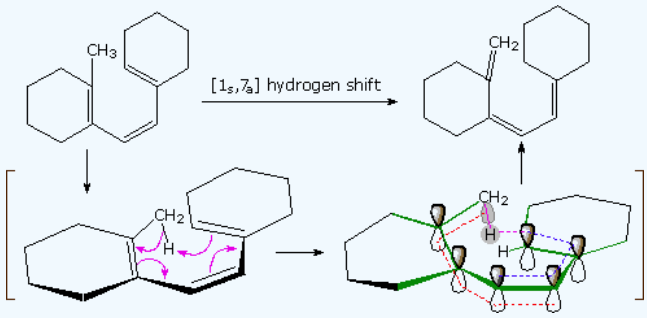
EXERCISE 29.7.1

For the following sigmatropic hydrogen shift please use braked number to describe the reaction. Predict if the hydrogen shift will be suprafacial and antarafacial. Lastly, draw in arrows to describe the mechanism for this reaction.



Answer

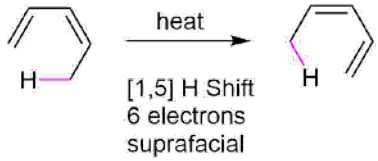
An example of an [1,7] hydrogen shift is shown in the following diagram. The conjugated alkene has three double bonds, which is an odd number, and the reaction is occuing under thermal conditions. This means the reaction is predicted to be suprafacial. The conjugated triene assumes a nearly planar coiled conformation in which a methyl hydrogen is oriented just above the end carbon atom of the last double bond. A [1_s,7_a] sigmatropic hydrogen shift may then take place, as described by the four curved arrows. With reference to the approximate plane of this π-electron system (defined by the green bonds), the hydrogen atom departs from the bottom face and bonds to the top face, so the transfer is antarafacial.



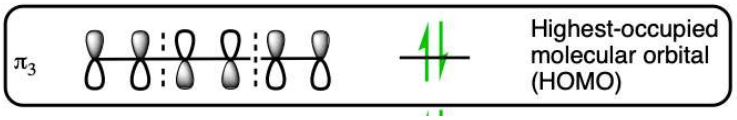
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29.8: SOME EXAMPLES OF SIGMATROPIC REARRANGEMENTS

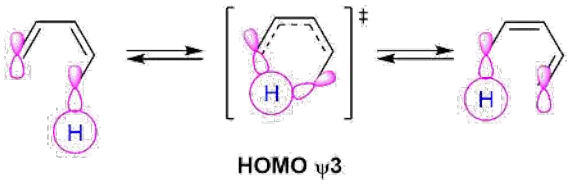
A sigmatropic rearrangement which involves a [1,5] hydrogen shift, like the one shown below illustrates, a hydrogen atom (s orbital) moving across a 5 atom system containing two conjugated double bonds. Since there are three curved arrows in the mechanism, this is a 6 pi reaction. The rules for sigmatropic rearrangements discussed in the last section predict the hydrogen atom will undergo a suprafacial shift. The C-H bond breaking and the C-H bond forming, magenta dashed lines, are both on the bottom face of the molecule's pi system.



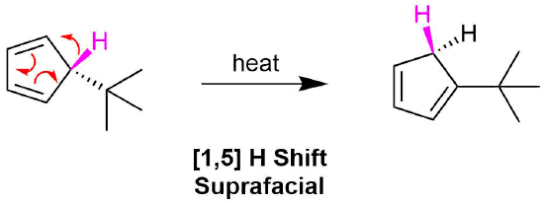
The suprafacial nature of this reaction comes from the orbital symmetry of the HOMO from a 6 pi electron molecular orbital. The orbital lobes on the terminal ends have the same sign on the same side.



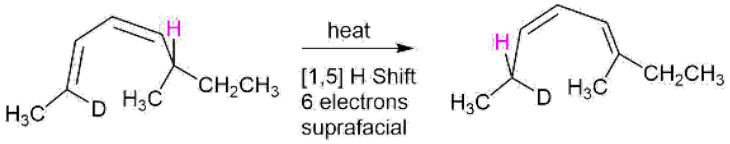
During the reaction mechanism the hydrogen atom, an s orbital, is passes from one molecular to another of the same sign on the same side of the molecule or suprafacial.



For example, 5-*t*-butyl-1,3-cyclopentadiene easily undergoes a [1,5] suprafacial shift of a hydrogen atom under thermal conditions to yield 1-*t*-butyl-1,3-cyclopentadiene as a rearranged product.

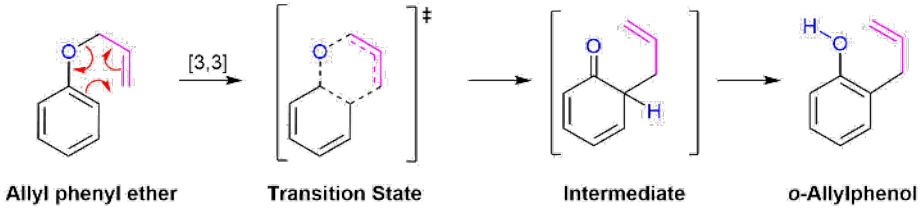


As another example, heating S-2-deuterio-6-methyl-(2E,4Z)-2,4-octadiene undergoes a thermal [1,5] suprafacial shift of a hydrogen to produce the product, R-2-deuterio-6-methyl-(2Z,4E)-3,5-octadiene with stereochemical control.

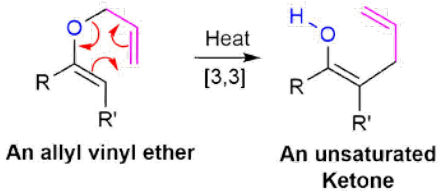


CLAISEN REARRANGEMENT

A very important example of a [3,3] sigmatropic reaction is the **Claisen rearrangement** of an allyl aryl ether or an allyl vinyl ether (**Section 18-4**). Heating an allyl aryl ether to 250 ºC causes an sigmatropic rearrangement to produce an *o*-allylphenol. This rearrangement initially produces the non-aromatic 6-allyl-2,4-cyclohexadienone intermediate which quickly undergoes a proton shift to reform the aromatic ring in the *o*-allylphenol product. Claisen rearrangement occurs in a six-membered, cyclic transition state involving the movement of six bonding electron.

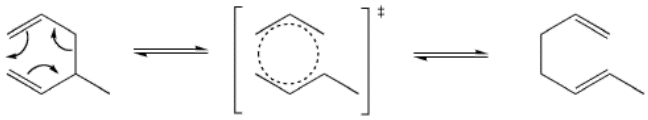


Allyl vinyl ethers can also undergo a Claisen rearrangement when heated to form gamma, delta -unsaturated ketones or aldehydes.



COPE REARRANGEMENT

Another important example of a [3,3] sigmatropic reaction is the **cope rearrangement**. This reaction converts between isomers of a 1,5-hexadiene through a cyclic transition state.

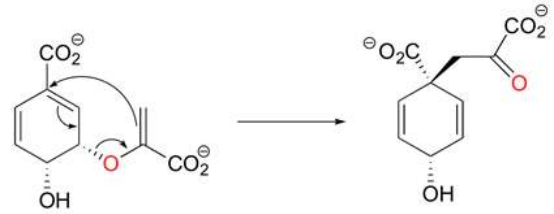


Both Cope and Claisen rearrangements involve the movement of six electrons which means they both react by suprafacial pathways under thermal conditions. These reactions can be considered to occur due to changes in overlap between orbitals around the cyclic transition state. Two orbitals which form the sigma bond being broken tilt away from each other while two orbitals that are pi bonding tilt toward each other to from a new sigma bond. After the change there are now two p orbitals parallel to each other on the left which then form new pi bonds.



Orbital rearrangement in a Cope rearrangement

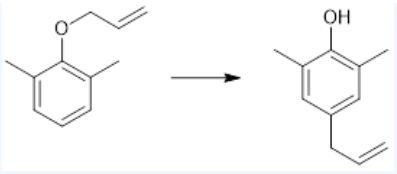
Sigmatropic rearrangements are rare in biological chemistry. One example is the chorismate mutase catalyzed Claisen rearrangement of chorismate (a allylic vinyl ether) to form prephenate. Prephenate is a precursor in the biosynthetic pathway of aromatic amino acids phenylalanine and tyrosine.



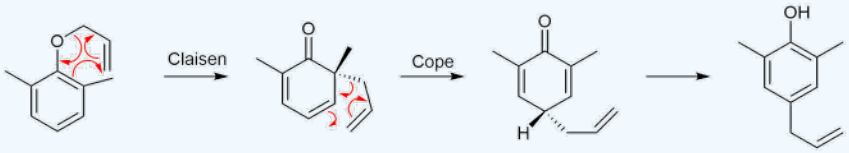
chorismate prephenate

? EXERCISE 29.8.1

A Claisen rearrangement performed in the presence of ortho-substituents exclusively leads to para-substituted rearrangement products. This occurs via a Claisen rearrangement followed by a Cope rearrangement. Draw out the intermediates formed during this transformation and the mechanisms for both rearrangements.



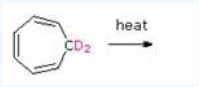
Answer



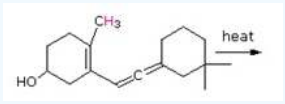
EXERCISE 29.8.2

Draw the expected products of the following [1,5] suprafacial shifts.

a)

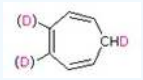


b)

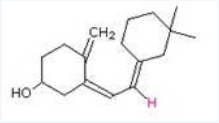


Answer

a)

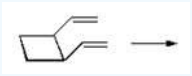


b)



EXERCISE 29.8.3

Draw the product of the following [3,3] suprafacial shifts.



Answer



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29.9: A SUMMARY OF RULES FOR PERICYCLIC REACTIONS

Before pericyclic reactions can be put to use in a predictable and controlled manner, a broad mechanistic understanding of the factors that influence these concerted transformations must be formulated. The simplest, albeit least rigorous, method for predicting the configurational path favored by a proposed pericyclic reaction is based upon a transition state electron count. In most of the earlier examples, pericyclic reactions were described by a cycle of curved arrows, each representing a pair of bonding electrons. The total number of electrons undergoing reorganization is always even, and is either a **4n+2** or **4n** number (where n is an integer). Once this electron count is made, the following table may be used for predictions. It is important to remember that going from thermal to photochemical conditions or going from 4n to 4n+2 reaction electrons changes the outcome of the reaction.

	Electron Count	Stereochemistry
Thermal Reactions (Ground State)	**4n + 2**	Suprafacial or Disrotatory
	4n	Antarafacial or Conrotatory
	Electron Count	**Stereochemistry**
Photochemical Reactions (Excited State)	**4n + 2**	Antarafacial or Conrotatory
	4n	Suprafacial or Disrotatory

? EXERCISE 29.9.1

Predict the stereochemistry of the following reactions:

a. The photochemical cyclization of a conjugated tetraene.
b. The thermal cyclization of a conjugated tetraene
c. A thermal [4+4] cycloaddition
d. A photochemical [2+5] cycloaddition
e. A thermal [3,5] sigmatropic rearrangement

Answer

1)a) Disrotatory
b) Conrotatory
c) Antarafacial
d) Suprafacial
e) Antarafacial

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CHAPTER OVERVIEW

30: SYNTHETIC POLYMERS

Synthetic polymer are man-made polymer that is not a biopolymer (e..g, proteins or complex carbohydrates). Synthetic polymers are mostly non-biodegradable and often synthesized from petroleum. The eight most common types of synthetic organic polymers are: Low-density polyethylene (LDPE), High-density polyethylene (HDPE), Polypropylene (PP), Polyvinyl chloride (PVC), Polystyrene (PS), Nylon, nylon 6, nylon 6,6, Teflon (Polytetrafluoroethylene) and Thermoplastic polyurethanes (TPU).

30.0: Chapter Objectives

30.1: Chain-Growth Polymers

30.2: Stereochemistry of Polymerization - Ziegler-Natta Catalysts

30.3: Copolymers

30.4: Step-Growth Polymers

30.5: Olefin Metathesis Polymerization

30.6: Polymer Structure and Physical Properties

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30.0: Chapter Objectives

Learning Objectives

By the end of this chapter, students should be able to:

- Explain how synthetic polymers are formed through various polymerization reactions.
- Identify how the molecular structure of polymers influences their macroscopic properties.
- Categorize synthetic polymers based on their structure, properties, and applications.
- Describe experimental techniques used to analyze and characterize polymers.
- Examine the diverse applications of synthetic polymers in different industries.

Synthetic polymers constitute a vast class of materials that play an indispensable role in numerous aspects of modern life. These polymers are engineered in laboratories and industrial settings through chemical processes, wherein small molecules known as monomers are repetitively linked together to form long chains or networks. The resulting macromolecules exhibit a wide range of properties and functionalities tailored to specific applications, making them ubiquitous in everyday products and industrial processes.

The synthesis of synthetic polymers typically involves polymerization reactions, where monomers undergo chemical bonding to form polymer chains. This can occur through various mechanisms, including addition polymerization, condensation polymerization, and ring-opening polymerization, each yielding polymers with distinct structures and properties (Figure 30.0.1).

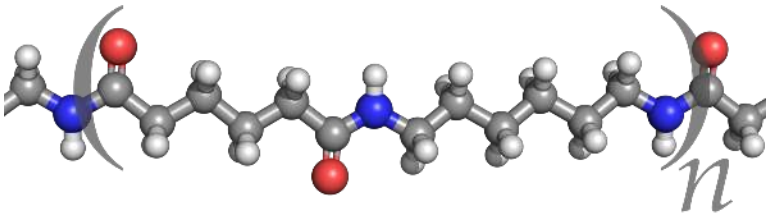


Figure 30.0.1: Nylon 6,6 chemical structure (CC BY 3.0; YassineMrabet via Wikipedia)

One of the most significant advantages of synthetic polymers is their versatility. By selecting different monomers and adjusting reaction conditions, polymer chemists can precisely control the molecular architecture, composition, and properties of the resulting polymers. This versatility enables the design of materials with tailored characteristics such as mechanical strength, flexibility, thermal stability, conductivity, and biocompatibility.

Synthetic polymers find applications across diverse industries and sectors. Plastics, for example, are ubiquitous in packaging, construction, electronics, automotive components, and consumer goods due to their lightweight, moldability, and durability. Synthetic fibers such as polyester, nylon, and acrylics are widely used in textiles, apparel, and industrial materials. Polymers also play critical roles in adhesives, coatings, biomedical implants, drug delivery systems, and advanced composites.

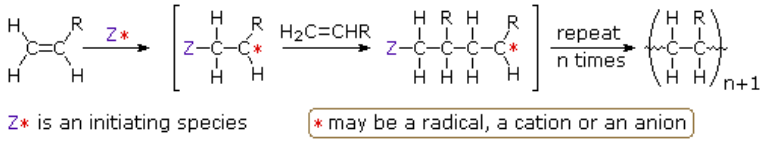
Understanding the structure-property relationships of synthetic polymers is essential for optimizing their performance and developing new materials with enhanced characteristics. Researchers continue to explore innovative polymerization techniques, advanced characterization methods, and sustainable alternatives to traditional polymers to address environmental concerns associated with plastic waste and pollution.

In summary, synthetic polymers represent a cornerstone of modern materials science and technology, providing tailored solutions to a myriad of societal challenges and driving innovation in various industries. Their versatility, tunable properties, and wide-ranging applications underscore their importance in shaping the world we live in today.

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30.1: CHAIN-GROWTH POLYMERS

Polymers resulting from additions to alkenes monomers are chain-growth polymers. In these processes each addition step results in a longer chain which ends in a reactive site. The mechanism of each addition step is the same, and each addition step adds another monomer to extend the chain by one repeating unit. The most common and thermodynamically favored chemical transformations of alkenes are addition reactions. Many of these addition reactions are known to proceed in a stepwise fashion by way of reactive intermediates, and this is the mechanism followed by most polymerizations. A general diagram illustrating this assembly of linear macromolecules, which supports the name chain growth polymers, is presented here. Since a pi-bond in the monomer is converted to a sigma-bond in the polymer, the polymerization reaction is usually exothermic by 8 to 20 kcal/mol. Indeed, cases of explosively uncontrolled polymerizations have been reported.

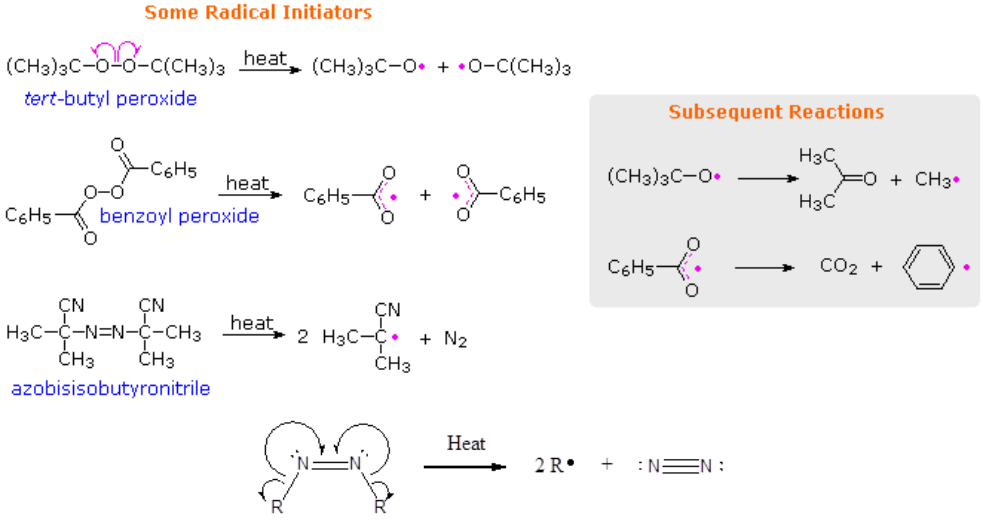


It is useful to distinguish four polymerization procedures fitting this general description.

• Radical Polymerization: The initiator is a radical, and the propagating site of reactivity (*) is a carbon radical.
• Cationic Polymerization: The initiator is an acid, and the propagating site of reactivity (*) is a carbocation.
• Anionic Polymerization: The initiator is a nucleophile, and the propagating site of reactivity (*) is a carbanion.
• Coordination Catalytic Polymerization: The initiator is a transition metal complex, and the propagating site of reactivity (*) is a terminal catalytic complex.

RADICAL CHAIN-GROWTH POLYMERIZATION

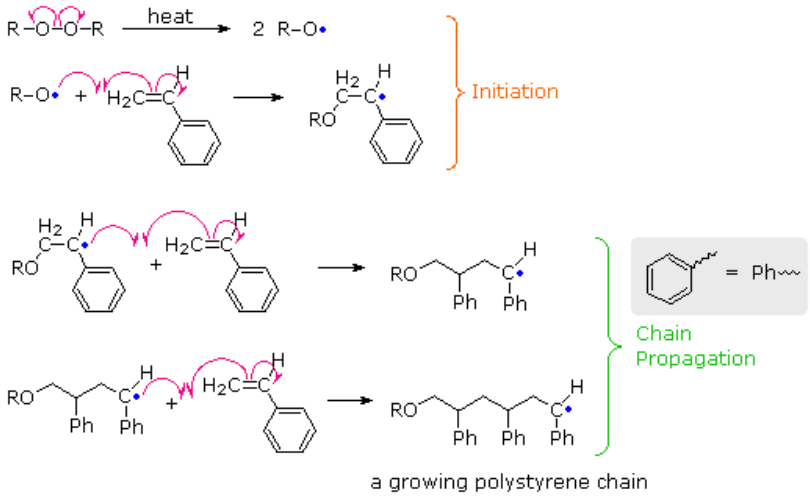
Virtually all of the monomers described above are subject to radical polymerization. Since this can be initiated by traces of oxygen or other minor impurities, pure samples of these compounds are often "stabilized" by small amounts of radical inhibitors to avoid unwanted reaction. When radical polymerization is desired, it must be started by using a radical initiator, such as a peroxide or certain azo compounds. The formulas of some common initiators, and equations showing the formation of radical species from these initiators are presented below.



By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples of chain propagation. Each monomer unit adds to the growing chain in a manner that generates the most stable radical. Since carbon radicals are stabilized by substituents of many kinds, the preference for head-to-tail regioselectivity in most addition polymerizations is understandable. Because radicals are tolerant of many functional groups and solvents (including water), radical polymerizations are widely used in the chemical industry.

Each step in this polymer formation is an addition to an alkene. The mechanism is in most cases a *free radical* addition. In free radical reactions the pi pair of electrons separates. One of these electrons pairs with an electron from the attacking reagent to form a sigma bond with one of the alkene carbons. and the other electron remains attached to the other alkene carbon. (Curved arrows with only one "barb" on

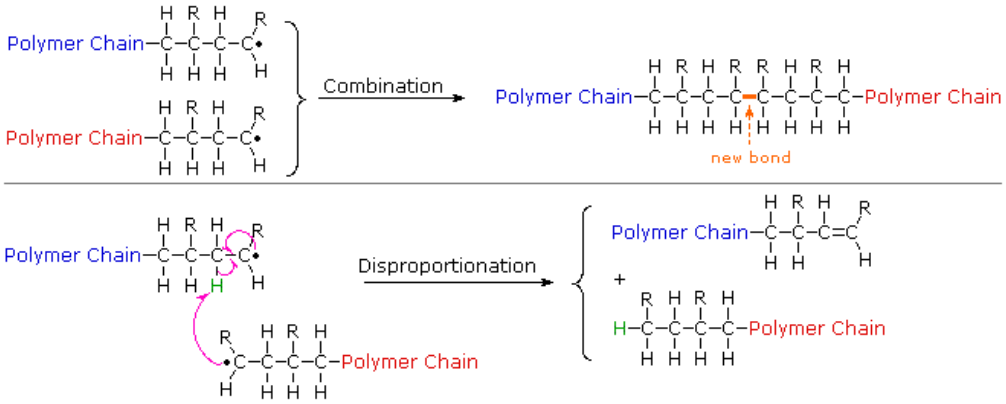
a point are used to follow the path of a single electron in the same way that "double-headed" arrows follow the path of an electron pair.) Intermediates with an unpaired electron are called free radicals, so this step can be described as adding a free radical to an alkene to lengthen the chain by two carbons and generate a new free radical. In its turn this new free radical can add to another molecule of monomer and continue the process.



a growing polystyrene chain

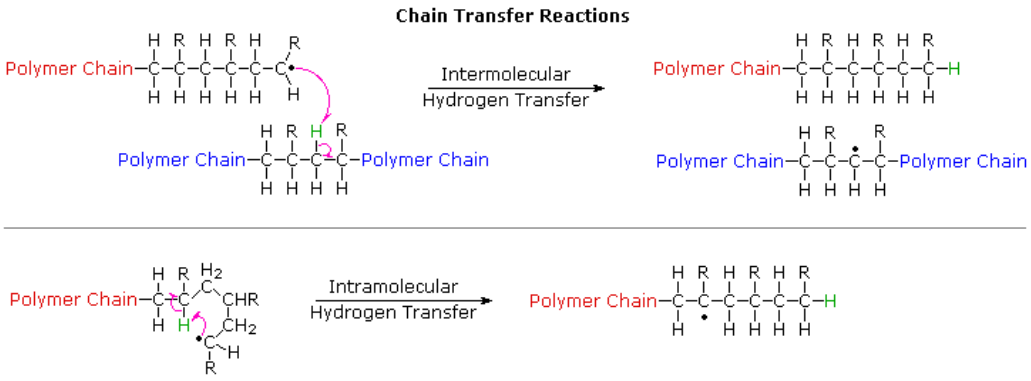
In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination processes are Radical Combination and Disproportionation. These reactions are illustrated by the following equations. The growing polymer chains are colored blue and red, and the hydrogen atom transferred in disproportionation is colored green. Note that in both types of termination two reactive radical sites are removed by simultaneous conversion to stable product(s). Since the concentration of radical species in a polymerization reaction is small relative to other reactants (e.g. monomers, solvents and terminated chains), the rate at which these radical-radical termination reactions occurs is very small, and most growing chains achieve moderate length before termination.

Chain Termination Reactions



The relative importance of these terminations varies with the nature of the monomer undergoing polymerization. For acrylonitrile and styrene combination is the major process. However, methyl methacrylate and vinyl acetate are terminated chiefly by disproportionation.

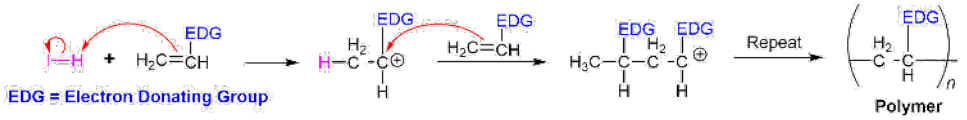
Another reaction that diverts radical chain-growth polymerizations from producing linear macromolecules is called chain transfer. As the name implies, this reaction moves a carbon radical from one location to another by an intermolecular or intramolecular hydrogen atom transfer (colored green). These possibilities are demonstrated by the following equations.



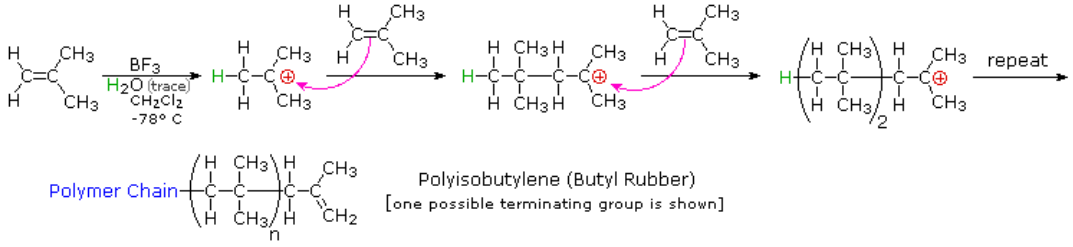
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by hydrogen atom transfer. Further polymerization at the new radical site generates a side chain radical, and this may in turn lead to creation of other side chains by chain transfer reactions. As a result, the morphology of LDPE is an amorphous network of highly branched macromolecules.

CATIONIC CHAIN-GROWTH POLYMERIZATION

Cationic polymerizations are typically acid-catalyzed. Electrophilic addition of H^+ to a double bond forms a carbocation which is propagated by repeated reactions with addition alkene monomers. Alkene monomers bearing cation stabilizing groups, such as alkyl, phenyl or vinyl can be polymerized by cationic processes.

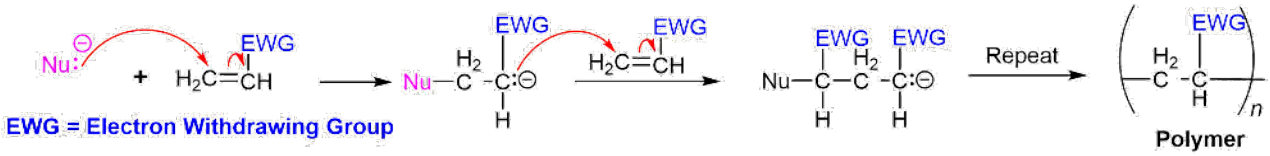


Polymerization of isobutylene (2-methylpropene) by traces of strong acids is an example of cationic polymerization. The initiation reagent cationic polymerization is commonly the Lewis acid, boron tribluoride (BF_3), along with traces of water to form the acidic $BF_3OH^-H^+$ catalyst. The polyisobutylene product is a soft rubbery solid, which is used for inner tubes. This process is similar to radical polymerization, as demonstrated by the following equations. Chain growth ceases when the terminal carbocation combines with a nucleophile or loses a proton, giving a terminal alkene (as shown here).

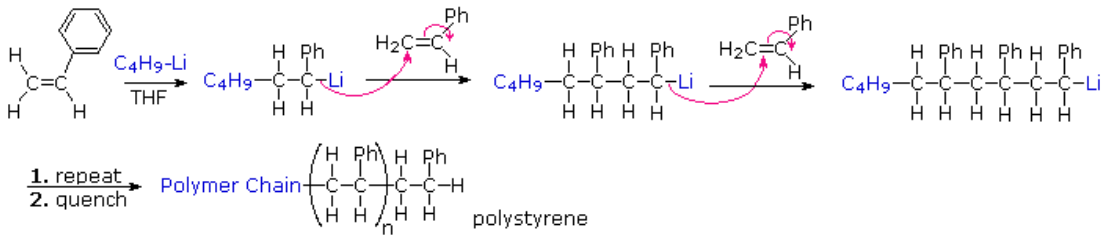


ANIONIC CHAIN-GROWTH POLYMERIZATION

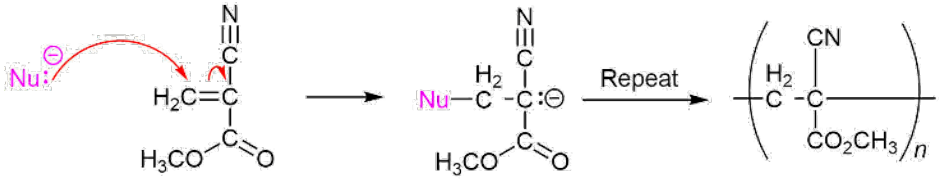
Only monomers having anion stabilizing electron-withdrawing groups (EWG) substituents, such as phenyl, cyano or carbonyl can undergo anionic polymerization.



Species that have been used to initiate anionic polymerization include alkali metals, alkali amides, alkyl lithiums and various electron sources. The fundamental reaction for anion polymerization is a conjugate nucleophilic addition (**Section 18-13**) Treatment of a cold THF solution of styrene with 0.001 equivalents of n-butyllithium causes an immediate polymerization. This is an example of anionic polymerization, the course of which is described by the following equations. Chain growth may be terminated by water or carbon dioxide, and chain transfer seldom occurs.



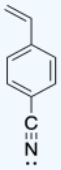
A practical application of anionic polymerization occurs in the use of superglue. This material is methyl 2-cyanoacrylate, $CH_2=C(CN)CO_2CH_3$. When exposed to water, amines or other nucleophiles, a rapid polymerization of this monomer takes place. Because the monomer has two electron withdrawing groups the polymerization particularly rapid.



Methyl 2-cyanoacrylate **Polymer**

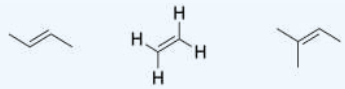
EXERCISE 30.1.1

1) Anionic polymerization of *p*-substituted styrene proceeds very well when the substituent is an electron-withdrawing group such as nitrile. Explain the reason for the success of this approach.

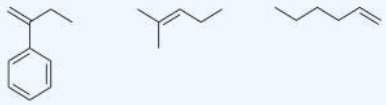


2) In each group, select the alkene monomer most suitable for cationic polymerization.

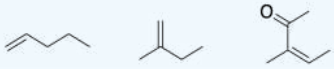
a)



b)

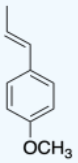


c)



3) Provide a mechanism for the formation of a protic initiator from the interaction of boron trifluoride with water.

4) Anethole in a naturally-occurring compound that has been used in cationic polymerizations. Show why anethole should be a good monomer for this method.



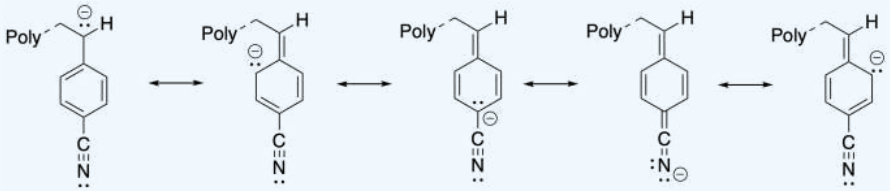
5) Show why radicals formed from the following monomers are relatively stable:

a) acrylonitrile, $CH_2=CHCN$

b) methyl acrylate, $CH_2=CHCO_2Me$

Answer

1) The additional resonance stabilization of the anion by the nitrile group makes anionic polymerization proceed smoothly.

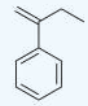


2)

a) tertiary cation



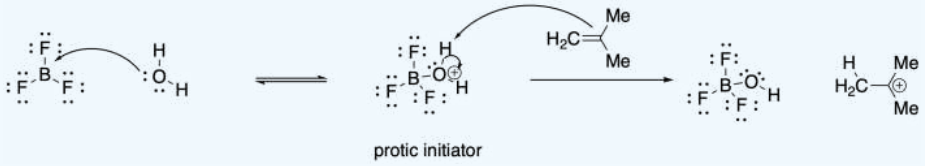
b) tertiary cation, resonance-stabilized



c) tertiary cation, without electron-withdrawing group

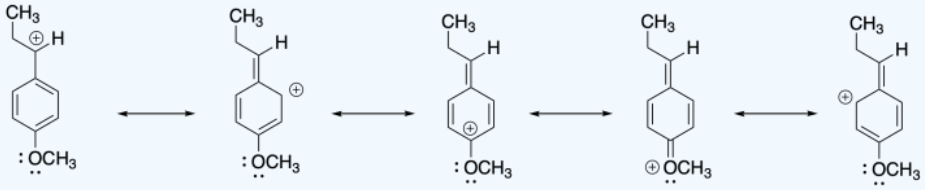


3)



protic initiator

4)

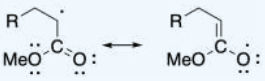


5)

a)



b)



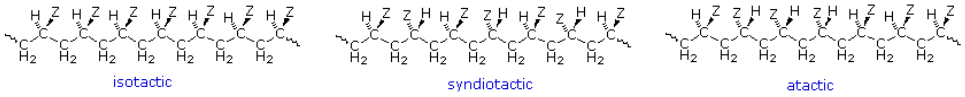
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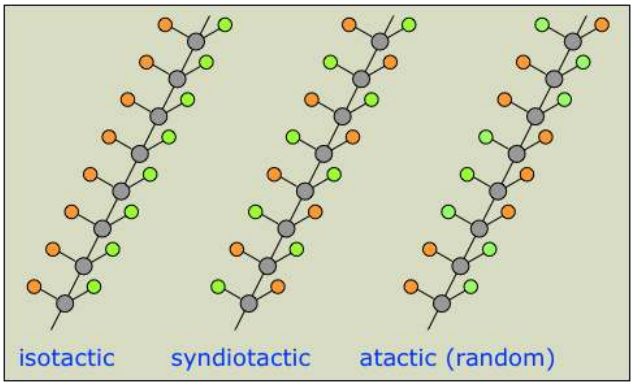
- **2.9: Radical Polymerization** by Chris Schaller is licensed CC BY-NC 3.0. Original source: https://employees.csbsju.edu/cschaller/Advanced/Polymers/Polycontents.htm.

30.2: STEREOCHEMISTRY OF POLYMERIZATION - ZIEGLER-NATTA CATALYSTS

ZIEGLER-NATTA CATALYTIC POLYMERIZATION

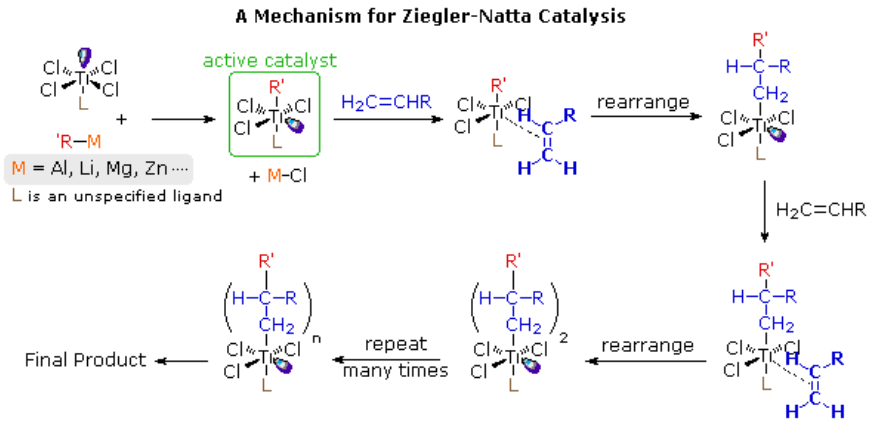
When propene is enchained into a polymer, a new chiral center is formed at every position where a methyl group branches from the backbone. Rather than trying to assign each of these chiral centers with stereochemical configurations (*R*) or (*S*), we instead describe the relative stereochemical relationships along the backbone. The term used to describe these relationships is "**tacticity**". If there is no apparent relationship between the projection of the methyl groups along the backbone, the polymer is termed "**atactic**". If the methyl groups alternate, pointing first one direction, then the other, all the way along the chain, then the polymer is termed "**syndiotactic**". If the methyl groups all project the same direction, the polymer is described as "isotactic".





An efficient and stereospecific catalytic polymerization procedure was developed by Karl Ziegler (Germany) and Giulio Natta (Italy) in the 1950's. Ziegler-Natta catalysts are prepared by reacting certain transition metal halides with organometallic reagents such as alkyl aluminum, lithium and zinc reagents. The catalyst formed by reaction of triethylaluminum with titanium tetrachloride is commonly used. Ziegler-Natta catalysts allowed for the first time, the stereochemically controlled synthesis of polymers with virtually no branching. By changing the catalyst, pure isotactic, syndiotactic, or atactic polymers could be created. For this important discovery, Ziegler and Natta received the 1963 Nobel Prize in chemistry. For example, the polymerization of ethylene, using a Ziegler-Natta catalyst produces a stronger (more crystalline) and more heat resistant product, called high-density polyethylene (HDPE), than typical radical polymerizations which produces low-density polyethlene (LDPE). HDPE is normally produced with molecular weights in the range of 200,000 to 500,000, but it can be made even higher. Polyethylene with molecular weights of three to six million is referred to as ultra-high molecular weight polyethylene, or UHMWPE. UHMWPE can be used to make fibers which are so strong they replaced Kevlar for use in bullet proof vests. Large sheets of it can be used instead of ice for skating rinks.

The following diagram presents one mechanism of the Ziegler-Natta polymerization. Formation of the Ziegler-Natta catalyst, adds an alkyl group ligand to create an organo transition metal compound with a vacant coordination site. An alkene ligand is then coordinated to the transition metal which is followed by a 1,2-insertion of the alkene into the metal-carbon bond. The insertion creates a vacant coordination site which can react with another alkene. These same elementary steps continue to occur to provide the polymerization.



EXERCISE 30.2.1

When the monomer vinylidene fluoride, $\mathbf{H_2C{=}CF_2}$, is polymerized it does not create isotactic, syndiotactic, and atactic forms. Please explain

Answer

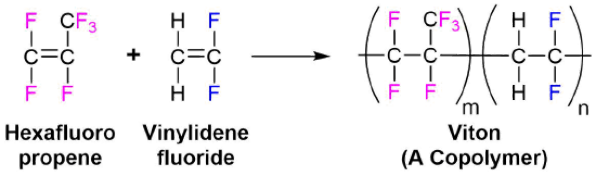
When vinylidene fluoride is polymerized it does not create a chiral center due to the symmetry created by the two fluorides. Chirality is necessary to create isotactic, syndiotactic, and atactic polymer forms.

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30.3: COPOLYMERS

Homopolymers are made with a single monomer and are made up of identical repeating units. Copolymers is made when two or more different monomers are polymerized together to create a polymer with variable repeating units. For example the monomers hexafluoropropene and vinylidene fluoride can be polymerized together to create the copolymer vitron which is used to create durable gaskets.

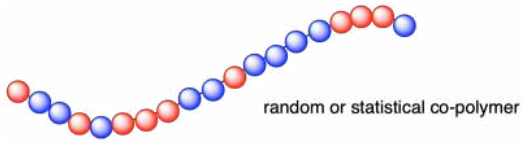


The synthesis of macromolecules composed of more than one repeating unit has been explored as a means of controlling the properties of the resulting material. In this respect, it is useful to distinguish several ways in which different monomeric units might be incorporated in a polymer. The following examples refer to a two component system, in which one monomer is designated A and the other B.

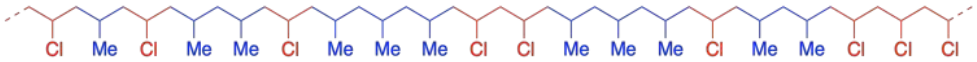
STATISTICAL COPOLYMERS

Also called random copolymers. Here the monomeric units are distributed randomly, and sometimes unevenly, in the polymer chain:

~ABBAAABAABBBABAABA~



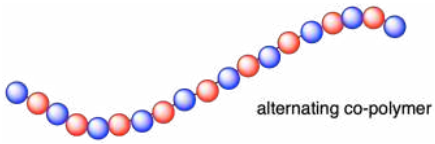
Most direct copolymerizations of equimolar mixtures of different monomers give statistical copolymers. If you take a mixture of alkenes that are capable of forming polymers and you polymerize them together, you may well get them randomly enchained into a growing polymer. For example, polymerizing propene and vinyl chloride together creates a polymer with random monmer unit.



ALTERNATING COPOLYMERS

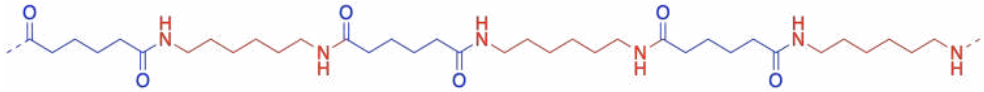
Here the monomeric units are distributed in a regular alternating fashion, with nearly equimolar amounts of each in the chain:

~ABABABABABABABAB~



Formation of alternating copolymers is favored when the monomers have different polar substituents (e.g. one electron withdrawing and the other electron donating), and both have similar reactivities toward radicals. For example, styrene and acrylonitrile copolymerize in a largely alternating fashion.

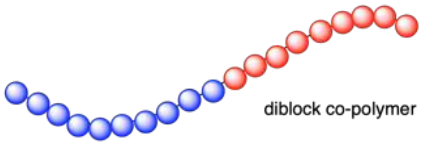
In some of the examples alternating copolymers, the chain is actually composed of two different monomers. This is the case in polyamides such as nylon-6,6, which is a chain is composed of difunctional amines alternating with difunctional carboxyloids (such as carboxylic acids or acid chlorides). Because of their complementary reactivity, the monomers have to alternate: an amine and then a carboxyloid, to form an amide, and so on. We can think of these polymers as "alternating co-polymers" because the two different monomers alternate with each other along the chain.



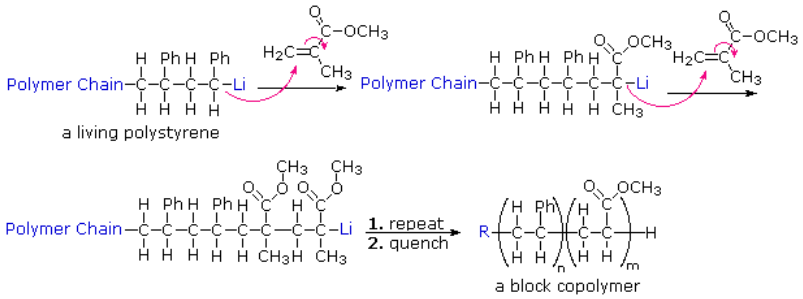
BLOCK COPOLYMERS

Instead of a mixed distribution of monomeric units, a long sequence or block of one monomer is joined to a block of the second monomer:

~AAAAA-BBBBBBB~AAAAAAA~BBB~



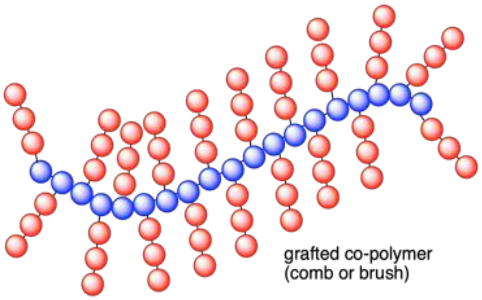
Several different techniques for preparing block copolymers have been developed, with a common example being anionic polymerization. In the anionic polymerization of styrene, a reactive site remains at the end of the chain until it is quenched. The unquenched polymer has been termed a living polymer because the polymerization can continue as long as monomer is present. If different suitable monomer, methyl methacrylate, is added the chain will continue grow by adding methyl methacrylate units and a block polymer will form. This is illustrated for in the following diagram.



GRAFT COPOLYMERS

As the name suggests, side chains of a given monomer are "grafted" to the main chain of a different monomer:

~AAAAAAA(BBBBBBB~)AAAAAAA(BBBB~)AAA~.



Graft polymers can be made in great profusion by attaching chains of one kind of polymer to the middle of another. A particularly simple but uncontrollable way of doing this is to knock groups off a polymer chain with x-ray or alpha radiation in the presence of a monomer. The polymer radicals so produced then can grow side chains made of the new monomer. A more elegant procedure is to use a photochemical reaction to dissociate groups from the polymer chains and form radicals capable of polymerization with an added monomer.

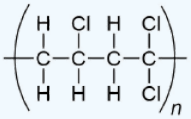
Some Useful Copolymers

Monomer A	Monomer B	Copolymer	Uses
$H_2C=CHCl$	$H_2C=CCl_2$	Saran	films & fibers
$H_2C=CHC_6H_5$	$H_2C=C-CH=CH_2$	SBR styrene butadiene rubber	tires
$H_2C=CHCN$	$H_2C=C-CH=CH_2$	Nitrile Rubber	adhesives hoses
$H_2C=C(CH_3)_2$	$H_2C=C-CH=CH_2$	Butyl Rubber	inner tubes
$F_2C=CF(CF_3)$	$H_2C=CHF$	Viton	gaskets

EXERCISE 30.3.1

Draw the structure of an alternating segment of Saran, a copolymer of vinyl chloride (chloroethene) and vinylidene chloride (1,1-dichloroethene).

Answer



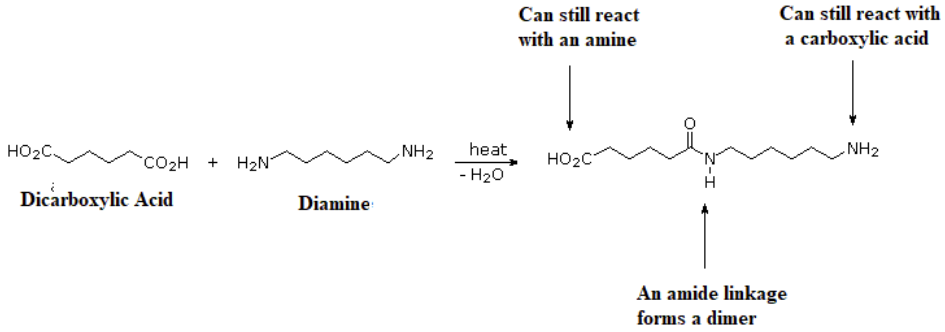
Saran

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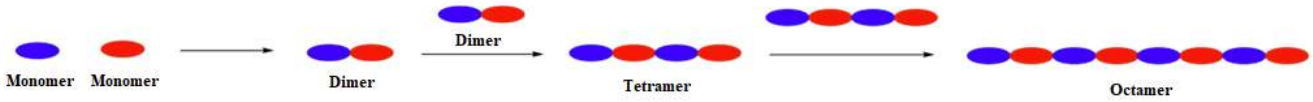
- **29.8: Block, Graft, and Ladder Polymers** by John D. Roberts and Marjorie C. Caserio is licensed CC BY-NC-SA 4.0.

30.4: STEP-GROWTH POLYMERS

The process of step-growth polymerizations are fundamentally different than in chain-growth. In step-growth polymerizations, monomers are generally linked by a carbon-heteroatom bond (C-O & C-N) formed in non-sequential steps. Often, the reactions used to link these monomers include multiple nucleophilic acyl substitutions. Step-growth polymerizations usually use two different monomers, neither of which would undergo polymerization on its own. The two monomers are multifuntional and complementary to each other, such that each provides the other with a reactive partner. In this section, we will be focusing on monomers which are **difunctional**, meaning they contain two of the same reactive functional group. A step-growth polymerization starts with two complementary functional groups on different monomers reacting to form a dimer. Because both monomers were difunctional, each retains a reactive group and can react with additional complementary monomers.

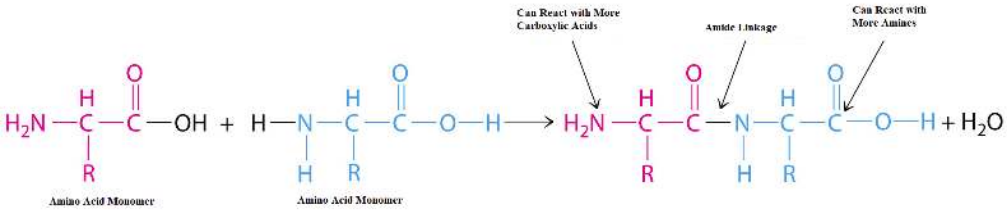


In fact the difuctionality of the monomers, allows step-growth polymers to grow in two directions at once. First, two complementary monomers react with each other to form a dimer. Assuming that monomers react at roughly similar rates, when one end of the dimer reacts again it will likely find another dimer and form a tetramer. Then when the tetramer goes to react again it will most likely find another tetramer and form an octamer. This process is repeated allowing the polymer to grow in two directions at the same time.



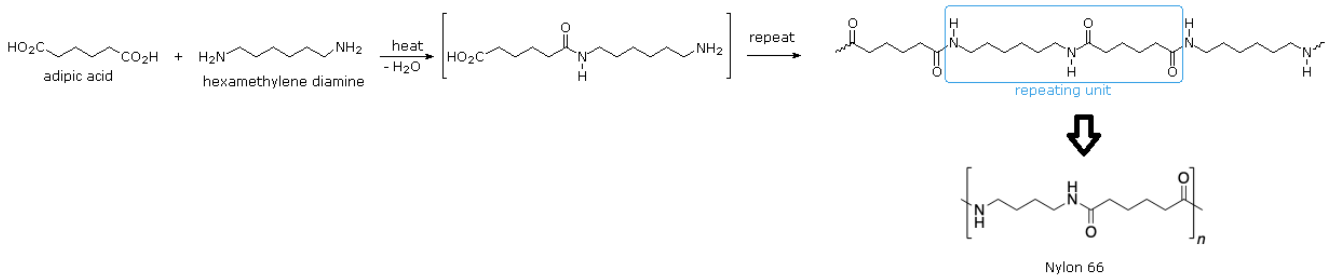
The Step-Growth Polymerization Process

Virtually all fibers are made from some form of polymer. In particular, silk and wool are composed of a naturally occurring protein polymer. The monomers of proteins are called **amino acid residues**. These residues are connected by amide linkages which are also called **peptide bonds**. Many of the early efforts of polymer chemistry were to artificially create fibers which mimicked the properties of silk and wool.

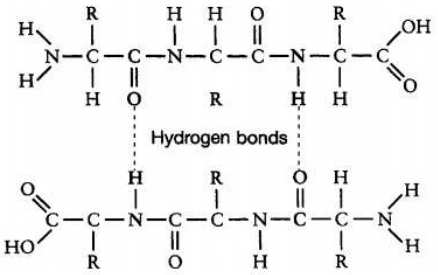


POLYAMIDES

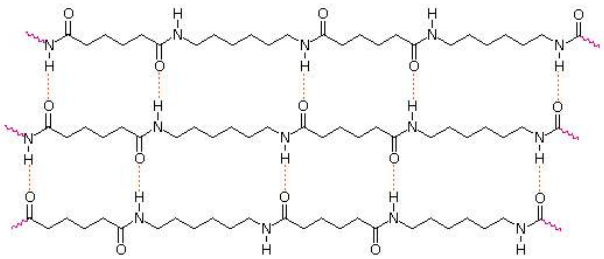
The first fully synthetic polymer fiber, nylon-6,6, was produced in 1938 by the company DuPont. The lead chemist of DuPont's work was Wallace H. Carothers, who reasoned that the properties of silk could be mimicked by constructing a polymer chain created with repeating amide bonds, just like the proteins in silk. Nylon-6,6 was created by first reacting 1,6-hexanedioic acid (adipic acid) and 1,6-hexanediamine to give a salt which was then heated creating multiple amide bonds through nucleophilic acyl substitution. The product of this particular reaction is a polyamide called nylon-6,6. The numbers of the name indicate how many carbons are contained in each monomer. The first “6” stands for the number of carbons in the diamine monomer while the second number indicated the number of carbons in the dicarboxylic acid. Simply by varying the number of carbons in each monomer, a wide variety of nylon polymers can be made.



Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. Known for their high strength and abrasion resistance, nylons can be molded into blocks for use in electrical equipment, gears, bearings, and valves. The strength of nylon fibers comes, in part, from their ability to form strong hydrogen bonding intermolecular forces with each other in much the same fashion as proteins.



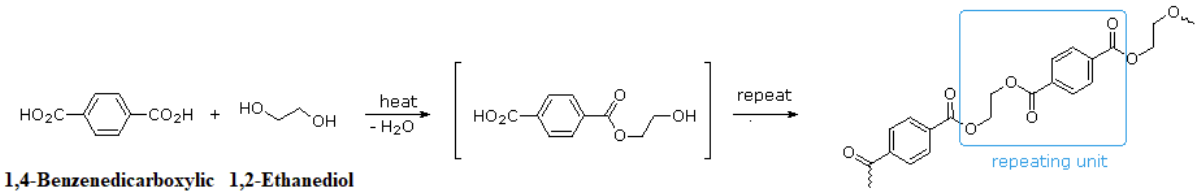
The Hydrogen Bonding between Proteins



The Hydrogen Bonding between Nylon Polyamides

POLYESTERS

Esterfication, via nucleophilic acyl substitutions, can also be used to form the primary linkages in step-growth polymers. A polyester is typically produced when a dicarboxylic acid and a diol are reacted together. After the initial reaction, the ester product contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other. Further esterification using a step-growth polymerization, produces a polyester. The most important polyester, polyethylene terephthalate (PET), is made from the reaction of 1,4-benzenedicarboxylic (terephthalic acid) and 1,2-ethanediol (ethylene glycol) monomers.



1,4-Benzenedicarboxylic 1,2-Ethanediol

poly(ethyleneterephthalate)
(PET)
A Polyester

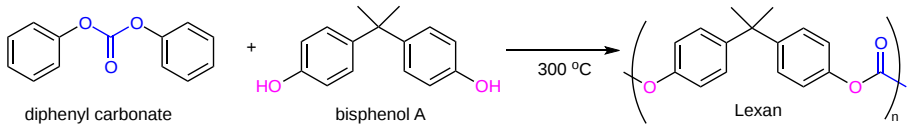
Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes.

POLYCARBONATES

Beyond carboxylic acid derivatives, virtually any reaction which involves reactive species on two different molecules can be used to perform a step-growth polymerization. A variation involves using a monomer containing a carbonate functional group (−O−(C=O)−O−). A carbonate acts like a double ester and can undergo a type of double transesterification reaction with two alcohols to form a new carbonate containing compound.



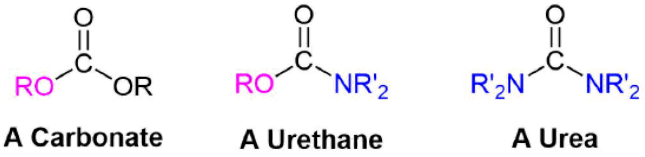
In effect, a carbonate is difunctional and can be reacted with a diol to form polymers containing repeated carbonate groups in their structure called polycarbonates. An example of a polycarbonate is the polymer, Lexan, which is created when diphenyl carbonate and bisphenol A (a diol) are reacted together.



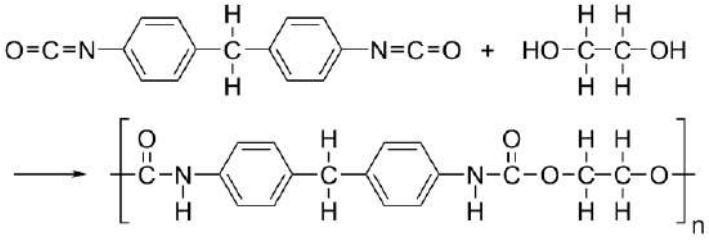
Bisphenol (BPA), primarily used to make polycarbonate, is one of the highest-volume chemicals produced in the world, with over six billion pounds made each year. Because polycarbonate is used to make plastic bottles, the lining for food cans, and the lining for beverage cans there has been much concern about trace amounts of BPA leaching from the containers and being ingested. A study conducted in 2003 and 2004 by the Center for Disease Control and Prevention found trace amounts BPA in the tissues of 93% of people in the United States. Consequently, this has led to many beverage companies switching to non-polycarbonate polymers.

POLYURETHANE

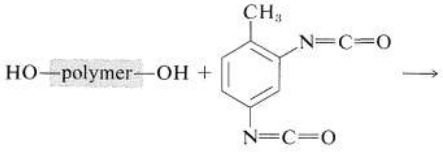
A urethane is a functional group similar to a carbonate and a urea. A urethane has an -OR and a -NR_2 group attached to the carbonyl carbon.

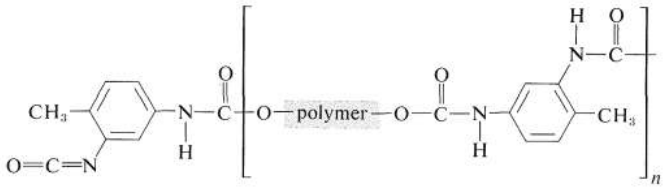


Polyurethane (**PUR** and **PU**) is a polymer composed of organic units joined by carbamate (urethane) links. Polyurethanes are produced by reacting an isocyanate containing two or more isocyanate groups per molecule ($R-(N=C=O)_n$) with a polyol containing on average two or more hydroxyl groups per molecule ($R'-(OH)_n$) in the presence of a catalyst or by activation with ultraviolet light.

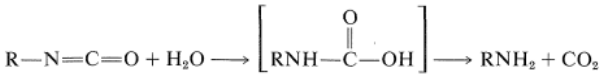


The very widely used polyurethane foams can be considered to be either block polymers or copolymers. The essential ingredients are a diisocyanate and a diol. The diisocyanate most used is 2,4-diisocyano-1-methylbenzene, and the diol can be a polyether or a polyester with hydroxyl end groups. The isocyano groups react with the hydroxyl end groups to form initially an addition polymer, which has polycarbamate (polyurethane) links, and isocyano end groups:

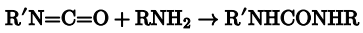




A foam is formed by addition of the proper amount of water. The water reacts with the isocyanate end groups to form carbamic acids which decarboxylate to give amine groups:

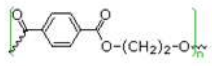
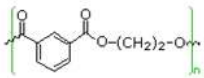
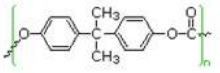
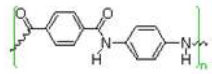
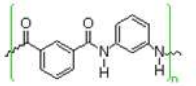


The carbon dioxide evolved is the foaming agent, and the amino groups formed at the same time extend the polymer chains by reacting with the residual isocyano end groups to form urea linkages:



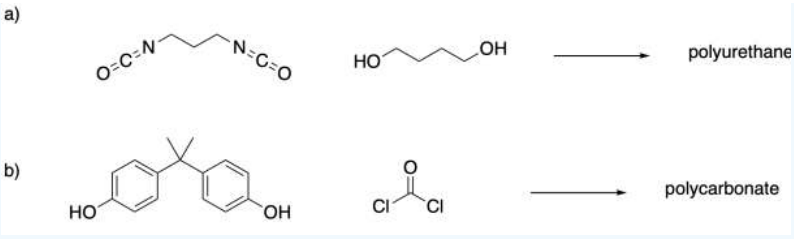
Polyurethanes are used in the manufacture of high-resilience foam seating, rigid foam insulation panels, microcellular foam seals and gaskets, durable elastomeric wheels and tires (such as roller coaster, escalator, shopping cart, elevator, and skateboard wheels), automotive suspension bushings, electrical potting compounds, high performance adhesives, surface coatings and surface sealants, synthetic fibers (e.g., Spandex), carpet underlay, hard-plastic parts (e.g., for electronic instruments), condoms,[1] and hoses.

Common Step Growth Polymers

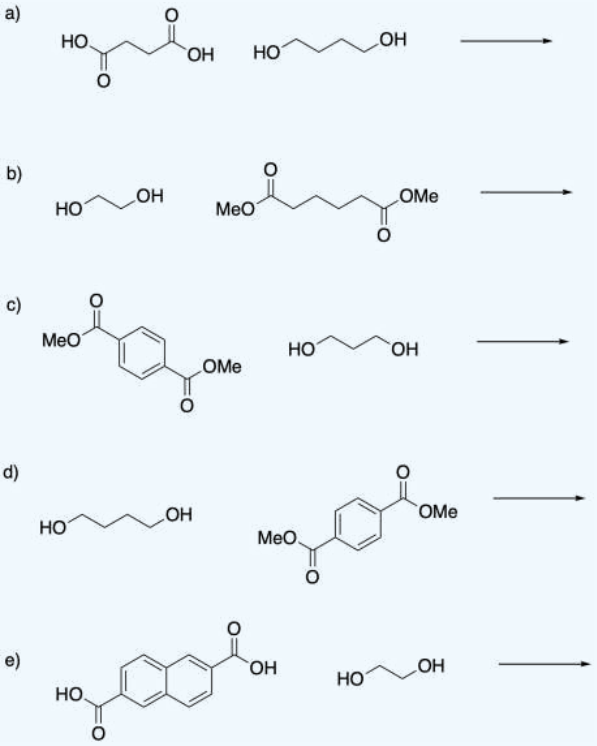
Formula	Type	Components	T_g ºC	T_m ºC
~[CO(CH2)4CO-OCH2CH2O]n~	polyester	HO2C-(CH2)4-CO2H HO-CH2CH2-OH	< 0	50
	polyester Dacron, Mylar	para HO2C-C6H4-CO2H HO-CH2CH2-OH	70	265
	polyester	meta HO2C-C6H4-CO2H HO-CH2CH2-OH	50	240
	polycarbonate Lexan	(HO-C6H4-)2C(CH3)2 (Bisphenol A) X2C=O (X = OCH3 or Cl)	150	267
~[CO(CH2)4CO-NH(CH2)6NH]n~	polyamide Nylon 66	HO2C-(CH2)4-CO2H H2N-(CH2)6-NH2	45	265
~[CO(CH2)5NH]n~	polyamide Nylon 6 Perlon		53	223
	polyamide Kevlar	para HO2C-C6H4-CO2H para H2N-C6H4-NH2	---	500
	polyamide Nomex	meta HO2C-C6H4-CO2H meta H2N-C6H4-NH2	273	390

? EXERCISE 30.4.1

1) The following difunctional monomers would undergo polymerization together. Show the product that results.

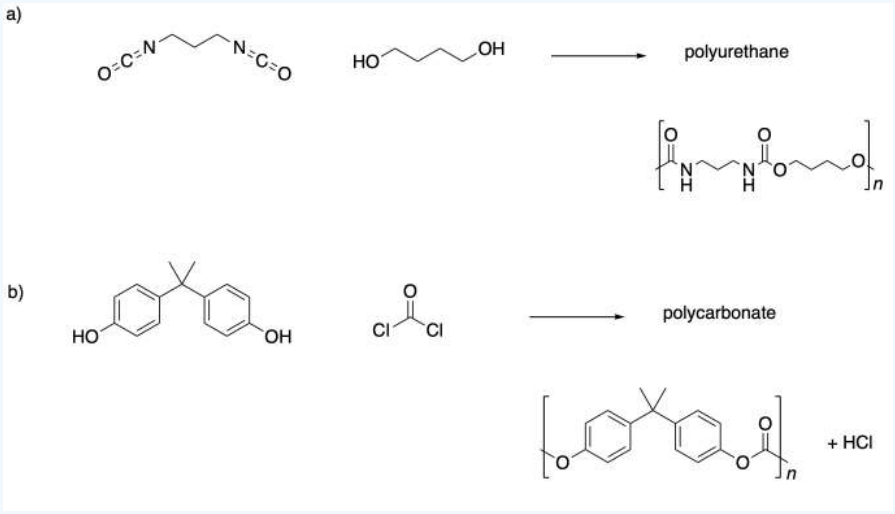


2) Provide structures of the polyesters made from the monomers as indicated.

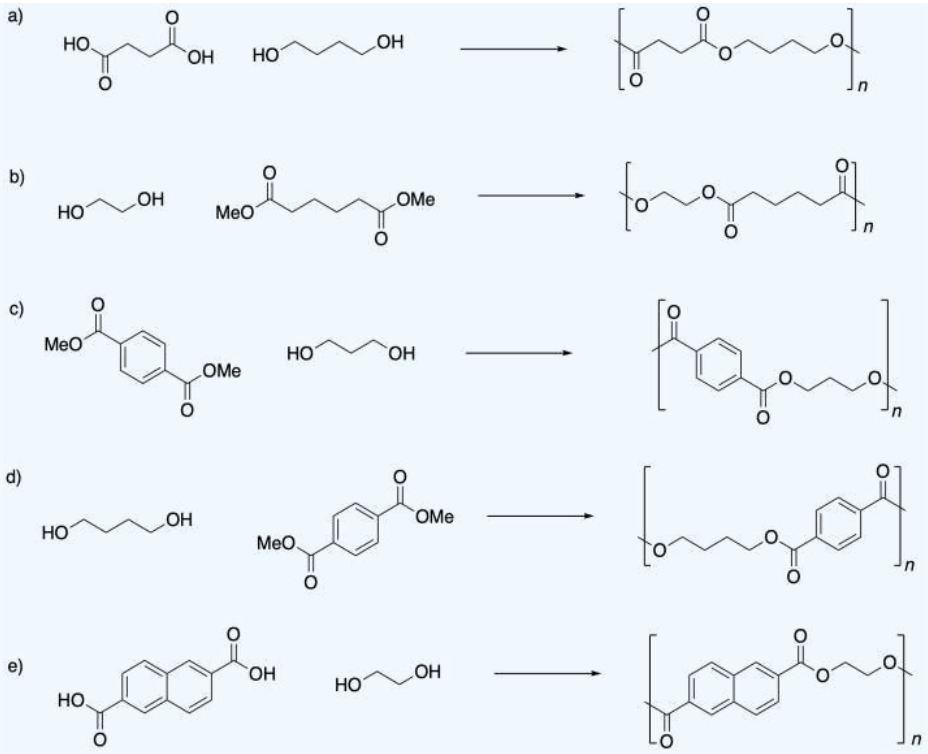


Answer

1)



2)



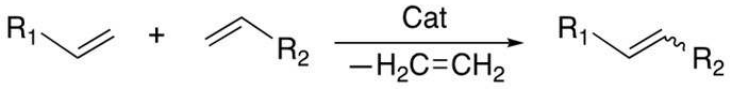
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- **21.9: Polyamides and Polyesters - Step-Growth Polymers** by Dietmar Kennepohl, Jim Clark, John Roberts, Layne Morsch, Marjorie C. Caserio, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.
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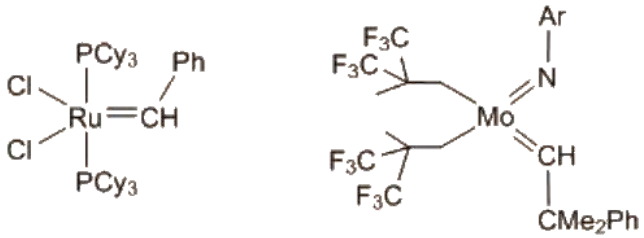
30.5: OLEFIN METATHESIS POLYMERIZATION

OLEFIN METATHESIS

The application of organometallic chemistry in homogenous catalysis is progressively increasing with the fast pace of discovery of new catalysts in the area. Alkene metathesis reactions are gaining wide popularity in synthesizing unsaturated olefinic compounds. Central to this catalysis is a metal carbene intermediate that reacts with olefins to give different olefinic compounds. When two different olefin substrates are used, the reaction is called the "cross metathesis" owing to the fact that the olefinic ends are exchanged. In a process called **olefin metathesis polymerization**, unsaturated olefinic polymers can be created by a metathesis reaction.



Olefin metathesis catalysts contain a metal carbon double bond with two of the most notable being are the **Grubbs Ru catalyst** and the **Schrock's Mo catalyst**.



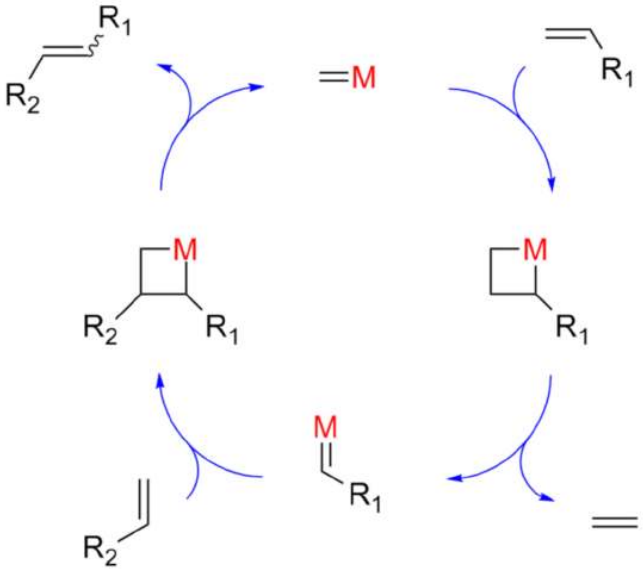
Grubbs catalyst

Schrock catalyst
(Ar = C_6H_3{2,6-*i*-Pr}$_2$)

The Grubb's and the Schrock's Catalyst

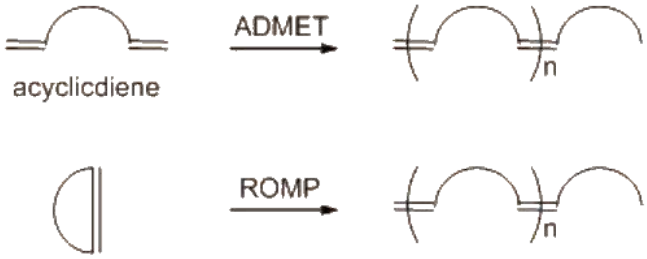
MECHANISM CROSS METATHESIS

An olefin metathesis catalyst is a transition metal compound that is capable of splitting the double bond of an alkene in half and putting the two pieces together with other alkenes. The key part of an olefin metathesis catalyst is a metal-carbon double bond. That is the group that is capable of switching the ends of alkenes around with different partners. The catalyst react reversibly with an alkene to produce a 4−membered metalacyclobutane intermediate called a metallacycle. The ring promptly opens to produce a different catalyst and alkene. The reaction of this new catalyst with the second alkene produces a second metallacycle intermediate. This ring opens to produce the metathesis product and yet another form of the catalyst. The ring opening and closing continues as the reaction moves forward.



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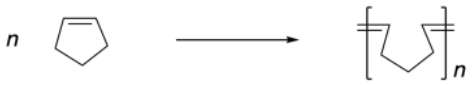
Olefin Metathesis Polymerization The variants of metathesis often used in producing polymers are: (*i*) the Acyclic Diene Metathesis (ADMET) and (*ii*) the Ring Opening Metathesis Polymerization (ROMP), both of which produce long chain polymers



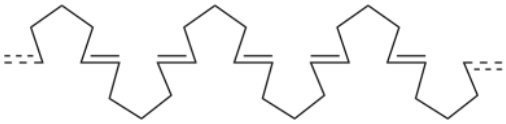
One method, called **ring-opening metathesis polymerization**, or ROMP, involves the use of a moderately strained cycloalkene, such as cyclopentene. The strain of the ring favors ring-opening, thereby driving formation of the open-chain product. The polymer that results has double bonds spaced regularly along the chain, allowing for either hydrogenation or further functionalization if desired.

Ring-opening metathesis polymerization (ROMP) takes a cyclic alkene, splits open its double bond, and knitting it together with other cyclic alkenes to produce a long polymer chain with regularly spaced double bonds. The ring-strain of the cycloalkenes favors the open-chain product and drives the polymerization reaction forward.

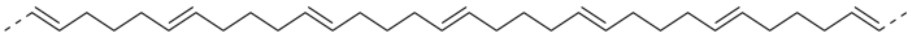
During a ROMP, a cyclopentene ring is opened up at the double bond and reaches out to join with other cyclopentene rings on either side of it.



The product polymer of a ROMP using cyclopentene rings would look something like this:

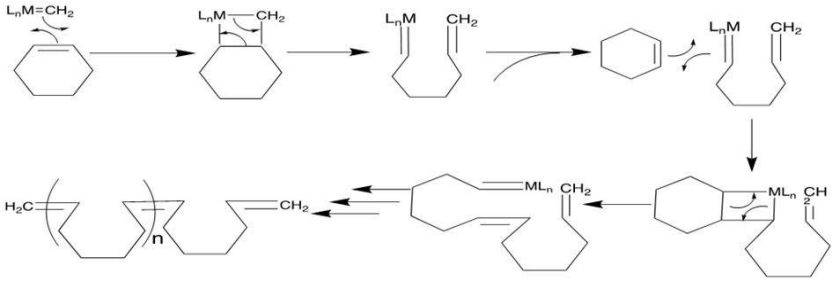


Which can draw it in an usual zig-zag conformation.

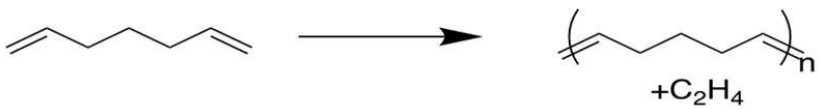


MECHANISM

The mechanism starts with a cycloalkene and a metathesis catalyst reacting to form a four-member metallacycle. Opening of the metallacycle forms a new alkene and catalyst both of which are part of the same intermediate molecule. The catalyst end of the intermediate molecule can then react with a different cycloalkene to form a new metallacycle. This process is repeated causing the polymer chain to from.



The second method is called **acyclic diene metathesis** (ADMET) which uses long open-chain substrates, which contain a double bond at both ends of the main chain, such as 1,6-heptadiene. A byproduct of the reaction, gaseous ethylene ($H_2C=CH_2$), escapes which drives the equilibrium forward.



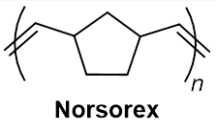
EXERCISE 30.5.1

The ring opening metathesis polymerization of norborene produces a commercial polymer called Norsore which is used a sealing material. Please draw the structure of Norsore.



Norbornene

Answer



Norsorex

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30.6: POLYMER STRUCTURE AND PHYSICAL PROPERTIES

POLYMER CRYSTALLINITY

To account for the physical differences between the different types of polymers, the nature of the aggregate macromolecular structure, or **morphology**, of each substance must be considered. Because polymer molecules are so large, they generally pack together in a non-uniform fashion, with ordered or crystalline-like regions, called **crystallites**, mixed together with disordered or amorphous domains. In some cases the entire solid may be amorphous, composed entirely of coiled and tangled macromolecular chains. Crystallinity occurs when linear polymer chains are structurally oriented in a uniform three-dimensional matrix. In the diagram on the right, crystalline domains are colored blue. Increased crystallinity is associated with an increase in rigidity, tensile strength and opacity (due to light scattering). Amorphous polymers are usually less rigid, weaker and more easily deformed. They are often transparent.

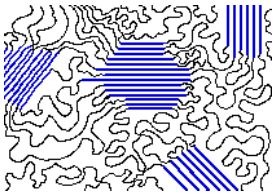


Figure **30.6.1**: CSchematic diagram of crystallites (in blue) in a largely crystalline polymer.

Three factors that influence the degree of crystallinity are:

1. **Chain length:** Longer polymer chains tend to have greater van der Waals forces and increased crystallinity than do shorter chains (**Section 2-12**)
2. **Chain branching:** Polymer chains without branching can pack closely together. Lack of branching increases the crystallinity of polymers.
3. **Interchain interactions:** (Intermolecular forces and Crosslinking). Crystallinity increases as the strength of the intermolecular forces between polymer chains increases. Croslining between polymer chains tends to increase crystallinity.

The importance of the first two factors is nicely illustrated by the differences between LDPE and HDPE. As noted earlier (Section 31-2), HDPE is composed of very long unbranched hydrocarbon chains. These pack together easily in crystalline domains that alternate with amorphous segments, and the resulting material, while relatively strong and stiff, retains a degree of flexibility. In contrast, LDPE is composed of smaller and more highly branched chains which do not easily adopt crystalline structures. This material is therefore softer, weaker, less dense and more easily deformed than HDPE.

The forces between the chains in the crystallites of polyethene are the so-called **van der Waals** or **dispersion** forces, which are the same forces acting between smaller hydrocarbon molecules. Although these forces are relatively weak, they increase with the size of the molecule. Polymer chains are large enough that the van der Waals forces create a strong and stiff material.

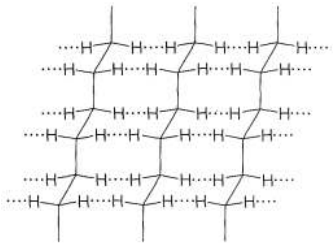


Figure **30.6.2**: CRepresentation of attractive interactions between the hydrogens in a crystallite of polyethene

In other kinds of polymers, even stronger intermolecular forces can be produced by hydrogen bonding. This is especially important in the polyamides, such as the nylons, of which nylon 66 is most widely used. The increase strength of the interactions between polymer chains makes polyamides among some of the strongest polymer materials known.

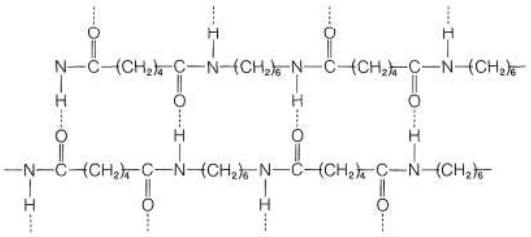


Figure 30.6.3: Possible hydrogen-bonded structure for crystallites of nylon 66, an amide-type polymer of hexanedioic acid and 1,6-hexanediamine.

Natural rubber is a completely amorphous polymer. Unfortunately, the potentially useful properties of raw latex rubber are limited by temperature dependence; however, these properties can be modified by chemical change. If the chains of rubber molecules are slightly cross-linked by sulfur atoms, a process called **vulcanization** which was discovered by Charles Goodyear in 1839, the desirable elastomeric properties of rubber are substantially improved. At 2 to 3% crosslinking a useful soft rubber, that no longer suffers stickiness and brittleness problems on heating and cooling, is obtained. At 25 to 35% crosslinking a rigid hard rubber product is formed. The following illustration shows a cross-linked section of amorphous rubber.

GLASS TRANSITION AND MELT TRANSITION TEMPERATURES

The effect of temperature on the physical properties of polymers is very important to their practical uses. At low temperatures, polymers become hard and glasslike because the motions of the segments of the polymer chains with relation to each other are slow. The approximate temperature below which glasslike behavior is apparent is called the **glass transition temperature** and is symbolized by T_g. When a polymer containing crystallites is heated, the crystallites ultimately melt, and this temperature is usually called the **melt transition temperature** and is symbolized as T_m. As the amount of crystallinity in a polymer increases, so does T_m.

T_g often depends on the history of the sample, particularly previous heat treatment, mechanical manipulation and annealing. It is sometimes interpreted as the temperature above which significant portions of polymer chains are able to slide past each other in response to an applied force. The introduction of relatively large and stiff substituents (such as benzene rings) will interfere with this chain movement, thus increasing T_g (note polystyrene below). The introduction of small molecular compounds called **plasticizers** (discussed later in this section) into the polymer matrix increases the interchain spacing, allowing chain movement at lower temperatures. with a resulting decrease in T_g. T_m and T_g values for some common addition polymers are listed below.

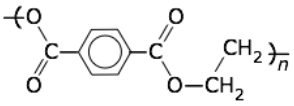
Polymer	LDPE	HDPE	PP	PVC	PS	PAN	PTFE	PMMA	Rubber
T_m (ºC)	110	130	175	180	175	>200	330	180	30
T_g (ºC)	−110	−100	−10	80	90	95	−110	105	−70

POLYMER CATEGORIES

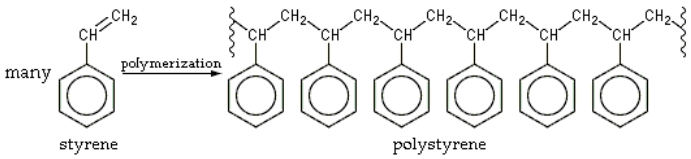
THERMOPLASTICS

Most of the polymers described in this chapter are classified as **thermoplastic**s. Plastics that soften when heated and become firm again when cooled. This is the more popular type of plastic because the heating and cooling may be repeated and the thermoplastic may be reformed. These polymers tend to have high Tg so they are hard solids at room temperature, however, above Tg they they become malleable and may be shaped, pressed into molds, spun, or cast from melts.

Polyethylene (poly(ethylene terephthalate) or PET is the most common thermoplastic . In 2017, PET made up 34% of the total plastics market with over 100 million tones of polyethylene resins being produced. PET is partially crystalline and is used to create clear plastic bottles such as 2-liter beverage bottles, milk jugs, detergent bottles, and water bottles.

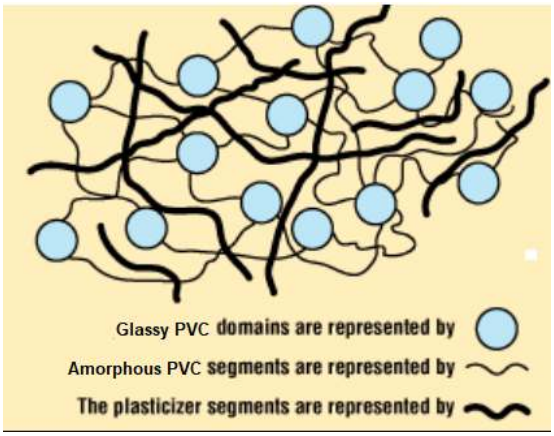


Polystyrene is also a common thermoplastic. The polymer is making it a solid but rather rather brittle at room temperature. Polystyrene is used to make hard clear plastic cups, foam cups, eating utensils, deli food containers, toy model kits, some packing popcorn.

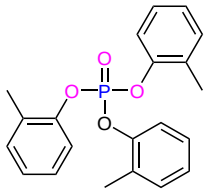


PLASTICIZERS

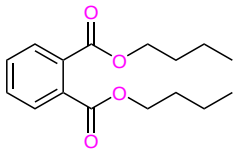
Plasticizers or **dispersants** are additives that increase the plasticity or decrease the viscosity of a material. These substances are compounded into certain types of plastics to render them more flexible by lowering the glass transition temperature. They accomplish this by taking up space between the polymer chains and acting as lubricants to enable the chains to more readily slip over each other. Many (but not all) are small enough to be diffusible and a potential source of health problems. Substantial concerns have been expressed over the safety of some plasticizers, especially because some low molecular weight ortho-phthalates have been classified as potential endocrine disruptors with some developmental toxicity reported.



Polyvinyl chloride (PVC) polymers are one of the most widely-plasticized types. PVC is usually is not very crystalline and is relatively brittle and glassy. The properties of polyvinyl chloride can be improved by blending it with substances of low volatility which tend to break down its glasslike structure. Common plasticizers used with PVC are tris-(2-methylphenyl) phosphate (tricresyl phosphate) and dibutyl benzene-1,2-dicarboxylate (dibutyl phthalate). Plasticized polyvinyl chloride is reasonably flexible and is widely used for flexible vinyl materials such as garden hoses, waterbeds, cheap shower curtains, raincoats and upholstery. The pungent oder associated with these products are a testament to the ability of plasticizers to migrate into the environment.



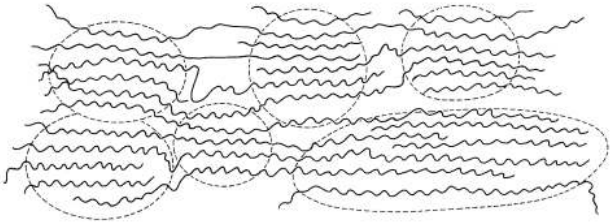
tris-(2-Methylphenyl) phosphate



Dibutyl phthalate

FIBERS

Fibers are drawn into thin threads by forcing the melted or dissolved polymer through a spinneret to generate filaments that can be woven into fabrics. Part of this process, called **cold-drawing**, the polymer material is subjected to strong stress in one direction causing the material to elongate and the crystallites to be drawn together and oriented along the direction of the applied stress. Having the crystallites in a polymer oriented with respect to one another gives the polymer a much higher tensile strength than an unoriented polymer. Polymers such as nylon, which has strong intermolecular forces, has the crystallinity required to be drawn in oriented fibers.



Schematic representation of an oriented crystalline polymer produced by drawing the polymer in the horizontal direction. The crystalline regions are enclosed with dashed lines.

ELASTOMERS

Elastomers usually are amorphous polymers which have the ability to be stretched. The key to this elastic behavior is polymer chains with weak forces between the chains and a sufficiently irregular structure to be unstable in the crystalline state. A useful elastomer needs to have some kind of cross-linking. The important difference between an elastomer and a crystalline polymer is the size of the amorphous regions. When tension is applied and the material elongates, the chains in the amorphous regions straighten out and become more nearly parallel. The forces between the chains are too weak to maintain the crystalline state in the absence of tension. Thus when tension is released, contraction occurs and the original, amorphous polymer is produced. The entropy of the chains is more favorable in the relaxed state than in the stretched state.

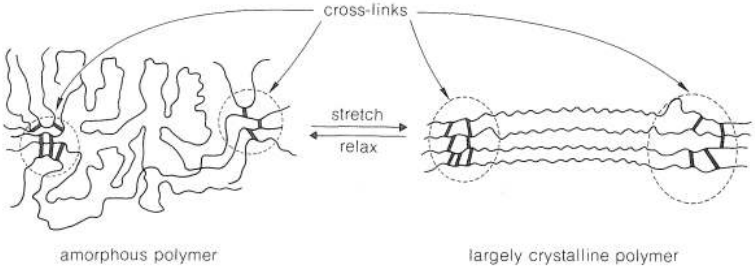
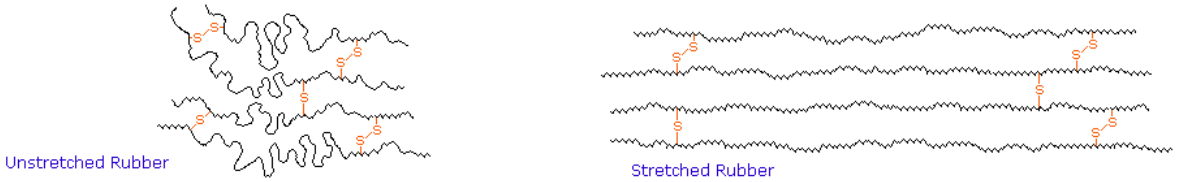
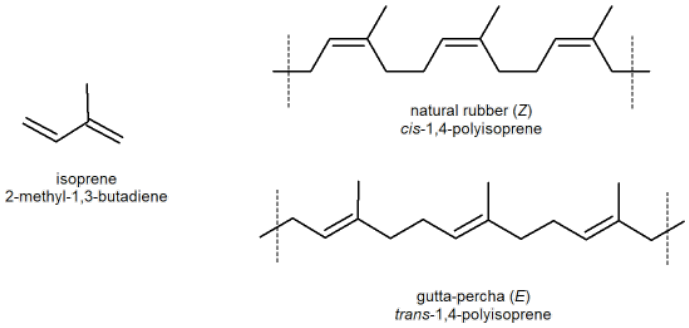


Figure **30.6.4**: Schematic representation of an elastomer in relaxed and stretched configurations.

A good elastomer should not undergo plastic flow in either the stretched or relaxed state, and when stretched should have a "memory" of its relaxed state. These conditions are best achieved with natural rubber (*cis*-poly-2-methyl-1,3-butadiene, *cis*-polyisoprene) by curing (*vulcanizing*) with sulfur. Natural rubber **(Section 14-6)** is tacky and undergoes plastic flow rather readily, but when it is heated with elemental sulfur, sulfur cross-links are introduced between the chains. These cross-links reduce plastic flow and provide a reference framework for the stretched polymer to return to when it is allowed to relax. Also the double bonds in rubber all have a Z-configuration, which causes this macromolecule to adopt a kinked or coiled conformation.



However, the gutta-percha (structure above) E-isomer of rubber adopts a uniform zig-zag conformation, which produces greater crystallinity making it not an elastomer.



THERMOSETS

Thermosets are plastics that soften when heated and can be molded, but harden permanently. In a thermoset, crosslinks connect the different chains in the material, forming bridges that span from chain to chain to chain, essentially uniting the material into one big molecule. If it is one big molecule, the chains can never move completely independently of each other, and the material cannot form a new shape.

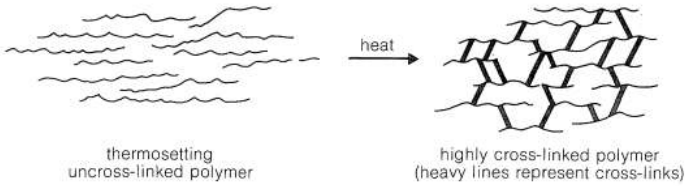
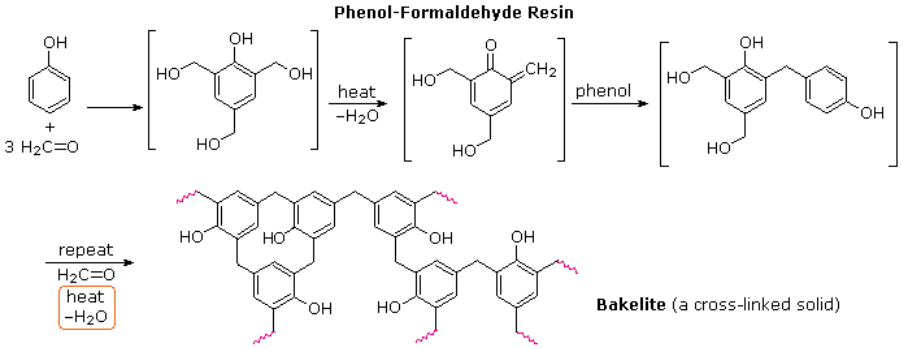


Figure **30.6.4**: Schematic representation of the conversion of an uncross-linked thermosetting polymer to a highly cross-linked polymer. The cross-links are shown in a two-dimensional network, but in practice three-dimensional networks are formed.

One of the oldest known thermosetting synthetic polymers, **Bakelite**, is made by condensation of phenol with formaldehyde. During the thermoset process water is lost and many crosslinks are formed. produce (4-hydroxyphenyl)methanol. **Bakelite** was patented on December 7, 1909 and was revolutionary for its electrical nonconductivity and heat-resistant properties used in electrical insulators, radio and telephone casings and such diverse products as kitchenware, jewelry, pipe stems, and children's toys.

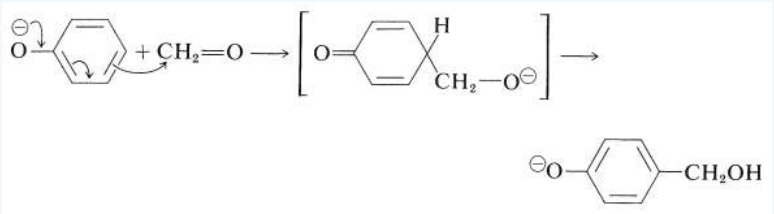


? EXERCISE 30.6.1

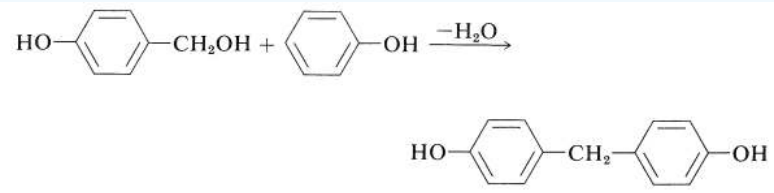
Propose a mechanism for the base-catalyzed polymerization of phenol and formaldehyde to form Bakelite.

Answer

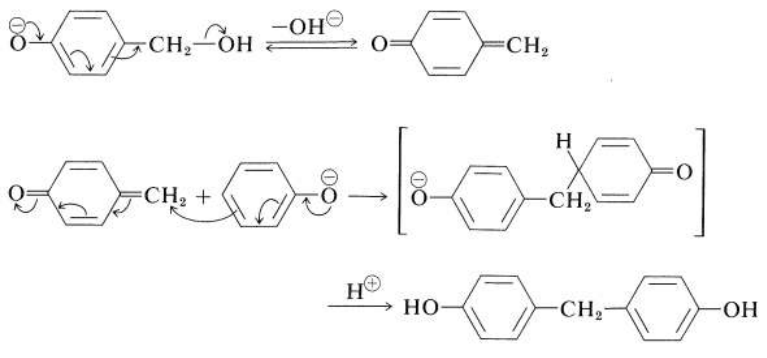
One of the oldest known thermosetting synthetic polymers is made by condensation of phenols with aldehydes using basic catalysts. The resins that are formed are known as **Bakelites**. The initial stage is the base-induced reaction of benzenol and methanal to give a (4-hydroxyphenyl)methanol, and this reaction closely resembles an aldol addition and can take place at either the 2- or the 4-position of the benzene ring:



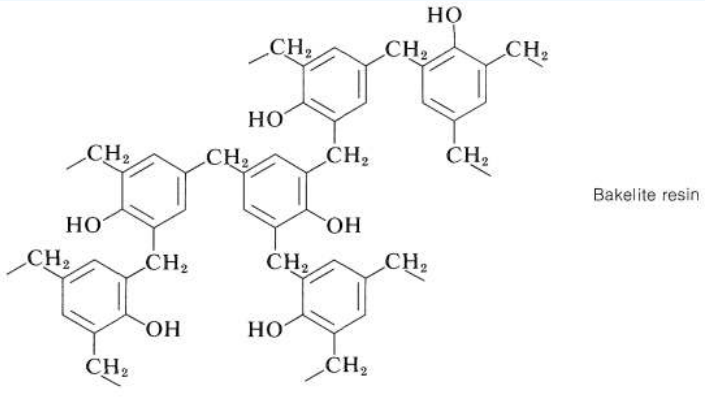
The next step in the condensation is formation of a bis(hydroxyphenyl)methane derivative, which for convenience is here taken to be the 4,4'-isomer:



This reaction is probably a Michael type of addition to a base-induced dehydration product of the (4-hydroxyphenyl)methanol:



Continuation of these reactions at the 2-, 4-, and 6-positions of the benzenol leads to the cross-linked three-dimensional Bakelite resin:



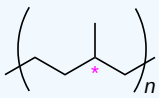
Bakelite resin

? EXERCISE 30.6.2

Would you expect the catalytic hydrogenation of gutta-percha to produce a product that is syndiotactic, atactic, or isotactic?

Answer

Atactic. The methyl groups in gutta-percha lack stereochemistry because they are attached to double bond. Catalytic hydrogenation does not provide stereochemical control so H2 could attack from either side of the double bond to produce a chiral center involving the methyl group which is R or S.



Atactic

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GLOSSARY

3′ End | The end of a nucleic acid chain with a free hydroxyl group at C3′.

5′ End | The end of a nucleic acid chain with a free hydroxyl group at C5′.

Absolute configuration | The exact three-dimensional structure of a chiral molecule. Absolute configurations are specified verbally by the Cahn–Ingold–Prelog *R*,*S* convention.

Absorbance (*A*) | In optical spectroscopy, the logarithm of the intensity of the incident light divided by the intensity of the light transmitted through a sample; $A = \log I_0/I$.

Absorption spectrum | A plot of wavelength of incident light versus amount of light absorbed. Organic molecules show absorption spectra in both the infrared and the ultraviolet regions of the electromagnetic spectrum.

Acetals | A type of functional group consisting of two −OR groups bonded to the same carbon, $R_2C(OR')_2$. Acetals are often used as protecting groups for ketones and aldehydes.

Acetoacetic ester synthesis | The synthesis of a methyl ketone by alkylation of an alkyl halide with ethyl acetoacetate, followed by hydrolysis and decarboxylation.

Acetyl group | The CH_3CO^- group.

Acetylide anion | The anion formed by removal of a proton from a terminal alkyne, $R{-}C{\equiv}C:^-$.

Achiral | Having a lack of handedness. A molecule is achiral if it has a plane of symmetry and is thus superimposable on its mirror image.

Acid anhydrides | A type of functional group with two acyl groups bonded to a common oxygen atom, RCO_2COR'.

Acid halides | A type of functional group with an acyl group bonded to a halogen atom, RCOX.

Acidity constant | A measure of acid strength. For any acid HA, the acidity constant is given by the expression $K_a = [H_3O^+][A^-][HA]$.

Activating groups | Electron-donating groups such as hydroxyl (−OH) or amino ($-NH_2$) that increase the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Activation energy | The difference in energy between ground state and transition state in a reaction. The amount of activation energy determines the rate at which the reaction proceeds. Most organic reactions have activation energies of 40–100 kJ/mol.

Active site | The pocket in an enzyme where a substrate is bound and undergoes reaction.

Acyclic diene metathesis (ADMET) | A method of polymer synthesis that uses the olefin metathesis reaction of an open-chain diene.

Acyl group | A −COR group.

Acyl phosphates | A type of functional group with an acyl group bonded to a phosphate, $RCO_2PO_3^{2-}$.

Acylation | The introduction of an acyl group, −COR, onto a molecule. For example, acylation of an alcohol yields an ester, acylation of an amine yields an amide, and acylation of an aromatic ring yields an alkyl aryl ketone.

Acylium ion | A resonance-stabilized carbocation in which the positive charge is located at a carbonyl-group carbon, $R{-}\overset{+}{C}{=}O \leftrightarrow R{-}C{\equiv}O^+$. Acylium ions are intermediates in Friedel–Crafts acylation reactions.

Adams' catalyst | The PtO_2 catalyst used for alkene hydrogenations.

Addition reactions | Occur when two reactants add together to form a single product with no atoms left over.

Adrenocortical hormones | Steroid hormones secreted by the adrenal glands. There are two types of these hormones: mineralocorticoids and glucocorticoids.

Alcohols | A class of compounds with an −OH group bonded to a saturated, sp^3-hybridized carbon, ROH.

Aldaric acid | The dicarboxylic acid resulting from oxidation of an aldose.

Aldehydes (RCHO) | A class of compounds containing the −CHO functional group.

Alditol | The polyalcohol resulting from reduction of the carbonyl group of a sugar.

Aldol reaction | The carbonyl condensation reaction of an aldehyde or ketone to give a *β*-hydroxy carbonyl compound.

Aldonic acids | Monocarboxylic acids resulting from oxidation of the −CHO group of an aldose.

Aldoses | A type of carbohydrate with an aldehyde functional group.

Alicyclic | A nonaromatic cyclic hydrocarbon such as a cycloalkane or cycloalkene.

Aliphatic | A nonaromatic hydrocarbon such as a simple alkane, alkene, or alkyne.

Alkaloids | Naturally occurring organic bases, such as morphine.

Alkanes | A class of compounds of carbon and hydrogen that contains only single bonds.

Alkene | A hydrocarbon that contains a carbon–carbon double bond, R2C═CR2R2C═CR2.

Alkoxide ion | The anion formed by deprotonation of an alcohol.

Alkoxymercuration | A method for synthesizing ethers by mercuric-ion catalyzed addition of an alcohol to an alkene followed by demercuration on treatment with $NaBH_4$.

Alkyl group | The partial structure that remains when a hydrogen atom is removed from an alkane.

Alkyl halide | A compound with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

Alkylamines | Amino-substituted alkanes RNH_2, R_2NH, or R_3N.

Alkylation | Introduction of an alkyl group onto a molecule. For example, aromatic rings can be alkylated to yield arenes, and enolate anions can be alkylated to yield *α*-substituted carbonyl compounds.

Alkyne | A hydrocarbon that contains a carbon–carbon triple bond, RC≡CRRC≡CR.

Allyl group | A H2C═CHCH2−H2C═CHCH2− substituent.

Allylic | The position next to a double bond. For example, H2C═CHCH2BrH2C═CHCH2Br is an allylic bromide.

Amides | A class of compounds containing the $-CONR_2$ functional group.

Amidomalonate synthesis | A method for preparing *α*-amino acids by alkylation of diethyl amidomalonate with an alkyl halide followed by deprotection and decarboxylation.

Amines | A class of compounds containing one or more organic substituents bonded to a nitrogen atom, RNH_2, R_2NH, or R_3N.

Amino acid | *See α*-Amino acid.

Amino sugar | A sugar with one of its −OH groups replaced by $-NH_2$.

Amphiprotic | Capable of acting either as an acid or as a base. Amino acids are amphiprotic.

Amplitude | The height of a wave measured from the midpoint to the maximum. The intensity of radiant energy is proportional to the square of the wave's amplitude.

Anabolic steroids | Synthetic androgens that mimic the tissue-building effects of natural testosterone.

Anabolism | The group of metabolic pathways that build up larger molecules from smaller ones.

Androgen | A male steroid sex hormone.

Angle strain | The strain introduced into a molecule when a bond angle is deformed from its ideal value. Angle strain is particularly important in small-ring cycloalkanes, where it results from compression of bond angles to less than their ideal tetrahedral values.

Annulation | The building of a new ring onto an existing molecule.

Anomeric center | The hemiacetal carbon atom in the cyclic pyranose or furanose form of a sugar.

Anomers | Cyclic stereoisomers of sugars that differ only in their configuration at the hemiacetal (anomeric) carbon.

Antarafacial | A pericyclic reaction that takes place on opposite faces of the two ends of a π electron system.

Anti conformation | The geometric arrangement around a carbon–carbon single bond in which the two largest substituents are 180° apart as viewed in a Newman projection.

Anti periplanar | Describing the stereochemical relationship in which two bonds on adjacent carbons lie in the same plane at an angle of 180°.

Anti stereochemistry | The opposite of syn. An anti addition reaction is one in which the two ends of the double bond are attacked from different sides. An anti elimination reaction is one in which the two groups leave from opposite sides of the molecule.

Antiaromatic | Referring to a planar, conjugated molecule with $4n$ π electrons. Delocalization of the π electrons leads to an increase in energy.

Antibonding MO | A molecular orbital that is higher in energy than the atomic orbitals from which it is formed.

Anticodon | A sequence of three bases on tRNA that reads the codons on mRNA and brings the correct amino acids into position for protein synthesis.

Antisense strand | The template, noncoding strand of double-helical DNA that does not contain the gene.

Arene | An alkyl-substituted benzene.

Arenediazonium salt | An aromatic compound $Ar{-}\overset{+}{N}{\equiv}N\,X^-$; used in the Sandmeyer reaction.

Aromaticity | The special characteristics of cyclic conjugated molecules, including unusual stability and a tendency to undergo substitution reactions rather than addition reactions on treatment with electrophiles. Aromatic molecules are planar, cyclic, conjugated species with $4n + 2$ π electrons.

Arylamines | Amino-substituted aromatic compounds, $ArNH_2$.

Atactic | A chain-growth polymer in which the stereochemistry of the substituents is oriented randomly along the backbone.

Atomic mass | The weighted average mass of an element's naturally occurring isotopes.

Atomic number | The number of protons in the nucleus of an atom.

ATZ Derivative | An anilinothiazolinone, formed from an amino acid during Edman degradation of a peptide.

Aufbau principle | The rules for determining the electron configuration of an atom.

Axial bonds | Bonds or positions in chair cyclohexane that lie along the ring axis, perpendicular to the rough plane of the ring.

Azide synthesis | A method for preparing amines by S_N2 reaction of an alkyl halide with azide ion, followed by reduction.

Azo compounds | A class of compounds with the general structure $R{-}N{=}N{-}R'$.

Backbone | The continuous chain of atoms running the length of a protein or other polymer.

Base peak | The most intense peak in a mass spectrum.

Basicity constant | A measure of base strength in water. For any base B, the basicity constant is given by the expression msubH2O ⇄ BH+ + OH–Kb = [BH+] [OH–] [B]B + H2O ⇄ BH+ + OH–Kb = [BH+] [OH–][B]

Bent bonds | The bonds in small rings such as cyclopropane that bend away from the internuclear line and overlap at a slight angle, rather than head-on. Bent bonds are highly strained and highly reactive.

Benzoyl | The $C_6H_5CO^-$ group.

Benzyl | The $C_6H_5CH_2^-$ group.

Benzylic | The position next to an aromatic ring.

Benzyne | An unstable compound having a triple bond in a benzene ring.

Betaine | A neutral dipolar molecule with nonadjacent positive and negative charges. For example, the adduct of a Wittig reagent with a carbonyl compound is a betaine.

Bicycloalkane | A cycloalkane that contains two rings.

Bimolecular reaction | A reaction whose rate-limiting step occurs between two reactants.

Block copolymers | Polymers in which different blocks of identical monomer units alternate with one another.

Boat cyclohexane | A conformation of cyclohexane that bears a slight resemblance to a boat. Boat cyclohexane has no angle strain but has a large number of eclipsing interactions that make it less stable than chair cyclohexane.

Boc derivative | A butyloxycarbonyl N-protected amino acid.

Bond angle | The angle formed between two adjacent bonds.

Bond dissociation energy | The amount of energy needed to break a bond and produce two radical fragments.

Bond length | The equilibrium distance between the nuclei of two atoms that are bonded to each other.

Bond strength | An alternative name for bond dissociation energy.

Bonding MO | A molecular orbital that is lower in energy than the atomic orbitals from which it is formed.

Branched-chain alkanes | Alkanes that contain a branching connection of carbons as opposed to straight-chain alkanes.

Bridgehead | An atom that is shared by more than one ring in a polycyclic molecule.

Bromohydrin | A 1,2-bromoalcohol; obtained by addition of HOBr to an alkene.

Bromonium ion | A species with a divalent, positively charged bromine, R_2Br^+.

Brønsted–Lowry acid | A substance that donates a hydrogen ion (proton; H^+) to a base.

Brønsted–Lowry base | A substance that accepts H^+ from an acid.

C-terminal amino acid | The amino acid with a free $-CO_2H$ group at the end of a protein chain.

Cahn–Ingold–Prelog sequence rules | A series of rules for assigning relative rankings to substituent groups on a chirality center or a double-bond carbon atom.

Cannizzaro reaction | The disproportionation reaction of an aldehyde on treatment with base to yield an alcohol and a carboxylic acid.

Carbanion | A carbon anion, or substance that contains a trivalent, negatively charged carbon atom ($R_3C:^-$). Alkyl carbanions are sp^3-hybridized and have eight electrons in the outer shell of the negatively charged carbon.

Carbene | A neutral substance that contains a divalent carbon atom having only six electrons in its outer shell ($R_2C:$).

Carbinolamine | A molecule that contains the $R_2C(OH)NH_2$ functional group. Carbinolamines are produced as intermediates during the nucleophilic addition of amines to carbonyl compounds.

Carbocation | A carbon cation, or substance that contains a trivalent, positively charged carbon atom having six electrons in its outer shell (R_3C^+).

Carbohydrates | Polyhydroxy aldehydes or ketones. Carbohydrates can be either simple sugars, such as glucose, or complex sugars, such as cellulose.

Carbonyl condensation reactions | A type of reaction that joins two carbonyl compounds together by a combination of α-substitution and nucleophilic addition reactions.

Carbonyl group | The C═O functional group.

Carboxyl group | The $-CO_2H$ functional group.

Carboxylation | The addition of CO_2 to a molecule.

Carboxylic acid derivative | A compound in which an acyl group is bonded to an electronegative atom or substituent that can act as a leaving group in a substitution reaction. Esters, amides, and acid halides are examples.

Carboxylic acids | Compounds containing the $-CO_2H$ functional group.

Catabolism | The group of metabolic pathways that break down larger molecules into smaller ones.

Catalyst | A substance that increases the rate of a chemical transformation by providing an alternative mechanism but is not itself changed in the reaction.

Cation radical | A reactive species, typically formed in a mass spectrometer by loss of an electron from a neutral molecule and having both a positive charge and an odd number of electrons.

Chain reaction | A reaction that, once initiated, sustains itself in an endlessly repeating cycle of propagation steps. The radical chlorination of alkanes is an example of a chain reaction that is initiated by irradiation with light and then continues in a series of propagation steps.

Chain-growth polymers | Polymers whose bonds are produced by chain reaction mechanisms. Polyethylene and other alkene polymers are examples.

Chair conformation | A three-dimensional conformation of cyclohexane that resembles the rough shape of a chair. The chair form of cyclohexane is the lowest-energy conformation of the molecule.

Chemical shift | The position on the NMR chart where a nucleus absorbs. By convention, the chemical shift of tetramethylsilane (TMS) is set at zero, and all other absorptions usually occur downfield (to the left on the chart). Chemical shifts are expressed in delta units (δ), where 1 δ equals 1 ppm of the spectrometer operating frequency.

Chiral | Having handedness. Chiral molecules are those that do not have a plane of symmetry and are therefore not superimposable on their mirror image. A chiral molecule thus exists in two forms, one right-handed and one left-handed. The most common cause of chirality in a molecule is the presence of a carbon atom that is bonded to four different substituents.

Chiral environment | The chiral surroundings or conditions in which a molecule resides.

Chirality center | An atom (usually carbon) that is bonded to four different groups.

Chlorohydrin | A 1,2-chloroalcohol; obtained by addition of HOCl to an alkene.

Chromatography | A technique for separating a mixture of compounds into pure components. Different compounds adsorb to a stationary support phase and are then carried along it at different rates by a mobile phase.

Cis–trans isomers | Stereoisomers that differ in their stereochemistry about a ring or double bond.

Citric acid cycle | The metabolic pathway by which acetyl CoA is degraded to CO_2.

Claisen condensation reaction | The carbonyl condensation reaction of two ester molecules to give a β-keto ester product.

Claisen rearrangement | The pericyclic conversion of an allyl phenyl ether to an *o*-allylphenol or an allyl vinyl ether to a γ,δ-unsaturated ketone by heating.

Coding strand | The sense strand of double-helical DNA that contains the gene.

Codon | A three-base sequence on a messenger RNA chain that encodes the genetic information necessary to cause a specific amino acid to be incorporated into a protein. Codons on mRNA are read by complementary anticodons on tRNA.

Coenzyme | A small organic molecule that acts as a cofactor in a biological reaction.

Cofactor | A small nonprotein part of an enzyme that is necessary for biological activity.

Combinatorial chemistry | A procedure in which anywhere from a few dozen to several hundred thousand substances are prepared simultaneously.

Complex carbohydrates | Carbohydrates that are made of two or more simple sugars linked together by glycoside bonds.

Concerted reaction | A reaction that takes place in a single step without intermediates. For example, the Diels–Alder cycloaddition reaction is a concerted process.

Condensed structures | A shorthand way of writing structures in which carbon–hydrogen and carbon–carbon bonds are understood rather than shown explicitly. Propane, for example, has the condensed structure $CH_3CH_2CH_3$.

Configuration | The three-dimensional arrangement of atoms bonded to a chirality center.

Conformational analysis | A means of assessing the energy of a substituted cycloalkane by totaling the steric interactions present in the molecule.

Conformations | The three-dimensional shape of a molecule at any given instant, assuming that rotation around single bonds is frozen.

Conformers | Conformational isomers.

Conjugate acid | The product that results from protonation of a Brønsted–Lowry base.

Conjugate addition | Addition of a nucleophile to the β carbon atom of an α,β-unsaturated carbonyl compound.

Conjugate base | The product that results from deprotonation of a Brønsted–Lowry acid.

Conjugation | A series of overlapping *p* orbitals, usually in alternating single and multiple bonds. For example, 1,3-butadiene is a conjugated diene, 3-buten-2-one is a conjugated enone, and benzene is a cyclic conjugated triene.

Conrotatory | A term used to indicate that *p* orbitals must rotate in the same direction during electrocyclic ring-opening or ring-closure.

Constitutional isomers | Isomers that have their atoms connected in a different order. For example, butane and 2-methylpropane are constitutional isomers.

Cope rearrangement | The sigmatropic rearrangement of a 1,5-hexadiene.

Copolymers | Polymers obtained when two or more different monomers are allowed to polymerize together.

Coupled reactions | Two reactions that share a common intermediate so that the energy released in the favorable step allows the unfavorable step to occur.

Coupling constant | The magnitude (expressed in hertz) of the interaction between nuclei whose spins are coupled.

Covalent bond | A bond formed by sharing electrons between atoms.

Cracking | A process used in petroleum refining in which large alkanes are thermally cracked into smaller fragments.

Crown ethers | Large-ring polyethers; used as phase-transfer catalysts.

Crystallites | Highly ordered crystal-like regions within a long polymer chain.

Curtius rearrangement | The conversion of an acid chloride into an amine by reaction with azide ion, followed by heating with water.

Cyanohydrins | A class of compounds with an −OH group and a −CN group bonded to the same carbon atom; formed by addition of HCN to an aldehyde or ketone.

Cycloaddition reaction | A pericyclic reaction in which two reactants add together in a single step to yield a cyclic product. The Diels–Alder reaction between a diene and a dienophile to give a cyclohexene is an example.

Cycloalkane | An alkane that contains a ring of carbons.

d | The racemic mixture of a chiral compound.

D Sugars | Sugars whose hydroxyl group at the chirality center farthest from the carbonyl group has the same configuration as D-glyceraldehyde and points to the right when drawn in Fischer projection.

Deactivating groups | Electron-withdrawing substituents that decrease the reactivity of an aromatic ring toward electrophilic aromatic substitution.

Deamination | The removal of an amino group from a molecule, as occurs with amino acids during metabolic degradation.

Debyes (D) | Units for measuring dipole moments; 1 D = 3.336×10^{-30} coulomb meter (C · m).

Decarboxylation | The loss of carbon dioxide from a molecule. β-Keto acids decarboxylate readily on heating.

Degenerate orbitals | Two or more orbitals that have the same energy level.

Degree of unsaturation | The number of rings and/or multiple bonds in a molecule.

Dehydration | The loss of water from an alcohol to yield an alkene.

Dehydrohalogenation | The loss of HX from an alkyl halide. Alkyl halides undergo dehydrohalogenation to yield alkenes on treatment with strong base.

Delocalization | A spreading out of electron density over a conjugated π electron system. For example, allylic cations and allylic anions are delocalized because their charges are spread out over the entire π electron system. Aromatic compounds have $4n + 2$ π electrons delocalized over their ring.

Delta (δ) scale | An arbitrary scale used to calibrate NMR charts. One delta unit (δ) is equal to 1 part per million (ppm) of the spectrometer operating frequency.

Denatured | The physical changes that occur in a protein when secondary and tertiary structures are disrupted.

Deoxy sugar | A sugar with one of its −OH groups replaced by an −H.

Deoxyribonucleic acid (DNA) | The biopolymer consisting of deoxyribonucleotide units linked together through phosphate–sugar bonds. Found in the nucleus of cells, DNA contains an organism's genetic information.

Deoxyribonucleic acid (DNA) | Chemical carriers of a cell's genetic information.

DEPT-NMR | An NMR method for distinguishing among signals due to CH_3, CH_2, CH, and quaternary carbons. That is, the number of hydrogens attached to each carbon can be determined.

Deshielding | An effect observed in NMR that causes a nucleus to absorb toward the left (downfield) side of the chart. Deshielding is caused by a withdrawal of electron density from the nucleus.

Dess–Martin periodinane | An iodine-based reagent commonly used for the laboratory oxidation of a primary alcohol to an aldehyde or a secondary alcohol to a ketone.

Deuterium isotope effect | A tool used in mechanistic investigations to establish whether a C−H bond is broken in the rate-limiting step of a reaction.

Dextrorotatory | A word used to describe an optically active substance that rotates the plane of polarization of plane-polarized light in a right-handed (clockwise) direction.

Diastereomers | Non–mirror-image stereoisomers; diastereomers have the same configuration at one or more chirality centers but differ at other chirality centers.

Diastereotopic | Hydrogens in a molecule whose replacement by some other group leads to different diastereomers.

Diazonium salts | A type of compound with the general structure $RN_2^+ X^-$.

Diazotization | The conversion of a primary amine, RNH_2, into a diazonium ion, RN_2^+, by treatment with nitrous acid.

Dieckmann cyclization reaction | An intramolecular Claisen condensation reaction of a diester to give a cyclic β-keto ester.

Diels–Alder reaction | The cycloaddition reaction of a diene with a dienophile to yield a cyclohexene.

Dienophile | A compound containing a double bond that can take part in the Diels–Alder cycloaddition reaction. The most reactive dienophiles are those that have electron-withdrawing groups on the double bond.

Digestion | The first stage of catabolism, in which food is broken down by hydrolysis of ester, glycoside (acetal), and peptide (amide) bonds to yield fatty acids, simple sugars, and amino acids.

Dihedral angle | The angle between two bonds on adjacent carbons as viewed along the C−C bond.

Dipole moment | A measure of the net polarity of a molecule. A dipole moment arises when the centers of mass of positive and negative charges within a molecule do not coincide.

Dipole–dipole forces | Noncovalent electrostatic interactions between dipolar molecules.

Disaccharide | A carbohydrate formed by linking two simple sugars through an acetal bond.

Dispersion forces | Noncovalent interactions between molecules that arise because of constantly changing electron distributions within the molecules.

Disrotatory | A term used to indicate that *p* orbitals rotate in opposite directions during electrocyclic ring-opening or ring-closing reactions.

Disulfides (RSSR′) | A class of compounds of the general structure RSSR′.

Double bond | A covalent bond formed by sharing two electron pairs between atoms.

Double helix | The structure of DNA in which two polynucleotide strands coil around each other.

Doublet | A two-line NMR absorption caused by spin–spin splitting when the spin of the nucleus under observation couples with the spin of a neighboring magnetic nucleus.

Downfield | Referring to the left-hand portion of the NMR chart.

***E* geometry** | A term used to describe the stereochemistry of a carbon–carbon double bond. The two groups on each carbon are ranked according to the Cahn–Ingold–Prelog sequence rules, and the two carbons are compared. If the higher-ranked groups on each carbon are on opposite sides of the double bond, the bond has *E* geometry.

E1 reaction | A unimolecular elimination reaction in which the substrate spontaneously dissociates to give a carbocation intermediate, which loses a proton in a separate step.

E1cB reaction | A unimolecular elimination reaction in which a proton is first removed to give a carbanion intermediate, which then expels the leaving group in a separate step.

E2 reaction | A bimolecular elimination reaction in which C−H and C−X bond cleavages are simultaneous.

Eclipsed conformation | The geometric arrangement around a carbon–carbon single bond in which the bonds to substituents on one carbon are parallel to the bonds to substituents on the neighboring carbon as viewed in a Newman projection.

Eclipsing strain | The strain energy in a molecule caused by electron repulsions between eclipsed bonds. Eclipsing strain is also called torsional strain.

Edman degradation | A method for N-terminal sequencing of peptide chains by treatment with *N*-phenylisothiocyanate.

Eicosanoid | A lipid derived biologically from 5,8,11,14-eicosatetraenoic acid, or arachidonic acid. Prostaglandins, thromboxanes, and leukotrienes are examples.

Elastomer | An amorphous polymer that has the ability to stretch out and spring back to its original shape.

Electrocyclic reaction | A unimolecular pericyclic reaction in which a ring is formed or broken by a concerted reorganization of electrons through a cyclic transition state. For example, the cyclization of 1,3,5-hexatriene to yield 1,3-cyclohexadiene is an electrocyclic reaction.

Electromagnetic spectrum | The range of electromagnetic energy, including infrared, ultraviolet, and visible radiation.

Electron configuration | A list of the orbitals occupied by electrons in an atom.

Electron shells | A group of an atom's electrons with the same principal quantum number.

Electron-dot structure | A representation of a molecule showing valence electrons as dots.

Electron-transport chain | The final stage of catabolism in which ATP is produced.

Electronegativity (EN) | The ability of an atom to attract electrons in a covalent bond. Electronegativity increases across the periodic table from left to right and from bottom to top.

Electrophile | An "electron-lover," or substance that accepts an electron pair from a nucleophile in a polar bond-forming reaction.

Electrophilic addition reactions | Addition of an electrophile to a carbon–carbon double bond to yield a saturated product.

Electrophilic aromatic substitution reaction | A reaction in which an electrophile (E^+) reacts with an aromatic ring and substitutes for one of the ring hydrogens.

Electrophoresis | A technique used for separating charged organic molecules, particularly proteins and DNA fragments. The mixture to be separated is placed on a buffered gel or paper, and an electric potential is applied across the ends of the apparatus. Negatively charged molecules migrate toward the positive electrode, and positively charged molecules migrate toward the negative electrode.

Electrostatic potential maps | Molecular representations that use color to indicate the charge distribution in molecules as derived from quantum-mechanical calculations.

Elimination reactions | What occurs when a single reactant splits into two products.

Elution | The passage of a substance from a chromatography column.

Embden–Meyerhof pathway | An alternative name for glycolysis.

Enamines | Compounds with the $R_2N–CR=$ functional group.

Enantiomers | Stereoisomers of a chiral substance that have a mirror-image relationship. Enantiomers have opposite configurations at all chirality centers.

Enantioselective synthesis | A reaction method that yields only a single enantiomer of a chiral product starting from an achiral reactant.

Enantiotopic | Hydrogens in a molecule whose replacement by some other group leads to different enantiomers.

Endergonic | A reaction that has a positive free-energy change and is therefore nonspontaneous. In an energy diagram, the product of an endergonic reaction has a higher energy level than the reactants.

Endo | A term indicating the stereochemistry of a substituent in a bridged bicycloalkane. An endo substituent is syn to the larger of the two bridges.

Endothermic | A reaction that absorbs heat and therefore has a positive enthalpy change.

Energy diagram | A representation of the course of a reaction, in which free energy is plotted as a function of reaction progress. Reactants, transition states, intermediates, and products are represented, and their appropriate energy levels are indicated.

Enol | A vinylic alcohol that is in equilibrium with a carbonyl compound, C=C–O–H.

Enolate ion | The anion of an enol, C=C–O⁻.

Enthalpy change (Δ*H*) | The heat of reaction. The enthalpy change that occurs during a reaction is a measure of the difference in total bond energy between reactants and products.

Entropy change (Δ*S*) | The change in amount of molecular randomness. The entropy change that occurs during a reaction is a measure of the difference in randomness between reactants and products.

Enzyme | A biological catalyst. Enzymes are large proteins that catalyze specific biochemical reactions.

Epimers | Diastereomers that differ in configuration at only one chirality center but are the same at all others.

Epoxide | A three-membered-ring ether functional group.

Equatorial bonds | Bonds or positions in chair cyclohexane that lie along the rough equator of the ring.

ESI | Electrospray ionization; a "soft" ionization method used for mass spectrometry of biological samples of very high molecular weight.

Essential amino acid | One of nine amino acids that are biosynthesized only in plants and microorganisms and must be obtained by humans in the diet.

Essential monosaccharide | One of eight simple sugars that is best obtained in the diet rather than by biosynthesis.

Essential oil | The volatile oil obtained by steam distillation of a plant extract.

Esters | A class of compounds containing the $-CO_2R$ functional group.

Estrogens | Female steroid sex hormones.

Ethers | A class of compounds that has two organic substituents bonded to the same oxygen atom, ROR′.

Exergonic | A reaction that has a negative free-energy change and is therefore spontaneous. On an energy diagram, the product of an exergonic reaction has a lower energy level than that of the reactants.

Exo | A term indicating the stereochemistry of a substituent in a bridged bicycloalkane. An exo substituent is anti to the larger of the two bridges.

Exon | A section of DNA that contains genetic information.

Exothermic | A reaction that releases heat and therefore has a negative enthalpy change.

Fats | Solid triacylglycerols derived from an animal source.

Fatty acids | A long, straight-chain carboxylic acid found in fats and oils.

Fiber | A thin thread produced by extruding a molten polymer through small holes in a die.

Fibrous proteins | A type of protein that consists of polypeptide chains arranged side by side in long threads. Such proteins are tough, insoluble in water, and used in nature for structural materials such as hair, hooves, and fingernails.

Fingerprint region | The complex region of the infrared spectrum from 1500–400 cm^{-1}.

First-order reaction | Designates a reaction whose rate-limiting step is unimolecular and whose kinetics therefore depend on the concentration of only one reactant.

Fischer esterification reaction | The acid-catalyzed nucleophilic acyl substitution reaction of a carboxylic acid with an alcohol to yield an ester.

Fischer projections | A means of depicting the absolute configuration of a chiral molecule on a flat page. A Fischer projection uses a cross to represent the chirality center. The horizontal arms of the cross represent bonds coming out of the plane of the page, and the vertical arms of the cross represent bonds going back into the plane of the page.

Fmoc derivative | A fluorenylmethyloxycarbonyl N-protected amino acid.

Formal charges | The difference in the number of electrons owned by an atom in a molecule and by the same atom in its elemental state.

Formyl | A −CHO group.

Frequency | The number of electromagnetic wave cycles that travel past a fixed point in a given unit of time. Frequencies are expressed in units of cycles per second, or hertz.

Friedel–Crafts reaction | An electrophilic aromatic substitution reaction to alkylate or acylate an aromatic ring.

Frontier orbitals | The highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals.

FT-NMR | Fourier-transform NMR; a rapid technique for recording NMR spectra in which all magnetic nuclei absorb at the same time.

Functional | An atom or group of atoms that is part of a larger molecule and has a characteristic chemical reactivity.

Functional RNAs | An alternative name for small RNAs.

Furanose | The five-membered-ring form of a simple sugar.

Gabriel amine synthesis | A method for preparing an amine by S_N2 reaction of an alkyl halide with potassium phthalimide, followed by hydrolysis.

Gauche conformation | The conformation of butane in which the two methyl groups lie 60° apart as viewed in a Newman projection. This conformation has 3.8 kJ/mol steric strain.

Geminal | Referring to two groups attached to the same carbon atom. For example, the hydrate formed by nucleophilic addition of water to an aldehyde or ketone is a geminal diol.

Gibbs free-energy change (Δ*G*) | The free-energy change that occurs during a reaction, given by the equation $\Delta G = \Delta H - T\Delta S$. A reaction with a negative free-energy change is spontaneous, and a reaction with a positive free-energy change is nonspontaneous.

Gilman reagent (LiR_2Cu) | A diorganocopper reagent.

Glass transition temperature | The temperature at which a hard, amorphous polymer becomes soft and flexible.

Globular proteins | A type of protein that is coiled into a compact, nearly spherical shape. Globular proteins, which are generally water-soluble and mobile within the cell, are the structural class to which enzymes belong.

Gluconeogenesis | The anabolic pathway by which organisms make glucose from simple three-carbon precursors.

Glycal | An unsaturated sugar with a C1–C2 double bond.

Glycal assembly method | A method for linking monosaccharides together to synthesize polysaccharides.

Glycerophospholipids | Lipids that contain a glycerol backbone linked to two fatty acids and a phosphoric acid.

Glycoconjugate | A molecule in which a carbohydrate is linked through its anomeric center to another biological molecule such as a lipid or protein.

Glycol | A diol, such as ethylene glycol, $HOCH_2CH_2OH$.

Glycolipid | A biological molecule in which a carbohydrate is linked through a glycoside bond to a lipid.

Glycolysis | A series of ten enzyme-catalyzed reactions that break down glucose into 2 equivalents of pyruvate, $CH_3COCO_2^-$.

Glycoprotein | A biological molecule in which a carbohydrate is linked through a glycoside bond to a protein.

Glycoside | A cyclic acetal formed by reaction of a sugar with another alcohol.

Graft copolymers | Copolymers in which homopolymer branches of one monomer unit are "grafted" onto a homopolymer chain of another monomer unit.

Green chemistry | The design and implementation of chemical products and processes that reduce waste and minimize or eliminate the generation of hazardous substances.

Grignard reagent (RMgX) | An organomagnesium halide.

Ground-state electron configuration | The most stable, lowest-energy electron configuration of a molecule or atom.

Haloform reaction | The reaction of a methyl ketone with halogen and base to yield a haloform (CHX_3) and a carboxylic acid.

Halogenation | The reaction of halogen with an alkene to yield a 1,2-dihalide addition product or with an aromatic compound to yield a substitution product.

Halohydrin | A 1,2-haloalcohol, such as that obtained on addition of HOBr to an alkene.

Halonium ion | A species containing a positively charged, divalent halogen. Three-membered-ring bromonium ions are intermediates in the electrophilic addition of Br_2 to alkenes.

Hammond postulate | A postulate stating that we can get a picture of what a given transition state looks like by looking at the structure of the nearest stable species. Exergonic reactions have transition states that resemble reactant; endergonic reactions have transition states that resemble product.

Heat of combustion | The amount of heat released when a compound burns completely in oxygen.

Heat of hydrogenation | The amount of heat released when a carbon–carbon double bond is hydrogenated.

Heat of reaction | An alternative name for the enthalpy change in a reaction, Δ*H*.

Hell–Volhard–Zelinskii (HVZ) reaction | The reaction of a carboxylic acid with Br_2 and phosphorus to give an *α*-bromo carboxylic acid.

Hemiacetal | A functional group having one −OR and one −OH group bonded to the same carbon.

Henderson–Hasselbalch equation | An equation for determining the extent of dissociation of a weak acid at various pH values.

Hertz | A unit of measure of electromagnetic frequency, the number of waves that pass by a fixed point per second.

Heterocycle | A cyclic molecule whose ring contains more than one kind of atom. For example, pyridine is a heterocycle that contains five carbon atoms and one nitrogen atom in its ring.

Heterolytic bond breakage | The kind of bond-breaking that occurs in polar reactions when one fragment leaves with both of the bonding electrons: $A:B \rightarrow A^+ + B:^-$.

Highest occupied molecular orbital (HOMO) | The symmetries of the HOMO and LUMO are important in pericyclic reactions.

Hofmann elimination reaction | The elimination reaction of an amine to yield an alkene by reaction with iodomethane followed by heating with Ag_2O.

Hofmann rearrangement | The conversion of an amide into an amine by reaction with Br_2 and base.

Homolytic bond breakage | The kind of bond-breaking that occurs in radical reactions when each fragment leaves with one bonding electron: $A:B \rightarrow A^+ + B:^-$.

Homopolymers | A polymer made up of identical repeating units.

Homotopic | Hydrogens in a molecule that give the identical structure on replacement by X and thus show identical NMR absorptions.

Hormones | Chemical messengers that are secreted by an endocrine gland and carried through the bloodstream to a target tissue.

HPLC | High-pressure liquid chromatography; a variant of column chromatography using high pressure to force solvent through very small absorbent particles.

Hund's rule | If two or more empty orbitals of equal energy are available, one electron occupies each, with their spins parallel, until all are half-full.

Hybrid orbital | An orbital derived from a combination of atomic orbitals. Hybrid orbitals, such as the sp^3, sp^2, and *sp* hybrids of carbon, are strongly directed and form stronger bonds than atomic orbitals do.

Hydration | Addition of water to a molecule, such as occurs when alkenes are treated with aqueous sulfuric acid to give alcohols.

Hydride shift | The shift of a hydrogen atom and its electron pair to a nearby cationic center.

Hydroboration | Addition of borane (BH_3) or an alkylborane to an alkene. The resultant trialkylborane products can be oxidized to yield alcohols.

Hydrocarbons | A class of compounds that contain only carbon and hydrogen.

Hydrogen bond | A weak attraction between a hydrogen atom bonded to an electronegative atom and an electron lone pair on another electronegative atom.

Hydrogenated | Addition of hydrogen to a double or triple bond to yield a saturated product.

Hydrogenolysis | Cleavage of a bond by reaction with hydrogen. Benzylic ethers and esters, for instance, are cleaved by hydrogenolysis.

Hydrophilic | Water-loving; attracted to water.

Hydrophobic | Water-fearing; repelled by water.

Hydroquinones | 1,4-dihydroxybenzene.

Hydroxylation | Addition of two −OH groups to a double bond.

Hyperconjugation | An electronic interaction that results from overlap of a vacant *p* orbital on one atom with a neighboring C−H *σ* bond. Hyperconjugation is important in stabilizing carbocations and substituted alkenes.

Hückel 4*n* + 2 rule | A rule stating that monocyclic conjugated molecules having $4n + 2$ π electrons (*n* = an integer) are aromatic.

Imide | A compound with the −CONHCO− functional group.

Imines | A class of compounds with the $R_2C{=}$ functional group.

Inductive effect | The electron-attracting or electron-withdrawing effect transmitted through *σ* bonds. Electronegative elements have an electron-withdrawing inductive effect.

Infrared (IR) spectroscopy | A kind of optical spectroscopy that uses infrared energy. IR spectroscopy is particularly useful in organic chemistry for determining the kinds of functional groups present in molecules.

Initiator | A substance that is used to initiate a radical chain reaction or polymerization. For example, radical chlorination of alkanes is initiated when light energy breaks the weak Cl−Cl bond to form Cl · radicals.

Integrating | A technique for measuring the area under an NMR peak to determine the relative number of each kind of proton in a molecule.

Intermediate | A species that is formed during the course of a multistep reaction but is not the final product. Intermediates are more stable than transition states but may or may not be stable enough to isolate.

Intramolecular | A reaction that occurs within the same molecule is intramolecular; a reaction that occurs between two molecules is intermolecular.

Intron | A section of DNA that does not contain genetic information.

Ion pairs | A loose association between two ions in solution. Ion pairs are implicated as intermediates in S_N1 reactions to account for the partial retention of stereochemistry that is often observed.

Ionic bond | The electrostatic attraction between ions of unlike charge.

Isoelectric point (p*I*) | The pH at which the number of positive charges and the number of negative charges on a protein or an amino acid are equal.

Isomers | Compounds that have the same molecular formula but different structures.

Isoprene rule | An observation to the effect that terpenoids appear to be made up of isoprene (2-methyl-1,3-butadiene) units connected head-to-tail.

Isotactic | A chain-growth polymer in which the stereochemistry of the substituents is oriented regularly along the backbone.

Isotopes | Atoms of the same element that have different mass numbers.

IUPAC system of nomenclature | Rules for naming compounds, devised by the International Union of Pure and Applied Chemistry.

Kekulé structure | An alternative name for a line-bond structure, which represents a molecule by showing covalent bonds as lines between atoms.

Ketals | An alternative name for acetals derived from a ketone rather than an aldehyde and consisting of two −OR groups bonded to the same carbon, $R_2C(OR')_2$. Ketals are often used as protecting groups for ketones.

Ketones (R_2CO) | A class of compounds with two organic substituents bonded to a carbonyl group, $R_2C{=}$.

Ketoses | Carbohydrates with a ketone functional group.

Keto–enol tautomerism | The equilibration between a carbonyl form and vinylic alcohol form of a molecule.

Kiliani–Fischer synthesis | A method for lengthening the chain of an aldose sugar.

Kinetic control | A reaction that follows the lowest activation energy pathway is said to be kinetically controlled. The product is the most rapidly formed but is not necessarily the most stable.

Kinetics | Referring to reaction rates. Kinetic measurements are useful for helping to determine reaction mechanisms.

Koenigs–Knorr reaction | A method for the synthesis of glycosides by reaction of an alcohol with a pyranosyl bromide.

Krebs cycle | An alternative name for the citric acid cycle, by which acetyl CoA is degraded to CO_2.

L Sugar | A sugar whose hydroxyl group at the chirality center farthest from the carbonyl group points to the left when drawn in Fischer projection.

Lactams | Cyclic amides.

Lactones | Cyclic esters.

Lagging strand | The complement of the original 3′ → 5′ DNA strand that is synthesized discontinuously in small pieces that are subsequently linked by DNA ligases.

LD50 | The amount of a substance per kilogram body weight that is lethal to 50% of test animals.

LDA | Lithium diisopropylamide, $LiN(i\text{-}C_3H_7)_2$, a strong base commonly used to convert carbonyl compounds into their enolate ions.

Leading strand | The complement of the original 5′ → 3′ DNA strand that is synthesized continuously in a single piece.

Leaving group | The group that is replaced in a substitution reaction.

Levorotatory | An optically active substance that rotates the plane of polarization of plane-polarized light in a left-handed (counterclockwise) direction.

Lewis acid | A substance with a vacant low-energy orbital that can accept an electron pair from a base. All electrophiles are Lewis acids.

Lewis base | A substance that donates an electron lone pair to an acid. All nucleophiles are Lewis bases.

Lewis structures | Representations of molecules showing valence electrons as dots.

Lindlar catalyst | A hydrogenation catalyst used to convert alkynes to cis alkenes.

Line-bond structure | An alternative name for a Kekulé structure, which represents a molecule by showing covalent bonds as lines between atoms.

Lipid bilayer | The ordered lipid structure that forms a cell membrane.

Lipids | Naturally occurring substances isolated from cells and tissues by extraction with a nonpolar solvent. Lipids belong to many different structural classes, including fats, terpenoids, prostaglandins, and steroids.

Lipoprotein | A complex molecule with both lipid and protein parts that transports lipids through the body.

Locant | A number in a chemical name that locates the positions of the functional groups and substituents in the molecule.

Lone-pair electrons | Nonbonding valence-shell electron pairs. Lone-pair electrons are used by nucleophiles in their reactions with electrophiles.

Lowest unoccupied molecular orbital (LUMO) | The symmetries of the LUMO and the HOMO are important in determining the stereochemistry of pericyclic reactions.

Magnetic resonance imaging | A medical diagnostic technique based on nuclear magnetic resonance.

Magnetogyric ratio | A ratio of the isotope's magnetic moment to its angular momentum.

MALDI | Matrix-assisted laser desorption ionization; a soft ionization method used for mass spectrometry of biological samples of very high molecular weight.

Malonic ester synthesis | The synthesis of a carboxylic acid by alkylation of an alkyl halide with diethyl malonate, followed by hydrolysis and decarboxylation.

Markovnikov's rule | A guide for determining the regiochemistry (orientation) of electrophilic addition reactions. In the addition of HX to an alkene, the hydrogen atom bonds to the alkene carbon that has fewer alkyl substituents.

Mass number (*A*) | The total of protons plus neutrons in an atom.

Mass spectrometry (MS) | A technique for measuring the mass, and therefore the molecular weight (MW), of ions.

McLafferty rearrangement | A mass-spectral fragmentation pathway for carbonyl compounds.

Mechanism | A complete description of how a reaction occurs. A mechanism accounts for all starting materials and all products and describes the details of each individual step in the overall reaction process.

Meisenheimer complex | An intermediate formed by addition of a nucleophile to a halo-substituted aromatic ring.

Melt transition temperature | The temperature at which crystalline regions of a polymer melt to give an amorphous material.

Mercapto group | An alternative name for the thiol group, −SH.

Meso compounds | Compounds that contain chirality centers but are nevertheless achiral because they contain a symmetry plane.

Messenger RNA (mRNA) | A kind of RNA formed by transcription of DNA and used to carry genetic messages from DNA to ribosomes.

Meta (*m*) | A naming prefix used for 1,3-disubstituted benzenes.

Metabolism | A collective name for the many reactions that go on in the cells of living organisms.

Metallacycle | A cyclic compound that contains a metal atom in its ring.

Methylene group | A $-CH_2-$ or msub group.

Micelles | Spherical clusters of soaplike molecules that aggregate in aqueous solution. The ionic heads of the molecules lie on the outside, where they are solvated by water, and the organic tails bunch together on the inside of the micelle.

Michael reaction | The conjugate addition reaction of an enolate ion to an unsaturated carbonyl compound.

Molar absorptivity (ε) | A quantitative measure of the amount of UV light absorbed by a sample.

Molecular ion | The cation produced in a mass spectrometer by loss of an electron from the parent molecule. The mass of the molecular ion corresponds to the molecular weight of the sample.

Molecular mechanics | A computer-based method for calculating the minimum-energy conformation of a molecule.

Molecular orbital (MO) theory | A description of covalent bond formation as resulting from a mathematical combination of atomic orbitals (wave functions) to form molecular orbitals.

Molecule | A neutral collection of atoms held together by covalent bonds.

Molozonide | The initial addition product of ozone with an alkene.

Monomers | The simple starting units from which polymers are made.

Monosaccharides | Simple sugars.

Monoterpenoids | Ten-carbon lipids.

Multiplet | A pattern of peaks in an NMR spectrum that arises by spin–spin splitting of a single absorption because of coupling between neighboring magnetic nuclei.

Mutarotation | The change in optical rotation observed when a pure anomer of a sugar is dissolved in water. Mutarotation is caused by the reversible opening and closing of the acetal linkage, which yields an equilibrium mixture of anomers.

***n* + 1 rule** | A hydrogen with *n* other hydrogens on neighboring carbons shows *n* + 1 peaks in its ^{1}H NMR spectrum.

N-terminal amino acid | The amino acid with a free $-NH_2$ group at the end of a protein chain.

Natural gas | A naturally occurring hydrocarbon mixture consisting chiefly of methane, along with smaller amounts of ethane, propane, and butane.

Natural product | A catchall term generally taken to mean a secondary metabolite found in bacteria, plants, and other living organisms.

New molecular entity | A new biologically active chemical substance approved for sale as a drug by the U.S. Food and Drug Administration.

Newman projection | A means of indicating stereochemical relationships between substituent groups on neighboring carbons. The carbon–carbon bond is viewed end-on, and the carbons are indicated by a circle. Bonds radiating from the center of the circle are attached to the front carbon, and bonds radiating from the edge of the circle are attached to the rear carbon.

Nitration | The substitution of a nitro group onto an aromatic ring.

Nitriles | A class of compounds containing the **C≡N** functional group.

Nitrogen rule | A compound with an odd number of nitrogen atoms has an odd-numbered molecular weight.

Node | A surface of zero electron density within an orbital. For example, a *p* orbital has a nodal plane passing through the center of the nucleus, perpendicular to the axis of the orbital.

Nonbonding electrons | Valence electrons that are not used in forming covalent bonds.

Noncoding strand | An alternative name for the antisense strand of DNA.

Noncovalent interactions | One of a variety of nonbonding interactions between molecules, such as dipole–dipole forces, dispersion forces, and hydrogen bonds.

Nonessential amino acid | One of the eleven amino acids that are biosynthesized by humans.

Normal alkanes | Straight-chain alkanes, as opposed to branched alkanes. Normal alkanes are denoted by the suffix *n*, as in *n*-C_4H_{10} (*n*-butane).

NSAID | A nonsteroidal anti-inflammatory drug, such as aspirin or ibuprofen.

Nuclear magnetic resonance (NMR) spectroscopy | A spectroscopic technique that provides information about the carbon–hydrogen framework of a molecule. NMR works by detecting the energy absorptions accompanying the transitions between nuclear spin states that occur when a molecule is placed in a strong magnetic field and irradiated with radiofrequency waves.

Nucleic acid | Deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); biological polymers made of nucleotides joined together to form long chains.

Nucleophile | An electron-rich species that donates an electron pair to an electrophile in a polar bond-forming reaction. Nucleophiles are also Lewis bases.

Nucleophilic acyl substitution reaction | A reaction in which a nucleophile attacks a carbonyl compound and substitutes for a leaving group bonded to the carbonyl carbon.

Nucleophilic addition reaction | A reaction in which a nucleophile adds to the electrophilic carbonyl group of a ketone or aldehyde to give an alcohol.

Nucleophilic aromatic substitution reactions | The substitution reactions of an aryl halide by a nucleophile.

Nucleophilic substitution reactions | Reactions in which one nucleophile replaces another attached to a saturated carbon atom.

Nucleophilicity | The ability of a substance to act as a nucleophile in an S_N2 reaction.

Nucleoside | A nucleic acid constituent consisting of a sugar residue bonded to a heterocyclic purine or pyrimidine base.

Nucleotides | Nucleic acid constituents consisting of a sugar residue bonded both to a heterocyclic purine or pyrimidine base and to a phosphoric acid. Nucleotides are the monomer units from which DNA and RNA are constructed.

Nylons | Synthetic polyamide step-growth polymers.

Okazaki fragments | Short segments of a DNA lagging strand that is biosynthesized discontinuously and then linked by DNA ligases.

Olefin | An alternative name for an alkene.

Olefin metathesis polymerization | A method of polymer synthesis based on using an olefin metathesis reaction.

Olefin metathesis reaction | A reaction in which two olefins (alkenes) exchange substituents on their double bonds.

Oligonucleotides | Short segments of DNA.

Optical isomers | An alternative name for enantiomers. Optical isomers are isomers that have a mirror-image relationship.

Optically active | A property of some organic molecules wherein the plane of polarization is rotated through an angle when a beam of plane-polarized light is passed through a solution of the molecules.

Orbital | A wave function, which describes the volume of space around a nucleus in which an electron is most likely to be found.

Organic chemistry | The study of carbon compounds.

Organohalides | Compounds that contain one or more halogen atoms bonded to carbon.

Organometallic compound | A compound that contains a carbon–metal bond. Grignard reagents, RMgX, are examples.

Organophosphate | A compound that contains a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon.

Ortho (*o*) | A naming prefix used for 1,2-disubstituted benzenes.

Oxidation | A reaction that causes a decrease in electron ownership by carbon, either by bond formation between carbon and a more electronegative atom (usually oxygen, nitrogen, or a halogen) or by bond-breaking between carbon and a less electronegative atom (usually hydrogen).

Oximes | Compounds with the **R_2C═N–** functional group.

Oxirane | An alternative name for an epoxide.

Oxymercuration | A method for double-bond hydration by reaction of an alkene with aqueous mercuric acetate followed by treatment with $NaBH_4$.

Ozonide | The product initially formed by addition of ozone to a carbon–carbon double bond. Ozonides are usually treated with a reducing agent, such as zinc in acetic acid, to produce carbonyl compounds.

Para (*p*) | A naming prefix used for 1,4-disubstituted benzenes.

Paraffins | A common name for alkanes.

Parent peak | The peak in a mass spectrum corresponding to the molecular ion. The mass of the parent peak therefore represents the molecular weight of the compound.

Pauli exclusion principle | No more than two electrons can occupy the same orbital, and those two must have spins of opposite sign.

Peptide bond | An amide bond in a peptide chain.

Peptides | A type of short amino acid polymer in which the individual amino acid residues are linked by amide bonds.

Pericyclic reaction | A reaction that occurs in a single step by a reorganization of bonding electrons in a cyclic transition state.

Periplanar | A conformation in which bonds to neighboring atoms have a parallel arrangement. In an eclipsed conformation, the neighboring bonds are syn periplanar; in a staggered conformation, the bonds are anti periplanar.

Peroxides | Molecules containing an oxygen–oxygen bond functional group, ROOR′ or ROOH.

Peroxyacid | A compound with the $-CO_3H$ functional group. Peroxyacids react with alkenes to give epoxides.

Phenols | A class of compounds with an −OH group directly bonded to an aromatic ring, ArOH.

Phenoxide ion | The anion of a phenol.

Phenyl | The name for the $-C_6H_5$ unit when the benzene ring is considered as a substituent. A phenyl group is abbreviated as −Ph.

Phosphine | A trivalent phosphorus compound, R_3P.

Phosphite | A compound with the structure $P(OR)_3$.

Phospholipids | Lipids that contain a phosphate residue. For example, glycerophospholipids contain a glycerol backbone linked to two fatty acids and a phosphoric acid.

Phosphoramidite | A compound with the structure $R_2NP(OR)_2$.

Phosphoric acid anhydride | A substance that contains PO_2PO link, analogous to the CO_2CO link in carboxylic acid anhydrides.

Photochemical reactions | A reaction carried out by irradiating the reactants with light.

Physiological pH | The pH of 7.3 that exists inside cells.

Pi (*π*) bond | The covalent bond formed by sideways overlap of atomic orbitals. For example, carbon–carbon double bonds contain a π bond formed by sideways overlap of two *p* orbitals.

PITC | Phenylisothiocyanate; used in the Edman degradation.

pK_a | The negative common logarithm of the K_a; used to express acid strength.

Plane of symmetry | A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Plane-polarized light | Light that has its electromagnetic waves oscillating in a single plane rather than in random planes. The plane of polarization is rotated when the light is passed through a solution of a chiral substance.

Plasticizers | Small organic molecules added to polymers to act as a lubricant between polymer chains.

Polar aprotic solvents | Polar solvents that can't function as hydrogen ion donors. Polar aprotic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) are particularly useful in S_N2 reactions because of their ability to solvate cations.

Polar covalent bond | A covalent bond in which the electron distribution between atoms is unsymmetrical.

Polar reactions | Reactions in which bonds are made when a nucleophile donates two electrons to an electrophile and in which bonds are broken when one fragment leaves with both electrons from the bond.

Polarity | The unsymmetrical distribution of electrons in a molecule that results when one atom attracts electrons more strongly than another.

Polarizability | The measure of the change in a molecule's electron distribution in response to changing electrostatic interactions with solvents or ionic reagents.

Polycarbonates | Polyesters in which the carbonyl groups are linked to two −OR groups, [$\mathrm{O{-}C(OR)_2}$].

Polycyclic | Containing more than one ring.

Polycyclic aromatic compound | A compound with two or more benzene-like aromatic rings fused together.

Polymer | A large molecule made up of repeating smaller units. For example, polyethylene is a synthetic polymer made from repeating ethylene units, and DNA is a biopolymer made of repeating deoxyribonucleotide units.

Polymerase chain reaction (PCR) | A method for amplifying small amounts of DNA to produce larger amounts.

Polysaccharides | A type of carbohydrate that is made of many simple sugars linked together by glycoside (acetal) bonds.

Polyunsaturated fatty acids | Fatty acids that contain more than one double bond.

Polyurethane | A step-growth polymer prepared by reaction between a diol and a diisocyanate.

Posttranslational modification | A chemical modification of a protein that occurs after translation from DNA.

Primary structure | The amino acid sequence in a protein.

pro-*R* | One of two identical atoms or groups of atoms in a compound whose replacement leads to an *R* chirality center.

pro-*S* | One of two identical atoms or groups of atoms in a compound whose replacement leads to an *S* chirality center.

Prochiral | A molecule that can be converted from achiral to chiral in a single chemical step.

Prochirality center | An atom in a compound that can be converted into a chirality center by changing one of its attached substituents.

Promoter sequence | A short sequence on DNA located upstream of the transcription start site and recognized by RNA polymerase.

Propagation step | A step in a radical chain reaction that carries on the chain. The propagation steps must yield both product and a reactive intermediate.

Prostaglandins | Lipids derived from arachidonic acid. Prostaglandins are present in nearly all body tissues and fluids, where they serve many important hormonal functions.

Protecting group | A group that is introduced to protect a sensitive functional group toward reaction elsewhere in the molecule. After serving its protective function, the group is removed.

Protein Data Bank | A worldwide online repository of X-ray and NMR structural data for biological macromolecules. To access the Protein Data Bank, go to https://www.rcsb.org.

Proteins | Large peptides containing 50 or more amino acid residues. Proteins serve both as structural materials and as enzymes that control an organism's chemistry.

Protic solvents | Solvents such as water or alcohol that can act as a proton donor.

Pyramidal inversion | The rapid stereochemical inversion of a trivalent nitrogen compound.

Pyranose | The six-membered, cyclic hemiacetal form of a simple sugar.

Quadrupole mass analyzer | A type of mass spectrometer that uses four cylindrical rods to create an oscillating electrostatic field. Ion trajectories are determined by their *m*/*z* ratios. At a given field, only one *m*/*z* value will make it through the quadrupole region—the others will crash into the quadrupole rods or the walls of the instrument and never reach the detector.

Quartet | A set of four peaks in an NMR spectrum, caused by spin–spin splitting of a signal by three adjacent nuclear spins.

Quaternary ammonium salt | An ionic compound containing a positively charged nitrogen atom with four attached groups, $R_4N^+ X^-$.

Quaternary structure | The highest level of protein structure, involving an ordered aggregation of individual proteins into a larger cluster.

Quinone | A 2,5-cyclohexadiene-1,4-dione.

R | A generalized abbreviation for an organic partial structure.

***R* configuration** | The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

Racemate | A mixture consisting of equal parts (+) and (−) enantiomers of a chiral substance; also called a racemic mixture.

Radical | A species that has an odd number of electrons, such as the chlorine radical, Cl ·.

Radical reactions | Reactions in which bonds are made by donation of one electron from each of two reactants and in which bonds are broken when each fragment leaves with one electron.

Rate constant | The constant *k* in a rate equation.

Rate equation | An equation that expresses the dependence of a reaction's rate on the concentration of reactants.

Rate-limiting step | The slowest step in a multistep reaction sequence; also called the rate-determining step. The rate-limiting step acts as a kind of bottleneck in multistep reactions.

Re face | One of two faces of a planar, sp^2-hybridized atom.

Rearrangement reactions | What occurs when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product.

Reducing sugars | Sugars that reduce silver ion in the Tollens test or cupric ion in the Fehling or Benedict tests.

Reduction | A reaction that causes an increase of electron ownership by carbon, either by bond-breaking between carbon and a more electronegative atom or by bond formation between carbon and a less electronegative atom.

Reductive amination | A method for preparing an amine by reaction of an aldehyde or ketone with ammonia and a reducing agent.

Refining | The process by which petroleum is converted into gasoline and other useful products.

Regiochemistry | A term describing the orientation of a reaction that occurs on an unsymmetrical substrate.

Regiospecific | A term describing a reaction that occurs with a specific regiochemistry to give a single product rather than a mixture of products.

Replication | The process by which double-stranded DNA uncoils and is replicated to produce two new copies.

Replication forks | The point of unraveling in a DNA chain where replication occurs.

Residues | Amino acids in a protein chain.

Resolution | The process by which a racemate is separated into its two pure enantiomers.

Resonance effect | The donation or withdrawal of electrons through orbital overlap with neighboring π bonds. For example, an oxygen or nitrogen substituent donates electrons to an aromatic ring by overlap of the O or N orbital with the aromatic ring *p* orbitals.

Resonance forms | Individual structural forms of a resonance hybrid.

Resonance hybrid | A molecule, such as benzene, that can't be represented adequately by a single Kekulé structure but must instead be considered as an average of two or more resonance forms. The resonance forms themselves differ only in the positions of their electrons, not their nuclei.

Restriction endonucleases | Enzymes that are able to cleave a DNA molecule at points in the chain where a specific base sequence occurs.

Retrosynthetic | Planning an organic synthesis by working backward from the final product to the starting material.

Ribonucleic acid (RNA) | The biopolymer found in cells that serves to transcribe the genetic information found in DNA and uses that information to direct the synthesis of proteins.

Ribosomal RNA (rRNA) | A kind of RNA used in the physical makeup of ribosomes.

Ring-current | The circulation of π electrons induced in aromatic rings by an external magnetic field. This effect accounts for the downfield shift of aromatic ring protons in the ^{1}H NMR spectrum.

Ring-flip | A molecular motion that interconverts two chair conformations of cyclohexane. The effect of a ring-flip is to convert an axial substituent into an equatorial substituent.

Ring-opening metathesis polymerization (ROMP) | A method of polymer synthesis that uses an olefin metathesis reaction of a cycloalkene.

RNA | Ribonucleic acid.

Robinson annulation reaction | A method for synthesis of cyclohexenones by sequential Michael reaction and intramolecular aldol reaction.

***S* configuration** | The configuration at a chirality center as specified using the Cahn–Ingold–Prelog sequence rules.

***s*-Cis conformation** | The conformation of a conjugated diene that is cis-like around the single bond.

Saccharide | A sugar.

Salt bridge | An ionic attraction between two oppositely charged groups in a protein chain.

Sandmeyer reaction | The nucleophilic substitution reaction of an arenediazonium salt with a cuprous halide to yield an aryl halide.

Sanger dideoxy method | A commonly used method of DNA sequencing.

Saponification | An old term for the base-induced hydrolysis of an ester to yield a carboxylic acid salt.

Saturated | A molecule that has only single bonds and thus can't undergo addition reactions. Alkanes are saturated, but alkenes are unsaturated.

Sawhorse representations | A manner of representing stereochemistry that uses a stick drawing and gives a perspective view of the conformation around a single bond.

Schiff bases | An alternative name for an imine, $\mathrm{R_2C{=}NR'}$, used primarily in biochemistry.

Second-order reaction | A reaction whose rate-limiting step is bimolecular and whose kinetics are therefore dependent on the concentration of two reactants.

Secondary metabolite | A small naturally occurring molecule that is not essential to the growth and development of the producing organism and is not classified by structure.

Secondary structure | The level of protein substructure that involves organization of chain sections into ordered arrangements such as β-pleated sheets or α helices.

Semiconservative replication | The process by which DNA molecules are made containing one strand of old DNA and one strand of new DNA.

Sense strand | The coding strand of double-helical DNA that contains the gene.

Sequence rules | A series of rules for assigning relative rankings to substituent groups on a double-bond carbon atom or on a chirality center.

Sesquiterpenoids | 15-carbon lipids.

Sharpless epoxidation | A method for enantioselective synthesis of a chiral epoxide by treatment of an allylic alcohol with *tert*-butyl hydroperoxide, $(CH_3)_3C–OOH$, in the presence of titanium tetraisopropoxide and diethyl tartrate.

Shielding | An effect observed in NMR that causes a nucleus to absorb toward the right (upfield) side of the chart. Shielding is caused by donation of electron density to the nucleus.

Si face | One of two faces of a planar, sp^2-hybridized atom.

Sialic acid | One of a group of more than 300 carbohydrates based on acetylneuramic acid.

Side chain | The substituent attached to the α carbon of an amino acid.

Sigma (σ) bond | A covalent bond formed by head-on overlap of atomic orbitals.

Sigmatropic reaction | A pericyclic reaction that involves the migration of a group from one end of a π electron system to the other.

Silyl ether | A substance with the structure $R_3Si–O–R$. The silyl ether acts as a protecting group for alcohols.

Simmons–Smith reaction | The reaction of an alkene with CH_2I_2 and Zn−Cu to yield a cyclopropane.

Simple sugars | Carbohydrates that cannot be broken down into smaller sugars by hydrolysis.

Single bond | A covalent bond formed by sharing one electron pair between atoms.

Skeletal structures | A shorthand way of writing structures in which carbon atoms are assumed to be at each intersection of two lines (bonds) and at the end of each line.

Small RNAs | A type of RNA that has a variety of functions within the cell, including silencing transcription and catalyzing chemical modifications of other RNA molecules.

S_N1 reaction | A unimolecular nucleophilic substitution reaction.

S_N2 reaction | A bimolecular nucleophilic substitution reaction.

Solid-phase synthesis | A technique of synthesis whereby the starting material is covalently bound to a solid polymer bead and reactions are carried out on the bound substrate. After the desired transformations have been effected, the product is cleaved from the polymer.

Solvation | The clustering of solvent molecules around a solute particle to stabilize it.

***sp* hybrid orbitals** | Hybrid orbitals derived from the combination of an *s* and a *p* atomic orbital. The two *sp* orbitals that result from hybridization are oriented at an angle of 180° to each other.

***sp^2* hybrid orbitals** | Hybrid orbitals derived by combination of an *s* atomic orbital with two *p* atomic orbitals. The three sp^2 hybrid orbitals that result lie in a plane at angles of 120° to each other.

***sp^3* hybrid orbitals** | Hybrid orbitals derived by combination of an *s* atomic orbital with three *p* atomic orbitals. The four sp^3 hybrid orbitals that result are directed toward the corners of a regular tetrahedron at angles of 109° to each other.

Specific rotation | The optical rotation of a chiral compound under standard conditions.

Sphingomyelins | Phospholipids that have sphingosine as the backbone rather than glycerol.

Spin–spin splitting | The splitting of an NMR signal into a multiplet because of an interaction between nearby magnetic nuclei whose spins are coupled. The magnitude of spin–spin splitting is given by the coupling constant, *J*.

Staggered conformation | The three-dimensional arrangement of atoms around a carbon–carbon single bond in which the bonds on one carbon bisect the bond angles on the second carbon as viewed end-on.

Statin | A drug that controls cholesterol biosynthesis in the body by blocking the HMG-CoA reductase enzyme.

Step-growth polymers | Polymers in which each bond is formed independently of the others. Polyesters and polyamides (nylons) are examples.

Stereocenter | An alternative name for a chirality center.

Stereochemistry | The branch of chemistry concerned with the three-dimensional arrangement of atoms in molecules.

Stereogenic center | An alternative name for a chirality center.

Stereoisomers | Isomers that have their atoms connected in the same order but have different three-dimensional arrangements. The term *stereoisomer* includes both enantiomers and diastereomers.

Stereospecific | A term indicating that only a single stereoisomer is produced in a given reaction rather than a mixture.

Steric strain | The strain imposed on a molecule when two groups are too close together and try to occupy the same space. Steric strain is responsible both for the greater stability of trans versus cis alkenes and for the greater stability of equatorially substituted versus axially substituted cyclohexanes.

Steroids | Lipids whose structure is based on a tetracyclic carbon skeleton with three 6-membered and one 5-membered ring. Steroids occur in both plants and animals and have a variety of important hormonal functions.

Stork enamine reaction | The conjugate addition of an enamine to an α,β-unsaturated carbonyl compound, followed by hydrolysis to yield a 1,5-dicarbonyl product.

STR loci | Short tandem repeat sequences of noncoding DNA that are unique to every individual and allow DNA fingerprinting.

Straight-chain alkanes | Alkanes whose carbon atoms are connected without branching.

Substitution reactions | What occurs when two reactants exchange parts to give two new products. S_N1 and S_N2 reactions are examples.

Sulfides | A class of compounds that has two organic substituents bonded to the same sulfur atom, RSR′.

Sulfonation | The substitution of a sulfonic acid group ($-SO_3H$) onto an aromatic ring.

Sulfone | A compound of the general structure RSO_2R'.

Sulfonium ions | A species containing a positively charged, trivalent sulfur atom, R_3S^+.

Sulfoxide | A compound of the general structure RSOR′.

Suprafacial | A word used to describe the geometry of pericyclic reactions. Suprafacial reactions take place on the same side of the two ends of a π electron system.

Suzuki–Miyaura reaction | The palladium-catalyzed coupling reaction of an aromatic or vinylic halide with an aromatic or vinylic boronic acid.

Symmetry plane | A plane that bisects a molecule such that one half of the molecule is the mirror image of the other half. Molecules containing a plane of symmetry are achiral.

Symmetry-allowed | A symmetry-allowed reaction is a pericyclic process that has a favorable orbital symmetry for reaction through a concerted pathway. A symmetry-disallowed reaction is one that does not have favorable orbital symmetry for reaction through a concerted pathway.

Syn periplanar | Describing a stereochemical relationship in which two bonds on adjacent carbons lie in the same plane and are eclipsed.

Syn stereochemistry | The opposite of anti. A syn addition reaction is one in which the two ends of the double bond react from the same side. A syn elimination is one in which the two groups leave from the same side of the molecule.

Syndiotactic | A chain-growth polymer in which the stereochemistry of the substituents alternates regularly on opposite sides of the backbone.

Tautomers | Isomers that interconvert spontaneously, usually with the change in position of a hydrogen.

Terpenoids | Lipids that are formally derived by head-to-tail polymerization of isoprene units.

Tertiary structure | The level of protein structure that involves the manner in which the entire protein chain is folded into a specific three-dimensional arrangement.

Thermodynamic control | An equilibrium reaction that yields the lowest-energy, most stable product is said to be thermodynamically controlled.

Thermoplastics | Polymers that have a high T_g and are hard at room temperature but become soft and viscous when heated.

Thermosetting resins | Polymers that become highly cross-linked and solidify into a hard, insoluble mass when heated.

Thioesters | A class of compounds with the RCOSR′ functional group.

Thiolate ion | The anion of a thiol, RS^-.

Thiols | A class of compounds containing the −SH functional group.

TMS | Tetramethylsilane; used as an NMR calibration standard.

TOF | Time-of-flight mass spectrometry; a sensitive method of mass detection accurate to about 3 ppm.

Tollens' reagent | A solution of Ag_2O in aqueous ammonia; used to oxidize aldehydes to carboxylic acids.

Torsional strain | The strain in a molecule caused by electron repulsion between eclipsed bonds. Torsional strain is also called eclipsing strain.

Tosylate | A *p*-toluenesulfonate ester; useful as a leaving group in nucleophilic substitution reactions.

Transamination | The exchange of an amino group and a keto group between reactants.

Transcription | The process by which the genetic information encoded in DNA is read and used to synthesize RNA in the nucleus of the cell. A small portion of double-stranded DNA uncoils, and complementary ribonucleotides line up in the correct sequence for RNA synthesis.

Transfer RNA (tRNA) | A kind of RNA that transports amino acids to the ribosomes, where they are joined together to make proteins.

Transimination | The exchange of an amino group and an imine group between reactants.

Transition state | An activated complex between reactants, representing the highest energy point on a reaction curve. Transition states are unstable complexes that can't be isolated.

Translation | The process by which the genetic information transcribed from DNA onto mRNA is read by tRNA and used to direct protein synthesis.

Tree diagram | A diagram used in NMR to sort out the complicated splitting patterns that can arise from multiple couplings.

Triacylglycerols | Lipids, such as those found in animal fat and vegetable oil, that are a triester of glycerol with long-chain fatty acids.

Tricarboxylic acid cycle | An alternative name for the citric acid cycle by which acetyl CoA is degraded to CO_2.

Triple bonds | A type of covalent bond formed by sharing three electron pairs between atoms.

Triplet | A symmetrical three-line splitting pattern observed in the ^1H NMR spectrum when a proton has two equivalent neighbor protons.

Turnover number | The number of substrate molecules acted on by an enzyme molecule per unit time.

Twist-boat conformation | A conformation of cyclohexane that is somewhat more stable than a pure boat conformation.

Ultraviolet (UV) spectroscopy | An optical spectroscopy employing ultraviolet irradiation. UV spectroscopy provides structural information about the extent of π electron conjugation in organic molecules.

Unimolecular reaction | A reaction that occurs by spontaneous transformation of the starting material without the intervention of other reactants. For example, the dissociation of a tertiary alkyl halide in the S_N1 reaction is a unimolecular process.

Unsaturated | A molecule that has one or more multiple bonds.

Upfield | The right-hand portion of the NMR chart.

Urethane | A functional group in which a carbonyl group is bonded to both an −OR and an $-NR_2$.

Uronic acid | A monocarboxylic acid formed by oxidizing the $-CH_2OH$ end of an aldose without affecting the −CHO end.

Valence bond theory | A bonding theory that describes a covalent bond as resulting from the overlap of two atomic orbitals.

Valence shell | The outermost electron shell of an atom.

van der Waals forces | Intermolecular forces that are responsible for holding molecules together in the liquid and solid states.

Vegetable oils | Liquid triacylglycerols derived from a plant source.

Vicinal | A term used to refer to a 1,2-disubstitution pattern. For example, 1,2-dibromoethane is a vicinal dibromide.

Vinyl group | A $-CH^-$ substituent.

Vinyl monomer | A substituted alkene monomer used to make a chain-growth polymer.

Vinylic | A term that refers to a substituent at a double-bond carbon atom. For example, chloroethylene is a vinylic chloride, and enols are vinylic alcohols.

Vitamin | A small organic molecule that must be obtained in the diet and is required in trace amounts for proper growth and function.

Vulcanization | A technique for cross-linking and hardening a diene polymer by heating with a few percent by weight of sulfur.

Walden inversion | The inversion of configuration at a chirality center that accompanies an S_N2 reaction.

Wave equation | A mathematical expression that defines the behavior of an electron in an atom.

Wave function | A solution to the wave equation for defining the behavior of an electron in an atom. The square of the wave function defines the shape of an orbital.

Wavelength | The length of a wave from peak to peak. The wavelength of electromagnetic radiation is inversely proportional to frequency and inversely proportional to energy.

Waxes | A mixture of esters of long-chain carboxylic acids with long-chain alcohols.

Williamson ether synthesis | A method for synthesizing ethers by S_N2 reaction of an alkyl halide with an alkoxide ion.

Wittig reaction | The reaction of a phosphorus ylide with a ketone or aldehyde to yield an alkene.

Wohl degradation | A method for shortening the chain of an aldose sugar by one carbon.

Wolff–Kishner reaction | The conversion of an aldehyde or ketone into an alkane by reaction with hydrazine and base.

X-ray crystallography | A technique that uses X rays to determine the structure of molecules.

Ylide | A neutral species with adjacent + and − charges, such as the phosphoranes used in Wittig reactions.

***Z* geometry** | A term used to describe the stereochemistry of a carbon–carbon double bond. The two groups on each carbon are ranked according to the Cahn–Ingold–Prelog sequence rules, and the two carbons are compared. If the higher ranked groups on each carbon are on the same side of the double bond, the bond has *Z* geometry.

Zaitsev's rule | A rule stating that E2 elimination reactions normally yield the more highly substituted alkene as major product.

Ziegler–Natta catalysts | Catalysts of an alkylaluminum and a titanium compound used for preparing alkene polymers.

Zwitterion | A neutral dipolar molecule in which the positive and negative charges are not adjacent. For example, amino acids exist as zwitterions, $H_3C_{movermover}-CHR-CO_2^-$

***α* Anomer** | The cyclic hemiacetal form of a sugar that has the hemiacetal −OH group cis to the −OH at the lowest chirality center in a Fischer projection.

***α* Helix** | The coiled secondary structure of a protein.

***α* Position** | The position next to a carbonyl group.

***α*-Amino acids** | A type of difunctional compound with an amino group on the carbon atom next to a carboxyl group, $RCH(NH_2)CO_2H$.

***α*-Substitution reaction** | The substitution of the *α* hydrogen atom of a carbonyl compound by reaction with an electrophile.

***β* Anomer** | The cyclic hemiacetal form of a sugar that has the hemiacetal −OH group trans to the −OH at the lowest chirality center in a Fischer projection.

***β* Diketone** | A 1,3-diketone.

***β* Lactam** | A four-membered lactam, or cyclic amide. Penicillin and cephalosporin antibiotics contain *β*-lactam rings.

***β*-Keto ester** | A 3-oxoester.

***β*-Oxidation pathway** | The metabolic pathway for degrading fatty acids.

***β*-Pleated sheet** | A type of secondary structure of a protein.

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