ORGANIC CHEMISTRY

Wade Textmap

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Organic Chemistry

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Licensing

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CHAPTER OVERVIEW

1: Introduction and Review

Learning Objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- discuss the origins of organic chemistry - refer to section 1.1
- use and apply the language of Atomic Structure (atomic number, mass number, isotopes) - refer to section 1.2
- draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures - refer to sections 1.3, 1.4, 1.5, and 1.6
- apply bonding patterns and polarity to organic compounds - refer to section 1.7 and 1.8
- identify polar bonds and compounds - refer to section 1.9
- draw resonance forms and predict the relative contribution of each resonance form to the overall structure of the compound or ion - refer to section 1.10
- recognize acids and bases - refer to sections 1.11 and 1.12
- use the definition of Lewis Acids and Bases to recognize electron movement in reactions - refer to section 1.13
- predict reaction products of acid-base reactions - refer to sections 1.11, 1.12 ,and 1.13
- determine relative strengths of acids and bases from their pK_a values - refer to section 1.14
- determine the form of an acid or base at a specified pH (given the pK_a) - refer to section 1.14
- predict relative strengths of acids and bases from their structure, bonding and resonance - refer to section 1.15
- determine the empirical and molecular formulas from combustion data - refer to section 1.16

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1.2: Principles of Atomic Structure (Review)
1.3: Electronic Structure (Review)
1.4: Electron Configurations
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1.1: The Origins of Organic Chemistry

Learning Objective

- discuss the origins of 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. The widespread belief called vitalism held that organic compounds were formed by a vital force present only in living organisms. The German chemist Friedrich Wöhler was one of the early chemists to refute this aspect of vitalism, when, in 1828, he reported the synthesis of urea, a component of many body fluids, from nonliving materials. Since then, it has been recognized that organic molecules obey the same natural laws as inorganic substances, and the category of organic compounds has evolved to include both natural and synthetic compounds that contain carbon. Some carbon-containing compounds are not classified as organic, for example, carbonates and cyanides, and simple oxides, such as CO and CO_2. Although a single, precise definition has yet to be identified by the chemistry community, most agree that a defining trait of organic molecules is the presence of carbon as the principal element, bonded to hydrogen and other carbon atoms.

Figure **1.1.1**: 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)

Today, organic compounds are key components of plastics, soaps, perfumes, sweeteners, fabrics, pharmaceuticals, and many other substances that we use every day. 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.

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1.2: Principles of Atomic Structure (Review)

Learning Objective

- Use and apply the language of Atomic Structure (atomic number, mass number, isotopes)

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 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.

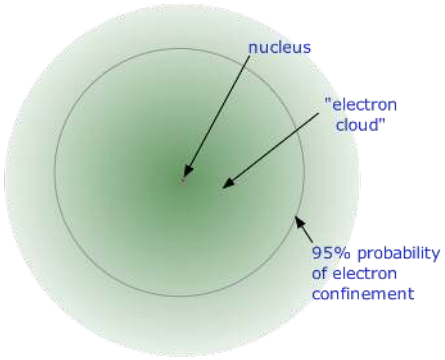

Figure **1.2.1**: The structure of the nuclear atom with a central nucleus and surrounding electrons.

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.*

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 **1.2.1**, 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 **1.2.1**: Properties of Subatomic Particles*

Particle	Mass (g)	Atomic Mass (amu)	Electrical Charge (coulombs)	Relative Charge
electron	9.109×10^{-28}	0.0005486	-1.602×10^{-19}	−1
proton	1.673×10^{-24}	1.007276	$+1.602 \times 10^{-19}$	+1
neutron	1.675×10^{-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 **1.2.2**.

Table **1.2.2**: 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.

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.

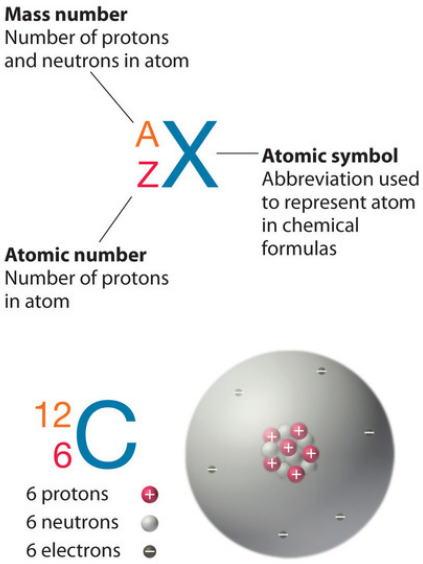

***Figure* 1.2.2**: *Formalism used for identifying specific nuclide (any particular kind of nucleus)*

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 **1.2.3**.

Table **1.2.3**: 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 1.2.1

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 1.2.1

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

Answer

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

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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1.3: Electronic Structure (Review)

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

The primary skills needed are the ability to determine the electron configurations of elements following the concepts of "aufbau" or "build up", Hund's Rule, and the Pauli Exclusion Principle, as well as visualizing the orbitals, subshells, and shells spatially and energetically. Converting electron configurations to orbital diagrams is a useful skill as we transition to organic chemistry. These skills are practiced in the next section.

The Wave Nature of Light

A wave is a periodic oscillation by which energy is transmitted through space. All waves are periodic, repeating regularly in both space and time. Waves are characterized by several interrelated properties.

- **Electronic structure**: arrangement of electrons in atoms
- **Electromagnetic radiation**: aka **radiant energy**; form of energy that has wave characteristics and carries energy through space. *All types of electromagnetic radiation move through a vacuum at a speed of 3.00 X 10^8 m/s (speed of light).*
- **Wavelength**: the distance between identical points on successive waves
- **Frequency**: the number of complete wavelengths that pass a given point in 1s

$$\nu\lambda = c \tag{1.3.1}$$

where ν = frequency, λ= wavelength, and c = speed of light

Wavelength is expressed in units of length.

- **Electromagnetic spectrum**: various types of electromagnetic radiations arranged in order of increasing wavelength.

Frequency is expressed in Hertz (Hz), also denoted by s^{-1} or /s

Quantum Effects and Photons

- **Quantum**: smallest quantity of energy that can be emitted or absorbed as electromagnetic radiation

$$E = h\nu \tag{1.3.2}$$

where E = energy, h = Planck's constant, ν = frequency

Planck's constant = 6.63 X 10^{-34} J/s

According to Planck's theory, energy is always emitted or absorbed in whole-number multiples of *hv*, for example, *hv*, *2hv*, *3hv*, and so forth. We say that the allowed energies are *quantized* (that is, their values are restricted to certain quantities).

Quantized Energy and Photons

Blackbody radiation is the radiation emitted by hot objects and could not be explained with classical physics. Max Planck postulated that energy was quantized and may be emitted or absorbed only in integral multiples of a small unit of energy, known as a quantum. The energy of a quantum is proportional to the frequency of the radiation; the proportionality constant h is a fundamental constant (Planck's constant). Albert Einstein used the quantization of energy to explain the photoelectric effect

- The photoelectric effect: when photons of sufficiently high energy strike a metal surface, electrons are emitted from the metal. The emitted electrons are drawn toward the other electrode, which is a positive terminal. As a result, current flows in a circuit.
- **Photon***:* smallest increment (a *quantum*) of radiant energy; a photon of light with frequency v has an energy equal to *hv*.
- When a photon strikes the metal, its energy is transferred to an electron in the metal. A certain amount of energy is required for the electron to overcome the attractive forces that hold it within the metal. If the photons have less energy that this energy

threshold, the electrons cannot escape from the metal surface. If a photon has sufficient energy, an electron is emitted. If the photon has more energy than necessary, the excess appears as kinetic energy of the emitted electron.

Line Spectra and the Bohr Model

There is an intimate connection between the atomic structure of an atom and its spectral characteristics. Most light is polychromatic and contains light of many wavelengths. Light that has only a single wavelength is monochromatic and is produced by devices called lasers, which use transitions between two atomic energy levels to produce light in a very narrow range of wavelengths. Atoms can also absorb light of certain energies, resulting in a transition from the ground state or a lower-energy e

Line Spectra

Radiation composed of a single wavelength is said to be *monochromatic*.

- **Spectrum**: distribution among various wavelengths of the radiant energy emitted or absorbed by an object
- **Continuous spectrum**: rainbow of colors, containing light of all wavelengths. *Not all radiation sources produce a continuous spectrum*
- **Line spectrum**: spectrum containing radiation of only specific wavelengths

$$v = C\left(\frac{1}{2^2} - \frac{1}{n^2}\right) \tag{1.3.3}$$

with n = 3, 4, 5, 6, and $C = 3.29 \times 10^{15} s^{-1}$ (constant)

Bohr's Model

Electrons in a permitted orbit have a specific energy and are said to be in an "allowed" energy state. An electron in an allowed energy state will not radiate energy and therefore will not spiral into the nucleus.

$$E_n = -R_H \frac{1}{n^2} \tag{1.3.4}$$

- R_H = Rydberg constant: 2.18 X 10^{-18} J
- n = principal quantum number, corresponds to the different allowed orbits for the electron

All energies given by this equation will be negative. The lower (more negative) the energy is, the more stable the atom is. The lowest energy state is that for which n=1.

- **Ground state:** lowest energy state of an atom, $n = 1$
- **Excited state:** when the electron is in higher energy orbit (less negative), n=2 or higher

If n becomes infinitely large (∞), the electron is completely separated from the nucleus:

$$E_\infty = (-2.18 \times 10^{-18} J)\left(\frac{1}{\infty^2}\right) = 0 \tag{1.3.5}$$

Thus, the state in which the electron is removed from the nucleus is the reference, or zero-energy, state of the hydrogen atom. It is important to remember that this zero-energy state is higher in energy than the states with negative energies

Electrons can change from one energy state to another by absorbing or emitting radiant energy. Radiant energy must be absorbed for an electron to move to a higher energy state, but is emitted when the electron moves to a lower energy state. .

$$\Delta E = E_f - E_i \tag{1.3.6}$$

- If $n_f > n_i$, then ΔE is positive, radiant energy is absorbed
- If $n_f < n_i$, then ΔE is negative, radiant energy is emitted

The Wave Behavior of Matter

An electron possesses both particle and wave properties. Louis de Broglie showed that the wavelength of a particle is equal to Planck's constant divided by the mass times the velocity of the particle. The electron in Bohr's circular orbits could thus be described as a standing wave, one that does not move through space. Werner Heisenberg's uncertainty principle states that it is impossible to precisely describe both the location and the speed of particles that exhibit wavelike behavior.

- **Momentum**: the product of the mass, *m*, and the velocity, *v*, of a particle
- **Matter waves**: term used to describe the wave characteristics of a particle

$$\lambda = \frac{h}{mv} \tag{1.3.7}$$

where λ is the wavelength, h is Planck's constant, m is the particle mass, and v is the velocity

The Uncertainty Principle

- **Uncertainty principle**: theory first put forth by Heisenberg, states that is it impossible to determine both the exact momentum of the electron and its exact location.

Quantum Mechanics and Atomic Orbitals

There is a relationship between the motions of electrons in atoms and molecules and their energies that is described by quantum mechanics. Because of wave–particle duality, scientists must deal with the probability of an electron being at a particular point in space. To do so required the development of quantum mechanics, which uses wavefunctions to describe the mathematical relationship between the motion of electrons in atoms and molecules and their energies.

- **Wave functions**: represented by ψ, square of wave function, ψ^2, provides information about an electron's location when it is in an allowed energy state.
- **Probability density**: represented by ψ^2, value that represents the probability that an electron will be found at a given point in space
- **Electron density**: the probability of finding and electron at any particular point in an atom. Equals ψ^2.

Orbitals and Quantum Numbers

-Orbital: allowed energy state of an electron in the quantum-mechanical model of the atom; also used to describe the spatial distribution of an electron. Defined by the value of 3 quantum numbers; *n, l, and* m_l.

Value of l	0	1	2	3
Letter used	s	p	d	f

1. The principal quantum number, *n*, can have integral values of 1, 2, 3 and so forth. As *n* increases, the orbital becomes larger; the electron has a higher energy and is farther away from the nucleus.
2. The second quantum number, *l*, can have integral values from 0 to *n* – 1 for each value of *n*. This quantum number defines the shape of the orbital. Generally designated by the letters *s*, *p*, *d*, and *f*. These correspond to values ranging from 0 to 3.
3. The magnetic quantum number, m_l, can have integral values between *l* and –*l*, including zero. This quantum number describes the orientation of the orbital in space.

Electron shell: collection of orbitals with the same value of *n*

Subshell: one or more orbitals with the same set of *n* and *l* values

1. Each shell is divided into the number of subshells equal to the principal quantum number, *n*, for that shell. The first shell consists of only the 1s subshell; the second shell consists of two subshells, 2s and 2p; the third of three subshell, 3s, 3p and 3d, and so forth.
2. Each subshell is divided into orbitals. Each *s* subshell consists of one orbital; each *p* subshell of three orbitals, each *d* subshell of five, and each *f* subshell of seven orbitals.

3D Representation of Orbitals

Orbitals with l = 0 are s orbitals and are spherically symmetrical, with the greatest probability of finding the electron occurring at the nucleus. Orbitals with values of n > 1 and l = 0 contain one or more nodes. Orbitals with l = 1 are p orbitals and contain a nodal plane that includes the nucleus, giving rise to a dumbbell shape. Orbitals with l = 2 are d orbitals and have more complex shapes with at least two nodal surfaces. l = 3 orbitals are f orbitals, which are still more complex.

The s Orbitals: 1s orbital: most stable, spherically symmetric, figure indicates that the probability decreases as we move away from the nucleus. ALL *s* ORBITALS ARE SPHERICALLY SYMMETRIC.

- **Nodal surfaces (nodes)**: intermediate regions where ψ^2 goes to zero. The number of nodes increases with increasing value for the principal quantum number, *n*.

The *p* Orbitals: Electron density is concentrated on two sides of the nucleus, separated by a node at the nucleus. The orbitals of a given subshell have the same size and shape but differ from each other in orientation. The axis along which the orbital is oriented is not related to m_l.

Many-Electron Atoms

In addition to the three quantum numbers (n, l, m_l) dictated by quantum mechanics, a fourth quantum number is required to explain certain properties of atoms. This is the electron spin quantum number (m_s), which can have values of +½ or −½ for any electron, corresponding to the two possible orientations of an electron in a magnetic field. This is important for chemistry because the Pauli exclusion principle implies that no orbital can contain more than two electrons (with opposite spin).

Although the shapes of the orbitals for many-electron atoms are the same as those for hydrogen, the presence of more than one electron greatly changes the energies of the orbitals. In hydrogen, the energy of an orbital depends only on its principal quantum number, however, in many-electron atoms, electron-electron repulsions cause different subshells to be at different energies

Effective Nuclear Charge

- *Effective nuclear charge*: net positive charge attracting electrons

$$Z_{eff} = Z–S \tag{1.3.8}$$

where Z_{eff} is the effective nuclear charge, Z is the number of protons in the nucleus, and S is the average number of electrons between the nucleus and electron in question.

- *Screening effect*: effect of inner electrons in decreasing the nuclear charge experienced by outer electrons

Energies of Orbitals

The extent to which an electron will be screened by the other electrons depends on its electron distribution as we move outward from the nucleus.

- *In a many-electron atom, for a given value of n, Z_{eff} decreases with increasing value of l.*
- *In a many-electron atom, for a given value of n, the energy of an orbital increases with increasing value of l.*

Degenerate: orbitals that have the same energy

Electron Spin and the Pauli Exclusion Principle

- **Electron spin**: property of the electron that makes it behave as though it were a tiny magnet. The electron behaves as if it were spinning on its axis; electron spin is quantized.
- **Electron spin quantum number**: denoted as m_s. It can only have two possible values, +½ and –½, which we can interpret as indicating the two opposite directions in which the electron can spin.
- **Pauli exclusion principle**: states that no two electrons in an atom can have the same set of four quantum numbers *n*, *l*, m_l, m_s. This means that if we wish to put two electrons in an orbital and satisfy Pauli's exclusion principle, our only choice is to assign different m_s values to the electrons. Because there are only two values, *we can conclude that an orbital can hold a maximum of two electrons and they must have opposite spins*.

Electron Configurations

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 parallel spins.

- **Electron configuration**: the way in which the electrons are distributed among the various orbitals. The most stable, or ground, electron configuration of an atom is that in which the electrons are in the lowest possible energy level
- **Orbital diagram**: representation of electron configuration in which each orbital is represented by a box and each electron by a half-arrow. A half-arrow pointing upward represents an electron with positive spin; one pointing downward represents an electron with a negative spin.

Writing Electron Configurations

- **Hund's rule**: rule stating that electrons occupy degenerate orbitals in such a way as to maximize the number of electrons with the same spin. In other words, each orbital has one electron placed in it before paring of electron in orbitals occurs. Note that this rule applies to orbitals that are *degenerate*, which means that they have the same energy.
- **Valence electrons**: electrons in the outer shells
- **Core electrons**: electrons in the inner shells
- **Transition elements**: aka **Transition metals**; elements of the *d* orbitals
- **Lanthanide elements**: aka **Rare-earth elements**; 14 elements of the 4f orbitals, # 58-71
- **Actinide elements**: 14 elements of 5f orbitals, # 90-103. Most are not found in nature.

Electron Configurations and the Periodic Table

The arrangement of atoms in the periodic table results in blocks corresponding to filling of the ns, np, nd, and nf orbitals to produce the distinctive chemical properties of the elements in the s block, p block, d block, and f block, respectively.

- **Main group elements**: aka **Representatives**; *s* and *p* block elements
- **F-block metals**: 28 elements located below the table, *f* block elements

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1.4: Electron Configurations

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

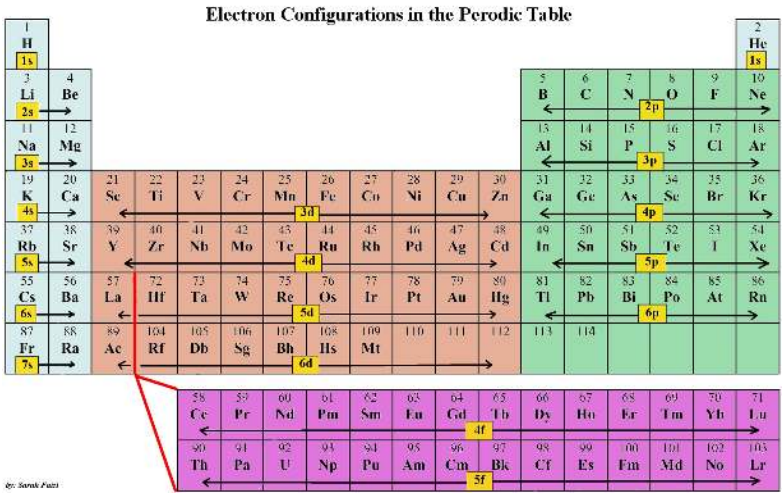
Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

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.

Introduction

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.

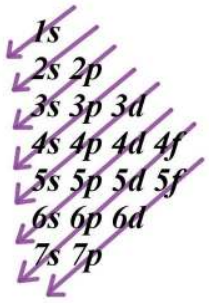
Rules for Assigning Electron Orbitals

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 order of levels filled looks like this:

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

One way to remember this pattern, probably the easiest, is to refer to the periodic table and remember where each orbital block falls to logically deduce this pattern. Another way is to make a table like the one below and use vertical lines to determine which subshells correspond with each other.

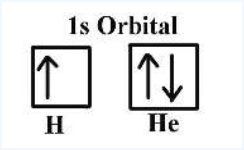


Pauli Exclusion Principle

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:



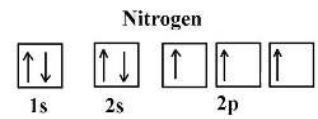
As shown, the 1s subshell can hold only two electrons and, when filled, the electrons have opposite spins.

Hund's Rule

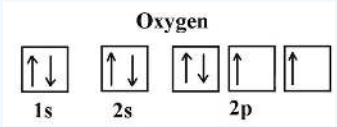
When assigning electrons in orbitals, each electron will first fill all the orbitals with similar energy (also referred to as degenerate) before pairing with another electron in a half-filled orbital. Atoms at ground states tend to have as many unpaired electrons as possible. When visualizing this processes, 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.

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.

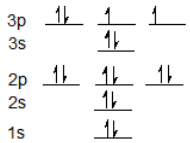
Example 3: 3rd row elements

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:$1s^2\ 2s^2\ 2p^6$

Example

The electron configuration for sulfur is $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^4$ and can be represented using the orbital diagram below.

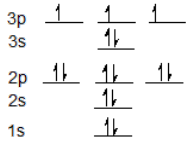


Exercises

Write the electron configuration for phosphorus and draw the orbital diagram.

Solution:

The electron configuration for phosphorus is $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^3$ and the orbital diagram is drawn below.



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1.5: Octet Rule - Ionic and Covalent Bonding (Review)

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

For organic chemistry, the emphasis is on the chemistry of carbon. The chemistry of carbon becomes more interesting when carbon is bonded to oxygen and/or nitrogen or other heteroatoms, atoms that are NOT carbon or hydrogen. Therefore, the octet rule is a strong factor in organic chemistry and is only violated by non-carbon elements like hydrogen, boron, aluminum, sulfur, and phosphorus.

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 will be discussed and the general properties found in typical substances in which the bond type occurs

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

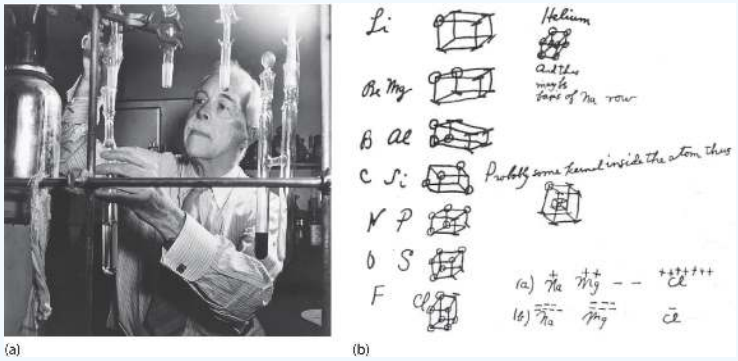

Figure **1.5.1**: G. N. Lewis and the Octet Rule. (a) Lewis is working in the laboratory. (b) In Lewis's original sketch for the octet rule, he initially placed the electrons at the corners of a cube rather than placing them as we do now.

The Octet Rule

In 1904, Richard Abegg formulated what is now known as *Abegg's rule*, which states that the difference between the maximum positive and negative valences of an element is frequently eight. This rule was used later in 1916 when Gilbert N. Lewis formulated the "octet rule" in his cubical atom theory. The **octet rule** refers to the tendency of atoms to prefer to have eight electrons in the *valence shell*. When atoms have fewer than eight electrons, they tend to react and form more stable compounds. Atoms will react to get in the most stable state possible. A complete octet is very stable because all orbitals will be full. Atoms with greater stability have less energy, so a reaction that increases the stability of the atoms will release energy in the form of heat or light ;reactions that decrease stability must absorb energy, getting colder.

> *The Octet Rule: 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.*

When discussing the octet rule, we do not consider *d* or *f* electrons. Only the s and p electrons are involved in the octet rule, making it a useful rule for the *main group elements* (elements not in the transition metal or inner-transition metal blocks); an

octet in these atoms corresponds to an electron configurations ending with s^2p^6.

Covalent Bonds

Covalent bonds form when atoms share electrons. Hydrogen is a first shell element with only one valence electron, so it can only form one bond creating a duet, an exception to the octet rule. With its four valence electrons, carbon can form four bonds to create an octet.

1. Normally two electrons pairs up and forms a bond, e.g., H_2
2. For most atoms there will be a maximum of eight electrons in the valence shell (octet structure), e.g., CH_4

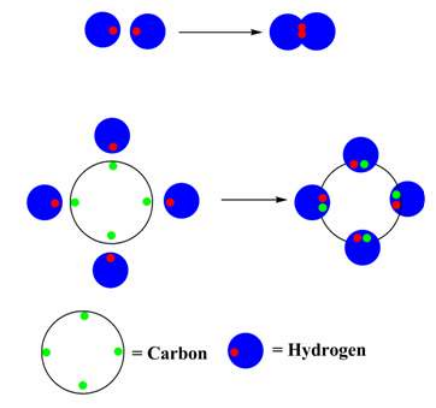

Figure 1: Bonding in H_2 and methane (CH_4)

The other tendency of atoms is to maintain a neutral charge. Only the noble gases (the elements on the right-most column of the periodic table) have zero charge with filled valence octets. All of the other elements have a charge when they have eight electrons all to themselves. The result of these two guiding principles is the explanation for much of the reactivity and bonding that is observed within atoms: atoms seek to share electrons in a way that minimizes charge while fulfilling an octet in the valence shell.

Ionic Bonds

Some atoms do not share electrons. Energetically, it is more favorable to fully gain or lose electrons to form ions. Ionic compounds form through the eletrostatic attraction of the ions to create a crystal lattice.

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 has one valence electron, so giving it up would result in the same electron configuration

as neon. Chlorine has seven valence electrons, so if it takes one it will have eight (an octet). Chlorine has the electron configuration of argon when it gains an electron.

The octet rule could have been satisfied if chlorine gave up all seven of its valence electrons and sodium took them. In that case, both would have the electron configurations of noble gasses, with a full valence shell. However, their charges would be much higher. It would be Na^{7-} and Cl^{7+}, which is much less stable than Na^{+} and Cl^{-}. Atoms are more stable when they have no charge, or a small charge.

Ionic Bonds Example

Lewis dot symbols can also be used to represent the ions in ionic compounds. The reaction of cesium with fluorine, for example, to produce the ionic compound CsF can be written as follows:

No dots are shown on Cs^{+} in the product because cesium has lost its single valence electron to fluorine. The transfer of this electron produces the Cs^{+} ion, which has the valence electron configuration of Xe, and the F^{-} ion, which has a total of eight valence electrons (an octet) and the Ne electron configuration. This description is consistent with the statement that among the main group elements, ions in simple binary ionic compounds generally have the electron configurations of the nearest noble gas. The charge of each ion is written in the product, and the anion and its electrons are enclosed in brackets. This notation emphasizes that the ions are associated electrostatically; no electrons are shared between the two elements.

Noble Gases

The noble gases rarely form compounds. They have the most stable 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.

Summary

Lewis dot symbols can be used to predict the number of bonds formed by most elements in their compounds. One convenient way to predict the number and basic arrangement of bonds in compounds is by using **Lewis electron dot symbols**, which consist of the chemical symbol for an element surrounded by dots that represent its valence electrons, grouped into pairs often placed above, below, and to the left and right of the symbol. The structures reflect the fact that the elements in period 2 and beyond tend to gain, lose, or share electrons to reach a total of eight valence electrons in their compounds, the so-called **octet rule**. Hydrogen, with only two valence electrons, does not obey the octet rule.

Exercises

Lewis

Contributors and Attributions

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1.6: Lewis Structures

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Lewis Structures

Lewis structures, also known as Lewis-dot diagrams, show the bonding relationship between atoms of a molecule and the lone pairs of electrons in a molecule. While it can be helpful initially to write the individual shared electrons, this approach quickly becomes awkward.

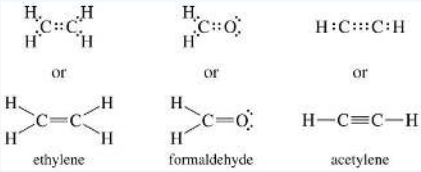
A single line is used to represent one pair of shared electrons. Line representations are only used for shared electrons. Lone pair (unshared) electrons are still shown as individual electrons. Double and triple bonds can also be communicated with lines as shown below.

2 shared electrons form a single bond shown as ':' or '–'

4 shared electrons form a double bond shown as '::' or '='

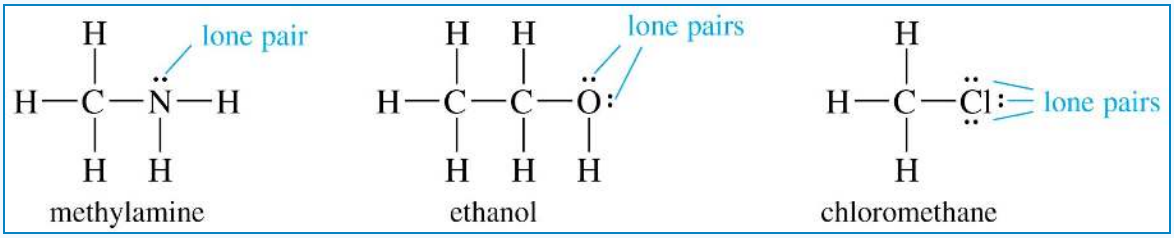
6 shared electrons form at triple bond shown as ':::' or HC≡CH

Unshared electrons are also called 'Lone Pairs' and are shown as ':'



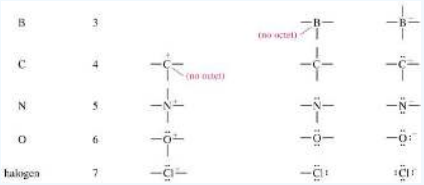
Drawing Lone Pairs

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



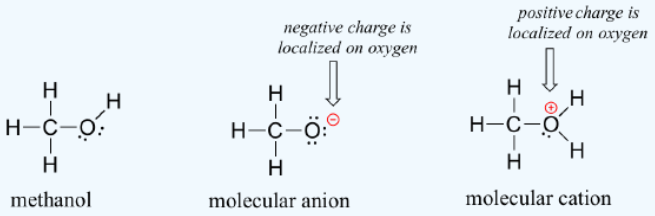
Bonding Patterns

For organic chemistry, the common bonding patterns of carbon, oxygen, and nitrogen have useful applications when evaluating chemical structures and reactivity.



Formal charges

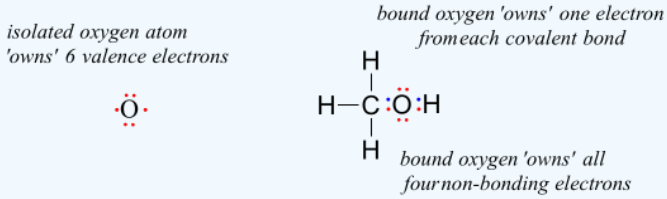
Organic molecules can also have positive or negative charges associated with them. During chemical reactions, it is common to have charge reactant, intermediates, and/or products. Recognizing and distinguishing between neutral and charged bonding patterns will be helpful in learning reaction mechanisms. Consider the Lewis structure of methanol, CH_3OH (methanol is the so-called 'wood alcohol' that unscrupulous bootleggers sometimes sold during the prohibition days in the 1920's, often causing the people who drank it to go blind). Methanol itself is a neutral molecule, but can lose a proton to become a molecular anion (CH_3O^-), or gain a proton to become a molecular cation ($CH_3OH_2^{+)}$.



The molecular anion and cation have overall charges of -1 and +1, respectively. But we can be more specific than that - we can also state for each molecular ion that a **formal charge** is located specifically on the oxygen atom, rather than on the carbon or any of the hydrogen atoms.

Figuring out the formal charge on different atoms of a molecule is a straightforward process - it's simply a matter of adding up valence electrons.

A unbound oxygen atom has 6 valence electrons. When it is bound as part of a methanol molecule, however, an oxygen atom is surrounded by 8 valence electrons: 4 nonbonding electrons (two 'lone pairs') and 2 electrons in each of its two covalent bonds (one to carbon, one to hydrogen). In the formal charge convention, we say that the oxygen 'owns' all 4 nonbonding electrons. However, it only 'owns' one electron from each of the two covalent bonds, because covalent bonds involve the sharing of electrons between atoms. Therefore, the oxygen atom in methanol owns 2 + 2 + (½ x 4) = 6 valence electrons.



The formal charge on an atom is calculated as the number of valence electrons owned by the isolated atom minus the number of valence electrons owned by the bound atom in the molecule:

Determining formal charge on an atom

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of valence electrons owned by the bound atom)

or . . .

formal charge =

(number of valence electrons owned by the isolated atom)

- (number of non-bonding electrons on the bound atom)

- (½ the number of bonding electrons on the bound atom)

Using this formula for the oxygen atom of methanol, we have:

formal charge on oxygen =

(6 valence electrons on isolated atom)

- (4 non-bonding electrons)

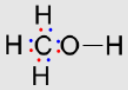
- (½ x 4 bonding electrons)

= 6 - 4 - 2 = **0**. Thus, oxygen in methanol has a formal charge of zero (in other words, it has *no formal charge*).

How about the carbon atom in methanol? An isolated carbon owns 4 valence electrons. The bound carbon in methanol owns (½ x 8) = 4 valence electrons:

isolated carbon atom 'owns' 4 valence electrons

bound carbon 'owns' one electron from each covalent bond



formal charge on carbon =

(4 valence electron on isolated atom)

- (0 nonbonding electrons)

- (½ x 8 bonding electrons)

= 4 - 0 - 4 = **0**. So the formal charge on carbon is zero.

For each of the hydrogens in methanol, we also get a formal charge of zero:

formal charge on hydrogen =

(1 valence electron on isolated atom)

- (0 nonbonding electrons)

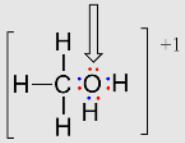
- (½ x 2 bonding electrons)

= 1 - 0 - 1 = **0**

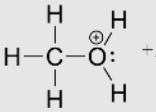
Now, let's look at the cationic form of methanol, $CH_3OH_2^+$. The bonding picture has not changed for carbon or for any of the hydrogen atoms, so we will focus on the oxygen atom.

isolated oxygen atom 'owns' 6 valence electrons

bound oxygen 'owns' both non-bonding electrons



bound oxygen 'owns' one electron from each of the three covalent bonds



+1 formal charge is located on oxygen

The oxygen owns 2 non-bonding electrons and 3 bonding elections, so the formal charge calculations becomes:

formal charge on oxygen =

(6 valence electrons in isolated atom)

- (2 non-bonding electrons)

- (½ x 6 bonding electrons)

= 6 - 2 - 3 = **1**. A formal charge of +1 is located on the oxygen atom.

For methoxide, the anionic form of methanol, the calculation for the oxygen atom is:

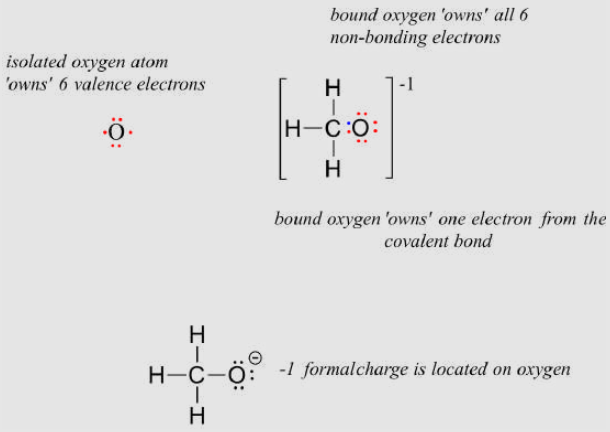
formal charge on oxygen =

(6 valence electrons in isolated atom)

- (6 non-bonding electrons)

- (½ x 2 bonding electrons)

= 6 - 6 - 1 = **-1**. A formal charge of -1 is located on the oxygen atom.

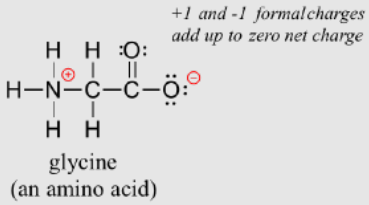


A very important rule to keep in mind is that *the sum of the formal charges on all atoms of a molecule must equal the net charge on the whole molecule.*

When drawing the structures of organic molecules, it is very important to show all non-zero formal charges, being clear about where the charges are located. *A structure that is missing non-zero formal charges is not correctly drawn, and will probably be marked as such on an exam!*

At this point, thinking back to what you learned in general chemistry, you are probably asking "What about dipoles? Doesn't an oxygen atom in an O-H bond 'own' more of the electron density than the hydrogen, because of its greater electronegativity?" This is absolutely correct, and we will be reviewing the concept of bond dipoles later on. For the purpose of calculating formal charges, however, bond dipoles don't matter - we always consider the two electrons in a bond to be shared equally, even if that is not an accurate reflection of chemical reality. Formal charges are just that - a formality, a method of electron book-keeping that is tied into the Lewis system for drawing the structures of organic compounds and ions. Later, we will see how the concept of formal charge can help us to visualize how organic molecules react.

Finally, don't be lured into thinking that just because the net charge on a structure is zero there are no atoms with formal charges: one atom could have a positive formal charge and another a negative formal charge, and the net charge would still be zero. **Zwitterions,** such as amino acids, have both positive and negative formal charges on different atoms:

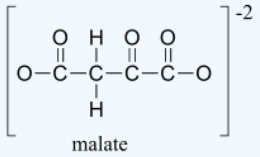


glycine
(an amino acid)

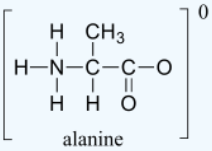
Even though the *net* charge on glycine is zero, it is still neccessary to show the location of the positive and negative formal charges.

Exercise 1.4

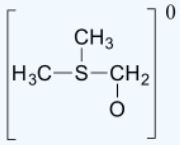
Fill in all missing lone pair electrons and formal charges in the structures below. Assume that all atoms have a complete valence shell of electrons. Net charges are shown outside the brackets.

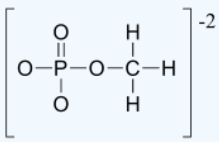
a) 

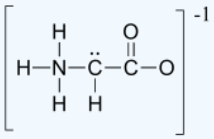
malate

b) 

alanine

c) 

d) 

e) 

Solutions to exercises

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1.7: Common Bonding Patterns for Organic Chemistry

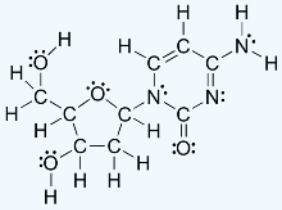
Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Common bonding patterns in organic structures

The Lewis structure below (of one of the four nucleoside building blocks that make up DNA) can appear complex and confusing at first glance. Fortunately, common bonding patterns occur that can allow for simplifications when drawing structures. The rules for the simplifies structures rely on the neutral bonding patterns for carbon, orygen, nitrogen, phosphorus, and sulfur primarily. Since organic compounds have a hydrocarbon backbone, the atoms that are NOT carbon and hydrogen are called heteroatoms. 2'-deoxycytidine contains seven heteroatoms: four oxygen atoms land three nitrogen atoms. Heteroatoms are a primary source of chemical reactivity for organic chemistry.



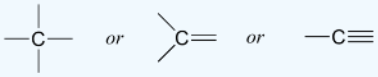
2'-deoxycytidine

Heteroatoms: atoms in an organic compound that are NOT carbon or hydrogen,

typically oxygen, nitrogen, phosphorus, and sulfur

The ability to quickly and efficiently draw large structures and determine formal charges is not terribly hard to come by - all it takes is a few shortcuts and some practice at recognizing common bonding patterns.

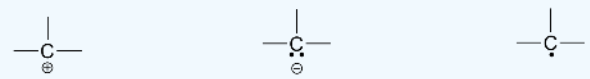
Let's start with carbon, the most important element for organic chemists. Carbon is said to be tetravalent, meaning that it tends to form four bonds. If you look at the simple structures of methane, methanol, ethane, ethene, and ethyne in the figures from the previous section, you should quickly recognize that in each molecule, the carbon atom has four bonds, and a formal charge of zero.



carbon usually has 4 bonds

This is a pattern that holds throughout most of the organic molecules we will see, but there are also exceptions.

<style type="text/css"></style> In carbon dioxide, the carbon atom has double bonds to oxygen on both sides (O=C=O). Later on in this chapter and throughout this book we will see examples of organic ions called 'carbocations' and carbanions', in which a carbon atom bears a positive or negative formal charge, respectively. If a carbon has only three bonds and an unfilled valence shell (in other words, if it does not fulfill the octet rule), it will have a positive formal charge.



3 bonds, no lone pair: carbocation

3 bonds + lone pair: carbanion

3 bonds + unpaired electron: carbon radical

If, on the other hand, it has three bonds plus a lone pair of electrons, it will have a formal charge of -1. Another possibility is a carbon with three bonds and a single, unpaired (free radical) electron: in this case, the carbon has a formal charge of zero. (One

last possibility is a highly reactive species called a ‘carbene’, in which a carbon has two bonds and one lone pair of electrons, giving it a formal charge of zero. You may encounter carbenes in more advanced chemistry courses, but they will not be discussed any further in this book).

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.

The pattern for hydrogens is easy: hydrogen atoms have only one bond, and no formal charge. The exceptions to this rule are the proton, H^+, and the hydride ion, H^-, which is a proton plus two electrons. Because we are concentrating in this book 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.

Let us next turn to oxygen atoms. Typically, you will see an oxygen bonding in three ways, all of which fulfill the octet rule.

neutral oxygen: 2 bonds + 2 lone pairs

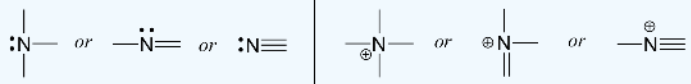
negative formal charge: 1 bond + 3 lone pairs

positive formal charge: 3 bonds + 1 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.

When we get to our discussion of free radical chemistry in chapter 17, we will see other possibilities, such as where an oxygen atom has one bond, one lone pair, 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 virtually everything we see until chapter 17.

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

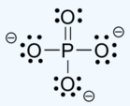


neutral nitrogen: 3 bonds, 1 lone pair

positive nitrogen: 4 bonds

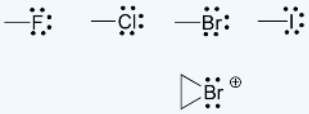
If a nitrogen has three bonds and a lone pair, it has a formal charge of zero. If it has four bonds (and no lone pair), it has a formal charge of +1. In a fairly uncommon bonding pattern, negatively charged nitrogen has two bonds and two lone pairs.

Two third row elements are commonly found in biological organic molecules: sulfur and phosphorus. 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 atoms of elements in the third row and below in the periodic table have 'expanded valence shells' with *d* orbitals available for bonding, and the the octet rule does not apply.



phosphate

Finally, 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.



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 1: Draw one structure that corresponds to each of the following molecular formulas, using the common bonding patters covered above. Be sure to include all lone pairs and formal charges where applicable, and assume that all atoms have a full valence shell of electrons. More than one correct answer is possible for each, so you will want to check your answers with your instructor or tutor.

a) $C_5H_{10}O$ b) C_5H_8O c) $C_6H_8NO^+$ d) $C_4H_3O_2^-$

Solutions to exercises

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1.8: Structural Formulas - Lewis, Kekule, Bond-line, Condensed,

Learning Objective

Draw, interpret, and convert between Lewis (Kekule), Condensed, and Bond-line Structures

Note: The review of general chemistry in sections 1.3 - 1.6 is integrated into the above Learning Objective for organic chemistry in sections 1.7 and 1.8.

Shorthand notations to represent organic molecules rely on our knowledge of common neutral bonding patterns. Knowing these patterns, we can fill in the missing structural information. Some of these shorthand ways of drawing molecules give us insight into the bond angles and relative positions of atoms in the molecule, while some notations eliminate the carbon and hydrogen atoms and only indicate the heteroatoms (the atoms that are NOT carbon or hydrogen).

There are three primary methods to communicate chemical structure of organic molecules:

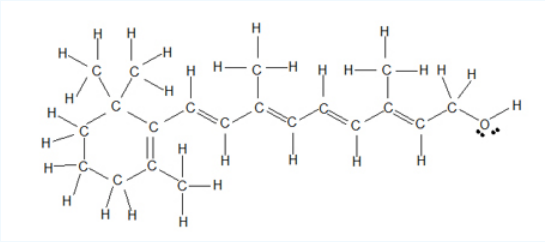
Kekule: Lewis structures using lines to represent covalent bonds and showing all atoms and lone pair electrons

Bond-line (Skeletl-line): shows bonds between carbon atoms and heteroatoms) (with lone pair electrons when requested)

Condensed: all atoms are written to communicate structure without drawing any chemical bonds based on the carbon backbone

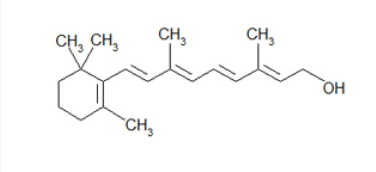
Introduction

Observe the following drawings of the structure of Retinol, the most common form of vitamin A. The first drawing follows the straight-line (a.k.a. Kekulé) structure which is helpful when you want to look at every single atom; however, showing all of the hydrogen atoms makes it difficult to compare the overall structure with other similar molecules and makes it difficult to focus in on the double bonds and OH group.



Retinol: Kekulé straight-line drawing

The following is a bond-line (a.k.a. zig-zag) formula for retinol. With this simiplified representation, one can easily see the carbon-carbon bonds, double bonds, OH group, and CH_3 groups sticking off of the the main ring and chain. Also, it is much quicker to draw this than the one above. You will learn to appreciate this type of formula writing after drawing a countless number of organic molecules.



Retinol: Bond-line or zig-zag formula

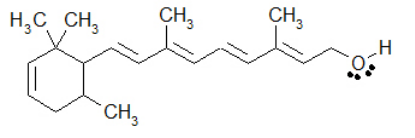
Importance of Structure

Learning and practicing the basics of Organic Chemistry will help you immensely in the long run as you learn new concepts and reactions. Some people say that Organic Chemistry is like another language, and in some aspects, it is. At first it may seem difficult or overwhelming, but the more you practice looking at and drawing organic molecules, the more familiar you will

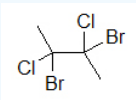
become with the structures and formulas. Another good idea is to get a model kit and physically make the molecules that you have trouble picturing in your head.

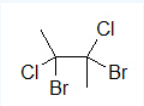
Through general chemistry, you may have already experienced looking at molecular structure. The different ways to draw organic molecules include Kekulé (straight-line), Condensed Formulas, and Bond-Line Formulas (zig-zag). It will be more helpful if you become comfortable going from one style of drawing to another, and look at drawings and understanding what they mean, than knowing which kind of drawing is named what.

An example of a drawing that incorporates all three ways to draw organic molecules would be the following additional drawing of Retinol. The majority of the drawing is Bond-line (zig-zag) formula, but the -CH_3 are written as condensed formulas, and the -OH group is written in Kekulé form.



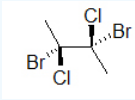
A widely used way of showing the 3D structure of molecules is the use of dashes, wedges, and straight lines. This drawing method is essential because the placement of different atoms could yield different molecules even if the molecular formulas were exactly the same. Below are two drawings of a 4-carbon molecule with two chlorines and two bromines attached.

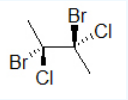




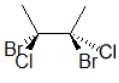
4-carbon molecule with 2 chlorines and 2 bromines 4-carbon molecule with 2 chlorines and 2 bromines

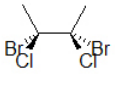
Both drawings look like they represent the same molecule; however, if we add dashes and wedged we will see that two different molecules could be depicted:





The two molecules above are different, prove this to yourself by building a model. An easier way to compare the two molecules is to rotate one of the bonds (here, it is the bond on the right):



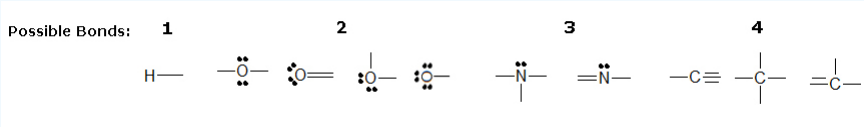


Notice how the molecule on the right has both bromines on the same side and chlorines on the same side, whereas the first molecule is different. Read about Dashed-Wedged Line structures, bottom of page, to understand what has been introduced above. You will learn more about the importance of atomic connectivity in molecules as you continue on to learn about Stereochemistry.

Drawing the Structure of Organic Molecules

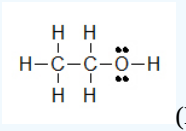
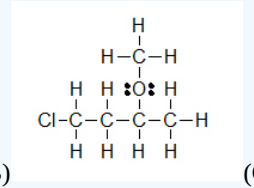
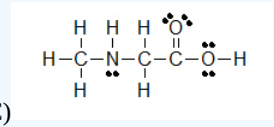
Although larger molecules may look complicated, they can be easily understood by breaking them down and looking at their smaller components.

All atoms want to have their valence shell full, a "closed shell." Hydrogen wants to have 2 e^- whereas carbon, oxygen, and nitrogen want to have 8 e^-. When looking at the different representations of molecules, keep in mind the Octet Rule. Also remember that hydrogen can bond one time, oxygen can bond up to two times, nitrogen can bond up to three times, and carbon can bond up to four times.



Kekulé (a.k.a. Lewis Structures)

Kekulé structures are similar to Lewis Structures, but instead of covalent bonds being represented by electron dots, the two shared electrons are shown by a line.

(A)  (B)  (C) 

Lone pairs remain as two electron dots, or are sometimes left out even though they are *still there*. Notice how the three lone pairs of electrons were not draw in around chlorine in example B.

Condensed Formulas

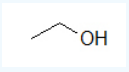
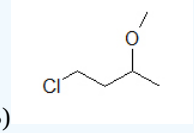
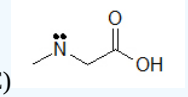
A condensed formula is made up of the elemental symbols. The order of the atoms suggests the connectivity. Condensed formulas can be read from either direction and H_3C is the same as CH_3, although the latter is more common because Look at the examples below and match them with their identical molecule under Kekulé structures and bond-line formulas.

(A) CH_3CH_2OH (B) $ClCH_2CH_2CH(OCH_3)CH_3$ (C) H_3CNHCH_2COOH

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.

Bond-Line (a.k.a. zig-zag) Formulas

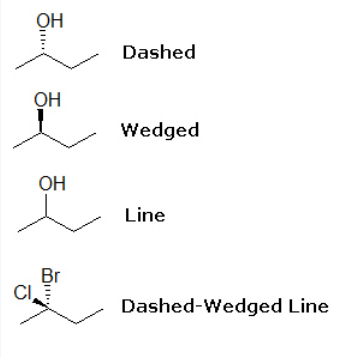
The name gives away how this formula works. This formula is full of bonds and lines, and because of the typical (more stable) bonds that atoms tend to make in molecules, they often end up looking like zig-zag lines. If you work with a molecular model kit you will find it difficult to make stick straight molecules (unless they contain sp triple bonds) whereas zig-zag molecules and bonds are much more feasible.

(A)  (B)  (C) 

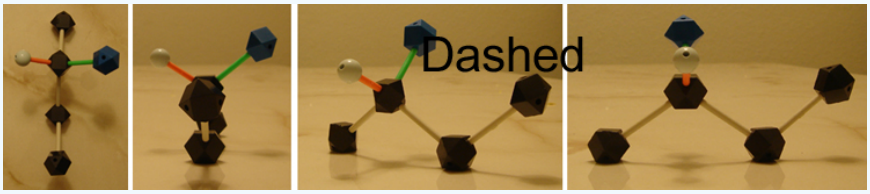
These molecules correspond to the exact same molecules depicted for Kekulé structures and condensed formulas. Notice how the carbons are no longer drawn in and are replaced by the ends and bends of a lines. In addition, the hydrogens have been omitted, but could be easily drawn in (see practice problems). 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.

Dashed-Wedged Line Structure

As you may have guessed, the Dashed-Wedged Line structure is all about lines, dashes, and wedges. At first it may seem confusing, but with practice, understanding dash-wedged line structures will become like second nature. The following are examples of each, and how they can be used together.

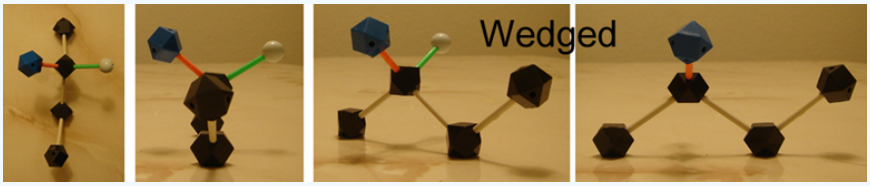


Above are 4-carbon chains with attached OH groups or Cl and Br atoms. Remember that each line represents a bond and that the carbons and hydrogens have been omitted. When you look at or draw these structures, the straight lines illustrate atoms and bonds that are in the same plane, the plane of the paper (in this case, computer screen). **Dashed lines** show atoms and bonds that go into the page, behind the plane, away from you. In the above example, the OH group is going into the plane, while at the same time a hydrogen comes out (wedged).



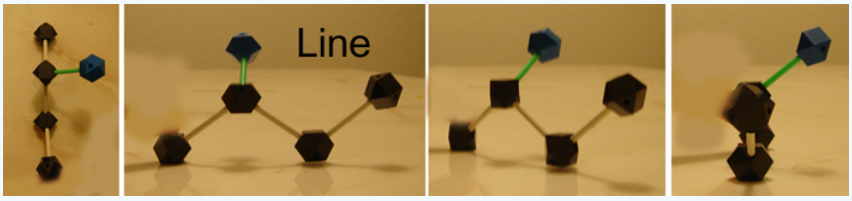
Blue bead= OH group; White bead=H

Wedged lines illustrate bonds and atoms that come out of the page, in front of the plane, toward you. In the 2D diagram above, the OH group is coming out of the plane of the paper, while a hydrogen goes in (dashed).



Blue bead= OH group; White bead=H

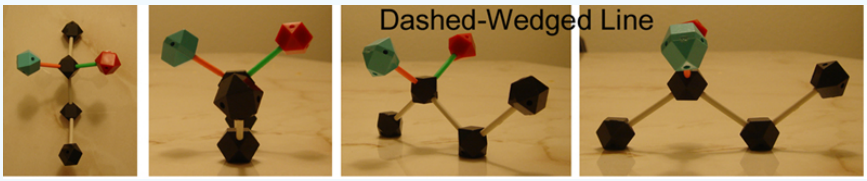
As stated before, straight lines illustrate atoms and bonds that are in the same plane as the paper, but in the 2D example, the straight line bond for OH means that it it unsure or irrelevant whether OH is going away or toward you. It is also assumed that hydrogen is also connected to the same carbon that OH is on.



Blue bead= OH group; H is not shown

Try using your model kit to see that the OH group cannot lie in the same plane at the carbon chain (don't forget your hydrogens!). In the final 2Dexample, both dashed and wedged lines are used because the attached atoms are not hydrogens

(although dashed and wedged lines *can* be used for hydrogens).The chlorine is coming out the page while bromine is going into the page.



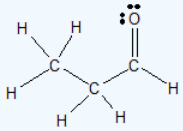
Blue bead=Cl; Red bead=Br

Example: Converting between Structural Formulas

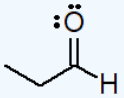
Throughout the course, it will be helpful to convert compounds into different structural formulas (Kekule (Lewis Structures), Bond-line, and Condensed) depending on the type of question that is asked. Standardized exams frequently include a high percentage of condensed formulas because it is easier and cheaper to type letters and numbers than to import figures. Initially, it can be tricky writing a bond-line structure directly from a condensed formula. First write the Kekule structure from the condensed formula and then draw the bond-line structure from the Kekule. Practice will quickly allow you to convert directly between condensed and bond-line structures.

The condensed formula for propanal is CH_3CH_2CHO. Can you visualize the bond-line structure of propanal? If yes, excellent, If no, the following practice will help.

The Kekule structure for propanal is shown below.

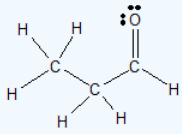


The bond-line structure for propanal is shown below.



All three structures represent the same compound, propanal.

CH_3CH_2CHO =



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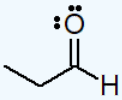
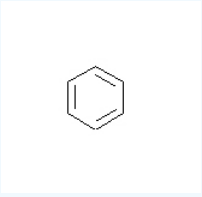
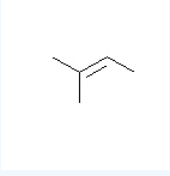


Exercises

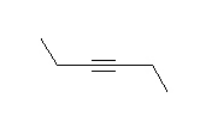
1. How many carbons are in the following drawing? How many hydrogens?



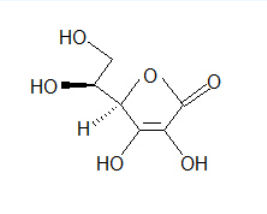
2. How many carbons are in the following drawing? How many hydrogens?



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



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

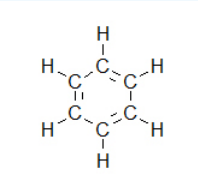


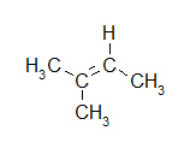
(hint: Do all of the carbons have 4 bonds? Do all the oxygens have a full octet?)

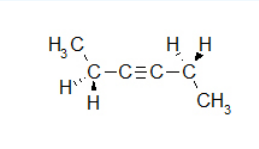
5. How many bonds can hydrogen make?
6. How many bonds can chlorine make?
7. Dashed lines means the atomic bond goes _____(away/toward) you.
8. Draw $ClCH_2CH_2CH(OCH_3)CH_3$ in Kekuléand zig-zag form.
9. Extra practice problems can be found _____?

Solutions

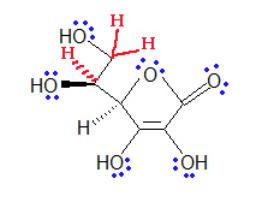
1. Remember the octet rule and how many times carbons and hydrogens are able to bond to other atoms.



2. 

3. 

4. Electron pairs drawn in blue and hydrogens draw in red.



5. Hygrogen can make one bond.
6. Chlorine can make one bond.
7. Away
8. See (B) under Kekulé and Bond-line (zig-zag) formulas.
9. Extra practice problems can be found: in your textbook, homework, lecture notes, online, reference books, and more. Try making up some of your own molecules, they may exist!

References

1. Vollhardt, K. Peter C., and Neil E. Schore. Organic Chemistry: Structure and Function. 5th ed. New York: W. H. Freeman Company, 2007. 38-40.
2. Klein, David R. Organic Chemistry I As a Second Language. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc, 2007. 1-14.

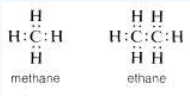
Outside Links

- Stereochemistry: en.Wikipedia.org/wiki/Stereochemistry
- Retinol: http://en.Wikipedia.org/wiki/Retinol
- Octet Rule: http://en.Wikipedia.org/wiki/Octet_rule
- Lewis Structures: chemwiki.ucdavis.edu/index.ph...wis+structures
- sp hybrid orbitals: chemwiki.ucdavis.edu/index.ph...s&highlight=sp
- For drawing organic molecules on the computer: http://bkchem.zirael.org/download_en.html

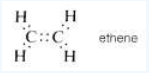
Contributors and Attributions

- Choo, Ezen (2009, UCD '11)

The building block of structural organic chemistry is the tetravalent carbon atom. With few exceptions, carbon compounds can be formulated with four covalent bonds to each carbon, regardless of whether the combination is with carbon or some other element. The two-electron bond, which is illustrated by the carbon-hydrogen bonds in methane or ethane and the carbon-carbon bond in ethane, is called a **single bond**. In these and many related substances, each carbon is attached to four other atoms:

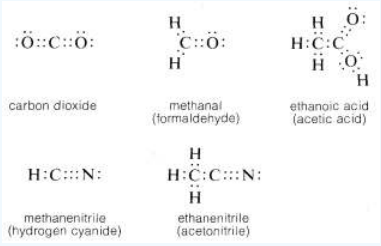


There exist, however, compounds such as ethene (ethylene), C_2H_4, in which two electrons from each of the carbon atoms are mutually shared, thereby producing *two* two-electron bonds, an arrangement which is called a **double bond**. Each carbon in ethene is attached to only three other atoms:

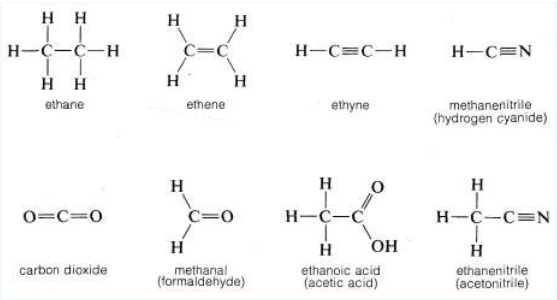


Similarly, in ethyne (acetylene), C_2H_2, three electrons from each carbon atom are mutually shared, producing *three* two-electron bonds, called a **triple bond**, in which each carbon is attached to only two other atoms:

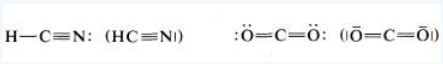
Of course, in all cases each carbon has a full octet of electrons. Carbon also forms double and triple bonds with several other elements that can exhibit a covalence of two or three. The carbon-oxygen (or carbonyl) double bond appears in carbon dioxide and many important organic compounds such as methanal (formaldehyde) and ethanoic acid (acetic acid). Similarly, a carbon-nitrogen triple bond appears in methanenitrile (hydrogen cyanide) and ethanenitrile (acetonitrile).



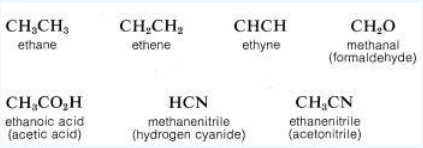
By convention, a single straight line connecting the atomic symbols is used to represent a single (two-electron) bond, two such lines to represent a double (four-electron) bond, and three lines a triple (six-electron) bond. Representations of compounds by these symbols are called **structural formulas**; some examples are



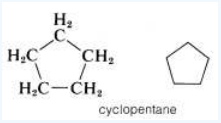
A point worth noting is that structural formulas usually do not indicate the *nonbonding* electron pairs. This is perhaps unfortunate because they play as much a part in the chemistry of organic molecules as do the bonding electrons and their omission may lead the unwary reader to overlook them. However, when it is important to represent them, this can be done best with pairs of dots, although a few authors use lines:



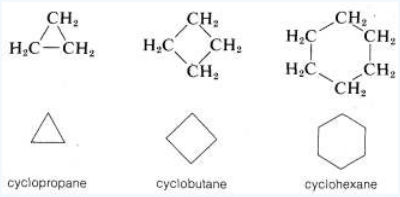
To save space and time in the representation of organic structures, it is common practice to use "condensed formulas" in which the bonds are not shown explicitly. In using condensed formulas, normal atomic valences are understood throughout. Examples of condensed formulas are



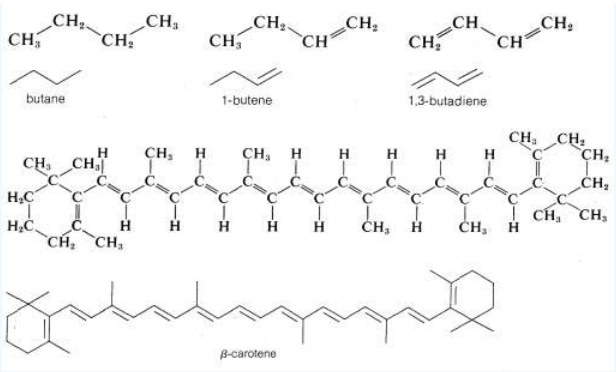
Another type of abbreviation that often is used, particularly for ring compounds, dispenses with the symbols for carbon and hydrogen atoms and leaves only the lines in a structural formula. For instance, cyclopentane, C_5H_{10}, often is represented as a regular pentagon in which it is understood that each apex represents a carbon atom with the requisite number of hydrogens to satisfy the tetravalence of carbon:



Likewise, cyclopropane, C_3H_6; cyclobutane, C_4H_8; and cyclohexane, C_6H_{12}, are drawn as regular polygons:



Although this type of line drawing is employed most commonly for cyclic structures, its use for open chain (acyclic) structures is becoming increasingly widespread. There is no special merit to this abbreviation for simple structures such as butane, C_4H_{10}; 1-butene, C_4H_8; or 1,3-butadiene, C_4H_6, but it is of value in representing more complex molecules such as β-carotene, $C_{40}H_{56}$:



Line structures also can be modified to represent the three-dimensional *shapes* of molecules, and the way that this is done will be discussed in detail in Chapter 5. At the onset of you study of organic chemistry, you should write out the formulas rather completely until you are thoroughly familiar with what these abbreviations stand for.

Contributors and Attributions

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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1.9: Electronegativity and Bond Polarity (Review)

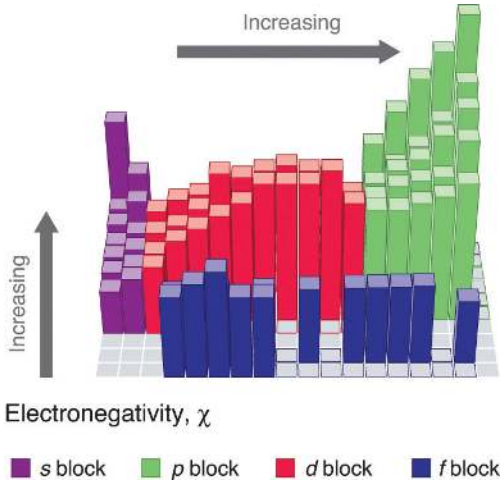
Learning Objective

- Identify polar bonds and compounds

Electronegativity is a measure of the tendency of an atom to attract a bonding pair of electrons. The Pauling scale is the most commonly used. Fluorine (the most electronegative element) is assigned a value of 4.0, and values range down to cesium and francium which are the least electronegative at 0.7.

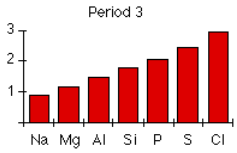
Patterns of electronegativity in the Periodic Table

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



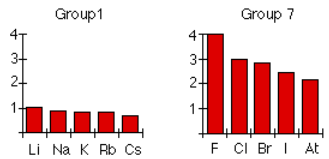
Trends in electronegativity across a period

The positively charged protons in the nucleus attract the negatively charged electrons. As the number of protons in the nucleus increases, the electronegativity or attraction will increase. Therefore electronegativity **increases** from **left to right** in a row in the periodic table. This effect only holds true for a row in the periodic table because the attraction between charges falls off rapidly with distance. The chart shows electronegativities from sodium to chlorine (ignoring argon since it does not does not form bonds).



Trends in electronegativity down a group

As you go down a group, electronegativity decreases. (If it increases up to fluorine, it must decrease as you go down.) The chart shows the patterns of electronegativity in Groups 1 and 7.



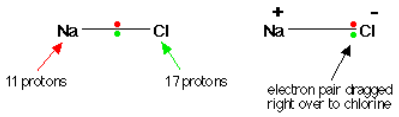
Explaining the patterns in electronegativity

The attraction that a bonding pair of electrons feels for a particular nucleus depends on:

- the number of protons in the nucleus;
- the distance from the nucleus;
- the amount of screening by inner electrons.

Why does electronegativity increase across a period?

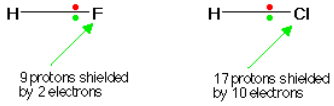
Consider sodium at the beginning of period 3 and chlorine at the end (ignoring the noble gas, argon). Think of sodium chloride as if it were covalently bonded.



Both sodium and chlorine have their bonding electrons in the 3-level. The electron pair is screened from both nuclei by the 1s, 2s and 2p electrons, but the chlorine nucleus has 6 more protons in it. It is no wonder the electron pair gets dragged so far towards the chlorine that ions are formed. Electronegativity increases across a period because the number of charges on the nucleus increases. That attracts the bonding pair of electrons more strongly.

Why does electronegativity fall as you go down a group?

As you go **down** a group, electronegativity **decreases** because the bonding pair of electrons is increasingly distant from the attraction of the nucleus. Consider the hydrogen fluoride and hydrogen chloride molecules:



The bonding pair is shielded from the fluorine's nucleus only by the $1s^2$ electrons. In the chlorine case it is shielded by all the $1s^2 2s^2 2p^6$ electrons. In each case there is a net pull from the center of the fluorine or chlorine of +7. But fluorine has the bonding pair in the 2-level rather than the 3-level as it is in chlorine. If it is closer to the nucleus, the attraction is greater.

Dipole moments occur when there is a separation of charge. They can occur between two ions in an ionic bond or between atoms in a covalent bond; dipole moments arise from differences in electronegativity. The larger the difference in electronegativity, the larger the dipole moment. The distance between the charge separation is also a deciding factor into the size of the dipole moment. The dipole moment is a measure of the polarity of the molecule.

Bond Polarity & Dipole Moment

Atoms with differences in electronegativity will share electrons unequally. The shared electrons of the covalent bond are held more tightly at the more electronegative element creating a partial negative charge, while the less electronegative element has a partial positive charge, . The larger the difference in electronegativity between the two atoms, the more polar the bond. To be considered a polar bond, the difference in electronegativity must >0.4 on the Pauling scale. Since the two electrical partial charges have opposite sign and equal magnitude and are separated by a distance, a **dipole** is established. Dipole moment is measured in debye units, which is equal to the distance between the charges multiplied by the charge (1 debye equals 3.34×10^{-30} coulomb-meters).

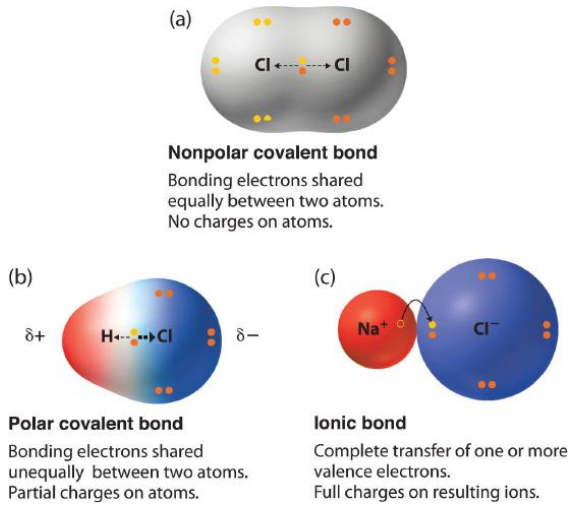


Figure **1.9.4**: The Electron Distribution in a Nonpolar Covalent Bond, a Polar Covalent Bond, and an Ionic Bond Using Lewis Electron Structures. In a purely covalent bond (a), the bonding electrons are shared equally between the atoms. In a purely ionic bond (c), an electron has been transferred completely from one atom to the other. A polar covalent bond (b) is intermediate between the two extremes: the bonding electrons are shared unequally between the two atoms, and the electron distribution is asymmetrical with the electron density being greater around the more electronegative atom. Electron-rich (negatively charged) regions are shown in blue; electron-poor (positively charged) regions are shown in red.

Polarity and Structure of Molecules

The shape of a molecule AND the polarity of its bonds. A molecule that contains polar bonds, might not have any overall polarity, depending upon its shape. The simple definition of whether a complex molecule is polar or not depends upon whether its overall centers of positive and negative charges overlap. If these centers lie at the same point in space, then the molecule has no overall polarity (and is non polar).

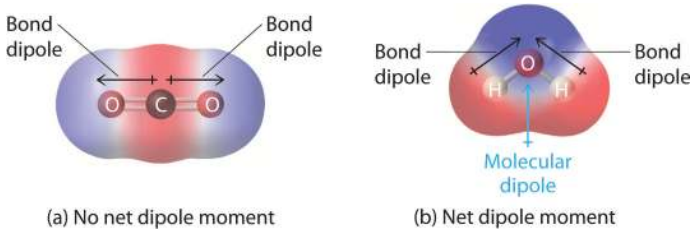


Figure 3: Charge distrubtions

If a molecule is completely symmetric, then the dipole moment vectors on each molecule will cancel each other out, making the molecule nonpolar. A molecule can only be polar if the structure of that molecule is not symmetric.

A good example of a nonpolar molecule that contains polar bonds is carbon dioxide. This is a linear molecule and the C=O bonds are, in fact, polar. The central carbon will have a net positive charge, and the two outer oxygens a net negative charge. However, since the molecule is linear, these two bond dipoles cancel each other out (i.e. vector addition of the dipoles equals zero). And the overall molecule has no dipole ($\mu = 0$.

Although a polar bond is a prerequisite for a molecule to have a dipole, not all molecules with polar bonds exhibit dipoles

Geometric Considerations

Example 1: Polar Bonds vs. Polar Molecules

In a simple diatomic molecule like HCl, if the bond is polar, then the whole molecule is polar. What about more complicated molecules?

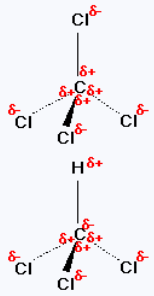


Figure: (left) CCl_4 (right) $CHCl_3$

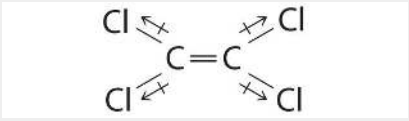
Consider CCl_4, (left panel in figure above), which as a molecule is not polar - in the sense that it doesn't have an end (or a side) which is slightly negative and one which is slightly positive. The whole of the outside of the molecule is somewhat negative, but there is no overall separation of charge from top to bottom, or from left to right.

In contrast, $CHCl_3$ is a polar molecule (right panel in figure above). 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.

A polar molecule will need to be "lop-sided" in some way.

Example 2:

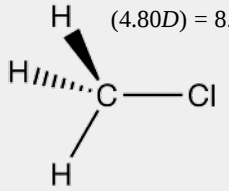
Although the C–Cl bonds are rather polar, the individual bond dipoles cancel one another in this symmetrical structure, and $Cl_2C=CCl_2$ does not have a net dipole moment.



Example 3:

C-Cl, the key polar bond, is 178 pm. Measurement reveals 1.87 D. From this data, % ionic character can be computed. If this bond were 100% ionic (based on proton & electron),

$$\mu = (4.80D) = 8.54D$$



Example 4:

Since measurement 1.87 D,
% ionic = (1.7/8.54)x100 = 22%
u = 1.03 D (measured) H-Cl bond length 127 pm
If 100% ionic,

$$\mu = (4.80D) = 6.09D$$

ionic = (1.03/6.09)x100 = 17%

A "spectrum" of bonds

The implication of all this is that there is no clear-cut division between covalent and ionic bonds. In a pure 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.

Summary

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

Example 1: Polar Bonds vs. Polar Molecules

In a simple diatomic molecule like HCl, if the bond is polar, then the whole molecule is polar. What about more complicated molecules?

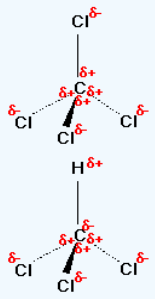


Figure: (left) CCl_4 (right) $CHCl_3$

Consider CCl_4, (left panel in figure above), 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). 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.

A polar molecule will need to be "lop-sided" in some way.

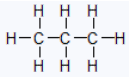
Exercises

For the following compounds,

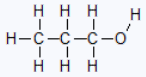
a) add lone pairs of electrons to complete octets

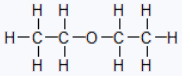
b) add dipole moment arrows or partial +/- signs to indicate polar bonds

c) predict the molecular polarity (Remember to visualize each compound in three dimensions.)

a) 

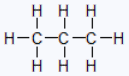
b)

c) 

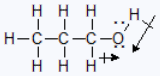
d) 

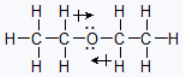
e)

Solutions

a)  nonpolar

b) nonpolar

c)  polar

d)  polar - molecular shape is bent around the oxygen atom

e) polar

Contributors and Attributions

- *Mike Blaber* (*Florida State University*)
- Jim Clark (Chemguide.co.uk)
- Prof. Richard Bank, Boise State University, Emeritus,

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1.10: Resonance

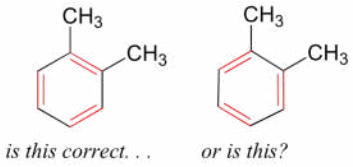
Learning Objective

- Draw resonance forms and predict the relative contribution of each resonance form to the overall structure of the compound or ion

Recognizing resonance

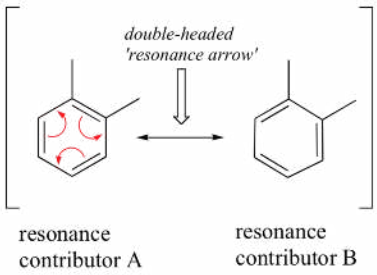
Resonance contributors involve the ‘imaginary movement’ of pi-bonded electrons or of lone-pair electrons that are adjacent to (i.e. conjugated to) pi bonds. You can never shift the location of electrons in sigma bonds – if you show a sigma bond forming or breaking, you are showing a chemical reaction 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 strucutres. 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:



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:

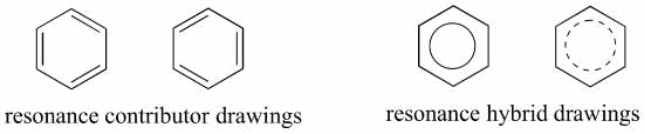


In order to make it easier to visualize the difference between two resonance contributors, small, curved arrows are often used. Each of these arrows depicts the ‘movement’ of two pi electrons. A few chapters from now when we begin to study organic reactions - a process in which electron density shifts and covalent bonds between atoms break and form - this ‘curved arrow notation’ will become extremely important in depicting electron movement. 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.

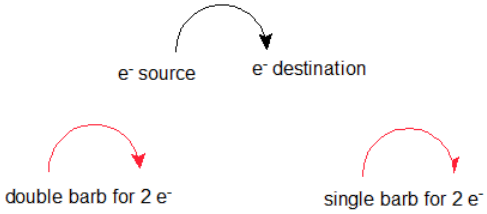
Caution! It is very important to be clear that in drawing two (or more) resonance contributors, we are not drawing two different molecules: they are simply *different depictions of the exact same molecule*. Furthermore, the double-headed resonance arrow does NOT mean that a chemical reaction has taken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

Usually, derivatives of benzene (and phenyl groups, when the benzene ring is incorporated into a larger organic structure) are depicted with only one resonance contributor, and it is assumed that the reader understands that resonance hybridization is implied. This is the convention that will be used for the most part in this book. In other books or articles, you may sometimes see benzene or a phenyl group drawn with a circle inside the hexagon, either solid or dashed, as a way of drawing a resonance hybrid.

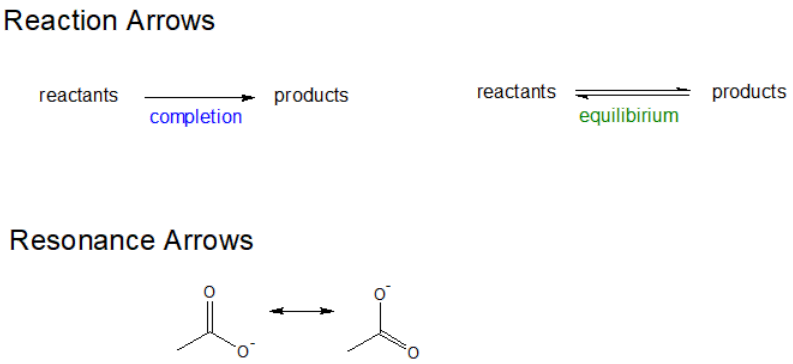


Curved arrows communicate electron flow (movement)

Curved arrows indicate electron flow. 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. A single barbed arrow represents one electron and a double barb represents two electrons. Electrons move from regions of relative high density to regions of low density or toward electronegative elements. It is important to use accuracy and precision when drawing curved arrows.



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, resonance forms. The three other types of arrows are shown below to build discernment between them.



Resonance Delocalizes Charge to Increase Stability

Resonance is most useful wen it delocalizes charge to stabilize reactive intermediates and products. Recognizing, drawing, and evaluating the relative stability of resonance contributors is essential to understanding organic reaction mechanisms.

Guidelines for drawing and working with resonance contributors

Learning to draw and interpret resonance structures, there are a few basic guidelines to help avoid drawing nonsensical structures. All of these guidellines make perfect sense as long as we remember that resonance contributors are merely a human-invented convention for depicting the delocalization of pi electrons in conjugated systems. When we see two different resonance contributors, we are not seeing a chemical reaction! We are seeing the exact same molecule or ion depicted in two different ways. All resonance contributors must be drawn as proper Lewis structures, with correct formal charges. Never show curved 'electron

movement' arrows that would lead to a situation where a second-row element (ie. carbon, nitrogen, or oxygen) has more than eight electrons: this would break the 'octet rule'. Sometimes, however, we will draw resonance contributors in which a carbon atom has only six electrons (ie. a carbocation). In general, all oxygen and nitrogen atoms should have a complete octet of valence electrons.

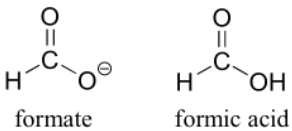
1. There is ONLY ONE STRUCTURE for each compound or ion. This structure takes its character from the sum of all the contributors, not all resonance structures contribute equally to the sum.
2. Atoms must maintain their same position.
3. Only e- move !
4. All resonance contributors for a molecule or ion must have the same net charge.
5. Recognize which electrons can participate in resonance
    a) unshared e^- pairs or radicals
    b) pi bond electrons
6. Recognize electron receptors
    a) atoms with a positive (+) charge
    b) electronegative atoms that can tolerate a negative charge
    c) atoms which possess delocalizable electrons - see #4 above
7. Common electron flow patterns
    a) move pi e^- toward positive (+) charge or other pi bonds
    b) move non-bonding e^- pairs toward pi bonds
    c) move single non-bonding e^- toward pi bonds

Evaluating Resonance Contributors

1. Identical structures are equally important.
2. Structures will a greater number of bonds are more important.
3. Structures with charge separation are less important.
4. Pay attention to electronegativities.
5. Neutral atoms need to have complete octets.

Resonance Contributors for the Carboxylate Group

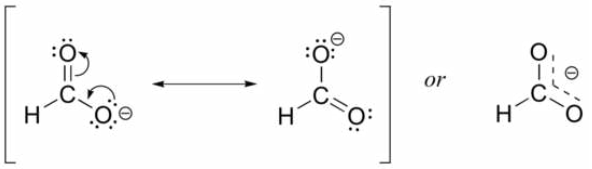
The convention of drawing two or more resonance contributors to approximate a single structure may seem a bit clumsy to you at this point, but as you gain experience you will see that the practice is actually very useful when discussing the manner in which many functional groups react. Let’s next consider the carboxylate ion (the conjugate base of a carboxylic acid). As our example, we will use formate, the simplest possible carboxylate-containing molecule. The conjugate acid of formate is formic acid, which causes the painful sting you felt if you have ever been bitten by an ant.



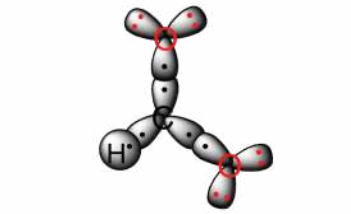
formate formic acid

Usually, you will see carboxylate groups drawn with one carbon-oxygen double bond and one carbon-oxygen single bond, with a negative formal charge located on the single-bonded oxygen. In actuality, however, the two carbon-oxygen bonds are the same length, and although there is indeed an overall negative formal charge on the group, it is shared equally between the two oxygens. Therefore, the carboxylate 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.

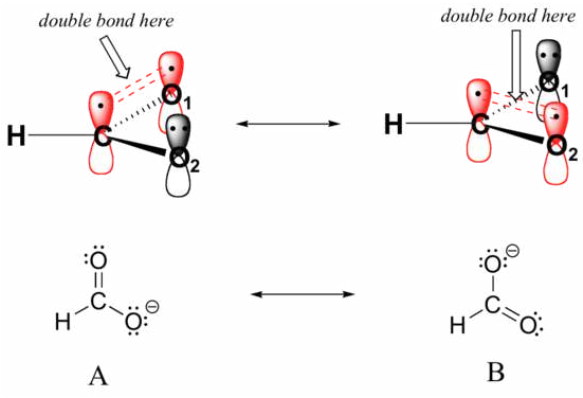


Let's see if we can correlate these drawing conventions to a valence bond theory picture of the bonding in a carboxylate group. We know that the carbon must be sp^2-hybridized, (the bond angles are close to 120˚, and the molecule is planar), and we will treat both oxygens as being sp^2-hybridized as 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

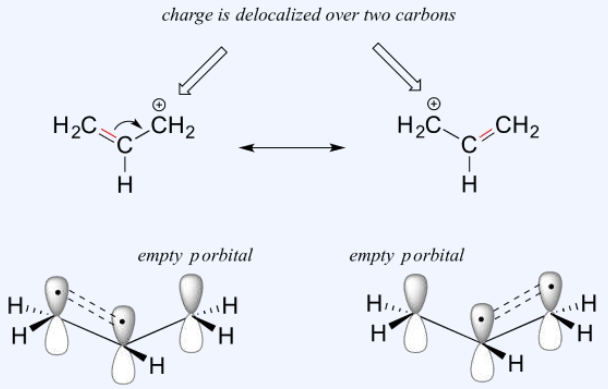
In addition, the carbon and both oxygens each have an unhybridized $2p_z$ orbital situated perpendicular to the plane of the sigma bonds. These three $2p_z$ orbitals are parallel to each other, and can overlap in a side-by-side fashion to form a delocalized pi bond.



Resonance contributor A shows oxygen #1 sharing a pair of electrons with carbon in a pi bond, and oxygen #2 holding a lone pair of electrons in its $2p_z$ orbital. Resonance contributor B, on the other hand, shows oxygen #2 participating in the pi bond with carbon, and oxygen #1 holding a lone pair in its $2p_z$ orbital. 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. This is the kind of 3D picture that resonance contributors are used to approximate, and once you get some practice you should be able to quickly visualize overlapping $2p_z$ orbitals and delocalized pi electrons whenever you see resonance structures being used. In this text, carboxylate groups will usually be drawn showing only one resonance contributor for the sake of simplicity, but you should always keep in mind that the two C-O bonds are equal, and that the negative charge is delocalized to both oxygens.

Exercise 2.13: There is a third resonance contributor for formate (which we will soon learn is considered a 'minor' contributor). Draw this resonance contributor.

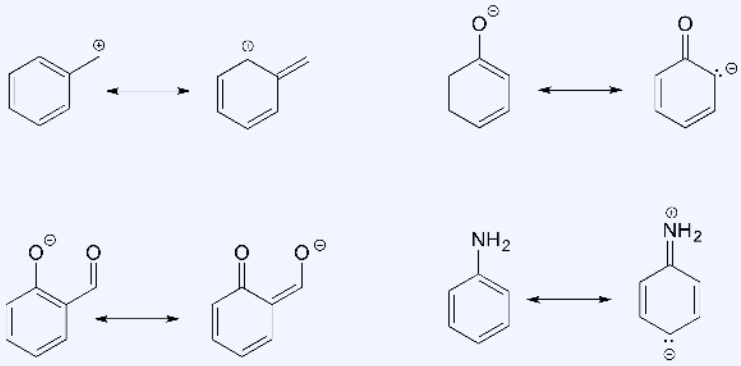
Here's another example, this time with a carbocation. Recall from section 2.1 that carbocations are sp^2-hybridized, with an empty *2p* orbital oriented perpendicular to the plane formed by three sigma bonds. If a carbocation is adjacent to a double bond, then three *2p* orbitals can overlap and share the two pi electrons - another kind of conjugated pi system in which the positive charge is shared over two carbons.



three *p* orbitals sharing two ≠ electrons

Exercise 2.14: Draw the resonance contributors that correspond to the curved, two-electron movement arrows in the resonance expressions below.

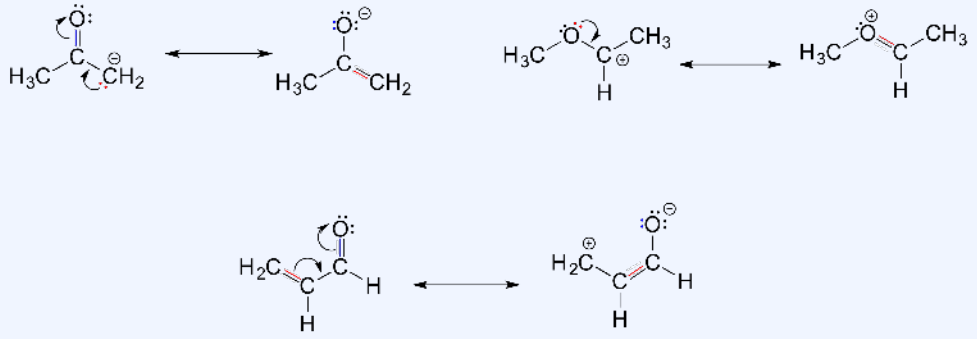
Exercise 2.15: In each resonance expression, draw curved two-electron movement arrows on the left-side contributor that shows how we get to the right-side contributor. Be sure to include formal charges.



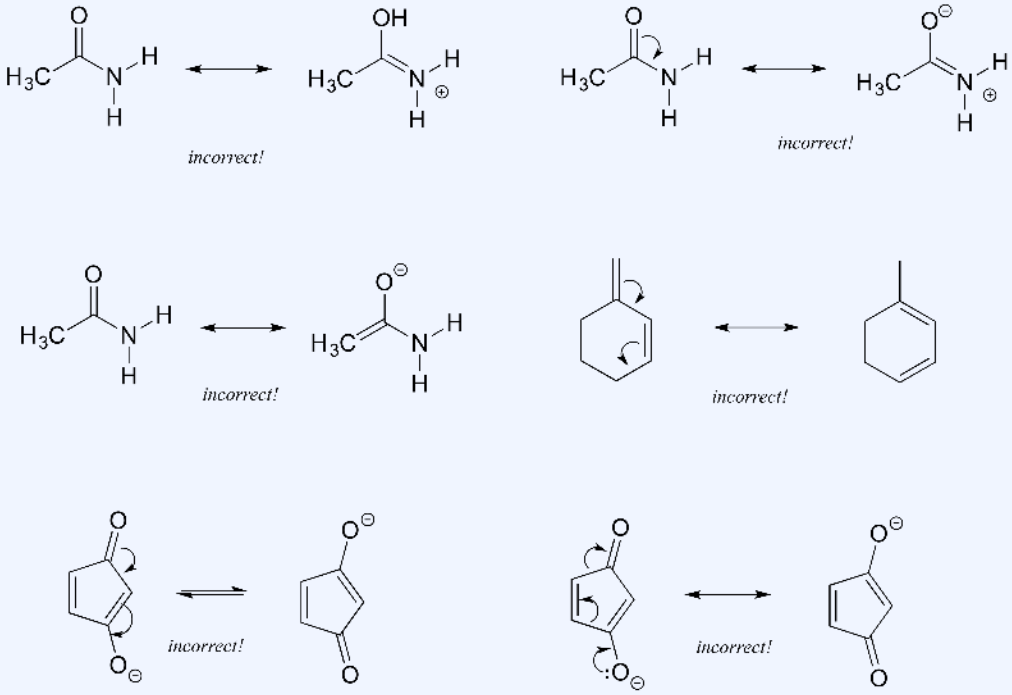
Solutions to exercises

Guided Resonance Practice

Below are a few more examples of 'legal' resonance expressions. Confirm for yourself that the octet rule is not exceeded for any atoms, and that formal charges are correct.



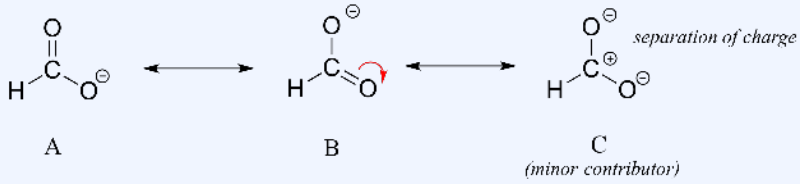
Exercise 2.16: Each of the 'illegal' resonance expressions below contains one or more mistakes. Explain what is incorrect in each.



Solutions to exercises

Major vs minor resonance contributors

Different resonance contributors do not always make the same contribution to the overall structure of the hybrid - rather, in many cases one contributor comes closer to depicting the actual bonding picture than another. 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 and both oxygens are single-bonded and bear negative charges.



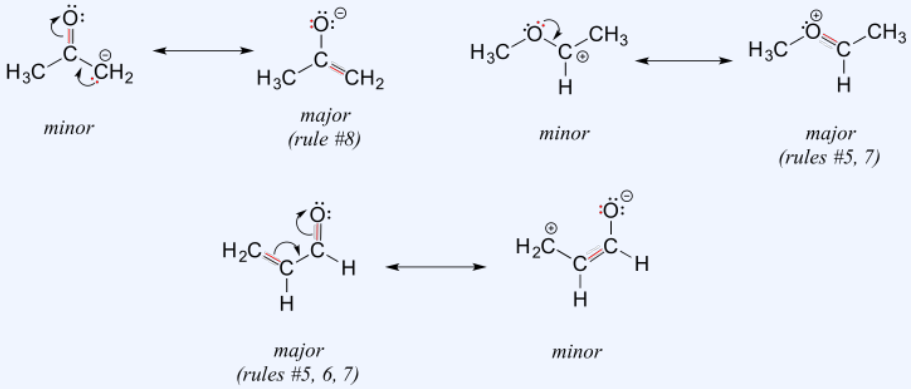
Structure C makes a less important contribution to the overall bonding picture of the group relative to A and B. How do we know that structure C is the 'minor' contributor? There are four basic rules which you need to learn in order

to evaluate the relative importance of different resonance contributors. We will number them 5-8 so that they may be added to in the 'rules for resonance' list earlier on this page.

Rules for determining major and minor resonance contributors:

5. 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.
6. In structure C, a separation of charge has been introduced that is not present in A or B. In general, resonance contributors in which there is a greater separation of charge are relatively less important.
7. 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.
8. 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.

Below are some additional examples of major and minor resonance contributors:

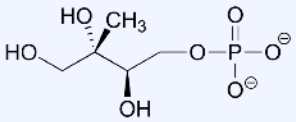


Why do we worry about a resonance contributor if it is the minor one? We will see later that very often a minor contributor can still be extremely important to our understanding of how a molecule reacts.

Exercise 2.17:

a. Draw a minor resonance structure for acetone (IUPAC name 2-propanone). Explain why it is a minor contributor.
b. Are acetone and 2-propanol resonance contributors of each other? Explain.

Exercise 2.18: Draw four additional resonance contributors for the molecule below. Label each one as major or minor (the structure below is of a major contributor).



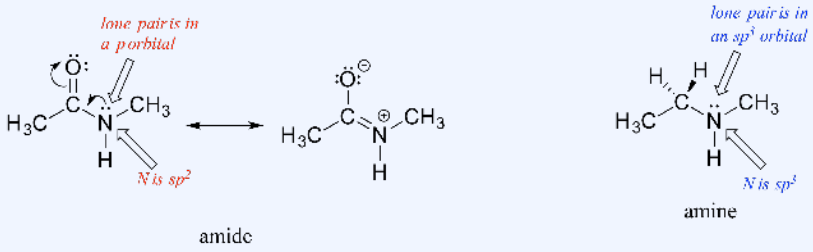
Exercise 2.19: Draw three resonance contributors of methyl acetate (IUPAC name methyl methanoate), and order them according to their relative importance to the bonding picture of the molecule. Explain your reasoning.

Solutions to exercises

Resonance and peptide bonds

What is the hybridization state of the nitrogen atom in an amide? At first glance, it would seem logical to say that it is sp^3-hybridized, because, like the nitrogen in an amine, the Lewis structure shows three single bonds and a lone pair. The picture looks quite different, though, if we consider another resonance contributor in which

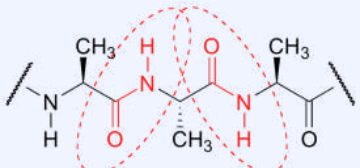
the nitrogen has a double bond to the carbonyl carbon: in this case, we would have to say that applicable hybridization is sp^2, and the bonding geometry trigonal planar rather than tetrahedral.



amide amine

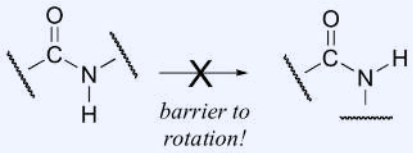
In fact, the latter picture is more accurate: the lone pair of electrons on an amide nitrogen are not localized in an sp^3 orbital, rather, they are delocalized as part of a conjugated pi system, and the bonding geometry around the nitrogen is trigonal planar as expected for sp^2 hybridization. This is a good illustration of an important point: conjugation and the corresponding delocalization of electron density is stabilizing, thus if conjugation can occur, it probably will.

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

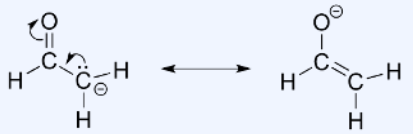
Critical to the structure of proteins is the fact that, although it is conventionally drawn as a single bond, *the C-N bond in a peptide linkage has a significant barrier to rotation*, indicating that to some degree, C-N pi overlap is present - in other words, there is some double bond character, and the nitrogen is sp^2 hybridized with trigonal planar geometry.



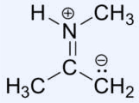
The barrier to rotation in peptide bonds is an integral part of protein structure, introducing more rigidity to the protein's backbone. If there were no barrier to rotation in a peptide bond, proteins would be much more 'floppy' and three dimensional folding would be very different.

Exercise 2.20: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in methyl amide. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping *2p* orbitals are sharing how many pi-bonded electrons?

Exercise 2.21: Draw two pictures showing the unhybridized *2p* orbitals and the location of pi electrons in the 'enolate' anion shown below. One picture should represent the major resonance contributor, the other the minor contributor. How many overlapping 2*p* orbitals are sharing how many pi-bonded electrons?

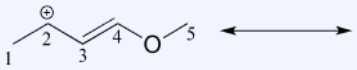


Exercise 2.22: Below is a minor resonance contributor of a species known as an 'enamine', which we will study more in chapter 12. Draw the major resonance contributor for the enamine, and explain why your contributor is the major one (refer to resonance rules #5-8 from this section).

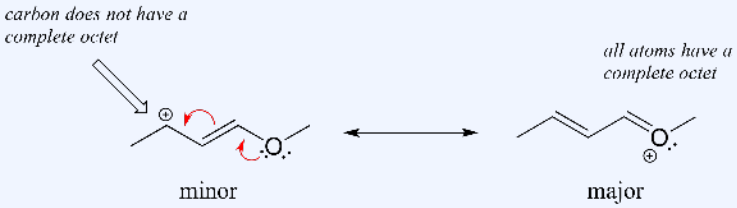


Solutions to exercises

Solved example: 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?

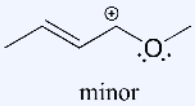


Solution: In the structure above, the carbon with the positive formal charge does not have a complete octet of valence electrons. Using the curved arrow convention, a lone pair on the oxygen can be moved to the adjacent bond to the left, and the electrons in the double bond shifted over to the left (see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



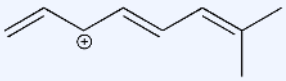
The resulting resonance contributor, in which the oxygen bears the formal charge, is the major one because all atoms have a complete octet, and there is one additional bond drawn (resonance rules #5 and #7 both apply). This system can be thought of as four parallel *2p* orbitals (one each on C_2, C_3, 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:



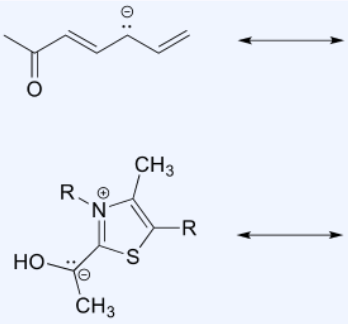
Exercise 2.23:

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

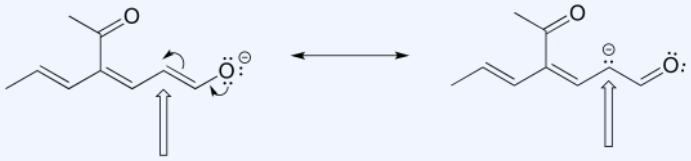


c) Fill in the blanks: the conjugated pi system in part (a) is composed of _____ *2p* orbitals containing _____ delocalized pi electrons.

Exercise 2.25: 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.



Solutions to exercises

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 you will be in for a rough ride, to say the least. More so than many other topics in organic chemistry, *understanding bonding, conjugation, and resonance is something that most students really need to work on 'in person' with an instructor or tutor, preferably using a molecular modeling kit*. Keep working problems, keep asking questions, and keep at it until it all makes sense!

Kahn Academy video tutorials

Drawing resonance structures

More on resonance

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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1.11: Arrhenius Acids and Bases (Review)

LEARNING objective

- recognize acids or bases

Introduction

In 1884, the Swedish chemist Svante Arrhenius proposed two specific classifications of compounds, termed acids and bases. When dissolved in an aqueous solution, certain ions were released into the solution. As defined by Arrhenius, acid-base reactions are characterized by acids, which dissociate in aqueous solution to form hydrogen ions (H^+) and bases, which form hydroxide (OH^-) ions. Arrhenius received the lowest passing score for his doctoral thesis with these innovative ideas about acids and bases. Ten years later he was awarded the Nobel Prize for his insights.

Acids are defined as a compound or element that releases hydrogen (H^+) ions into the solution (mainly water).

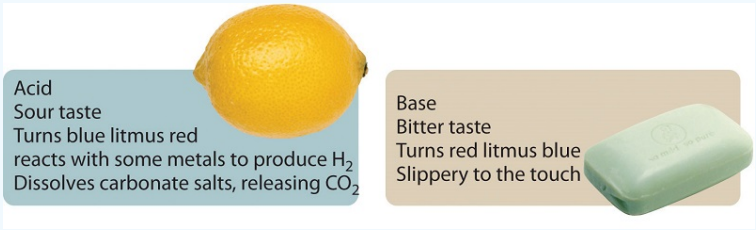
$$\mathbf{NHO_3\,(aq) + H_2O\,(l) \rightarrow H_3O^+ + NO_3^-\,(aq)} \tag{1.11.1}$$

In this reaction nitric acid (HNO_3) disassociates into hydrogen (H^+) and nitrate (NO_3^-) ions when dissolved in water. Bases are defined as a compound or element that releases hydroxide (OH^-) ions into the solution.

$$\mathbf{LiOH\,(s) \xrightarrow{H_2O} Li^+\,(aq) + OH^-\,(aq)} \tag{1.11.2}$$

In this reaction lithium hydroxide (**LiOH**) dissociates into lithium (Li^+) and hydroxide (OH^-) ions when dissolved in water.

One way to define a class of compounds is by describing the various characteristics its members have in common. In the case of the compounds known as acids, the common characteristics include a sour taste, the ability to change the color of the vegetable dye *litmus* to red, and the ability to dissolve certain metals and simultaneously produce hydrogen gas. For the compounds called bases, the common characteristics are a slippery texture, a bitter taste, and the ability to change the color of litmus to blue. Acids and bases also react with each other to form compounds generally known as salts.



Although we include their tastes among the common characteristics of acids and bases, we never advocate tasting an unknown chemical!

Chemists prefer, however, to have definitions for acids and bases in chemical terms. The Swedish chemist Svante Arrhenius developed the first chemical definitions of acids and bases in the late 1800s. Arrhenius defined an acid as a compound that increases the concentration of hydrogen ion (H^+) in aqueous solution. Many acids are simple compounds that release a hydrogen cation into solution when they dissolve. Similarly, Arrhenius defined a base as a compound that increases the concentration of hydroxide ion (OH^-) in aqueous solution. Many bases are ionic compounds that have the hydroxide ion as their anion, which is released when the base dissolves in water.

Table **1.11.1**: Formulas and Names for Some Acids and Bases

Acids		Bases	
Formula	Name	Formula	Name
HCl(aq)	hydrochloric acid	NaOH(aq)	sodium hydroxide
HBr(aq)	hydrobromic acid	KOH(aq)	potassium hydroxide
HI(aq)	hydriodic acid	$Mg(OH)_2$(aq)	magnesium hydroxide
H_2S(aq)	hydrosulfuric acid	$Ca(OH)_2$(aq)	calcium hydroxide
$HC_2H_3O_2$(aq)	acetic acid	NH_3(aq)	ammonia
HNO_3(aq)	nitric acid		
HNO_2(aq)	nitrous acid		
H_2SO_4(aq)	sulfuric acid		
H_2SO_3(aq)	sulfurous acid		
$HClO_3$(aq)	chloric acid		
$HClO_4$(aq)	perchloric acid		
$HClO_2$(aq)	chlorous acid		
H_3PO_4(aq)	phosphoric acid		
H_3PO_3(aq)	phosphorous acid		

Many bases and their aqueous solutions are named using the normal rules of ionic compounds that were presented previously; that is, they are named as hydroxide compounds. For example, the base sodium hydroxide (NaOH) is both an ionic compound and an aqueous solution. However, aqueous solutions of acids have their own naming rules. The names of *binary acids* (compounds with hydrogen and one other element in their formula) are based on the root of the name of the other element preceded by the prefix *hydro-* and followed by the suffix *-ic acid*. Thus, an aqueous solution of HCl [designated "HCl(aq)"] is called hydrochloric acid, H_2S(aq) is called hydrosulfuric acid, and so forth. Acids composed of more than two elements (typically hydrogen and oxygen and some other element) have names based on the name of the other element, followed by the suffix *-ic acid* or *-ous acid*, depending on the number of oxygen atoms in the acid's formula. Other prefixes, like *per-* and *hypo-*, also appear in the names for some acids. Unfortunately, there is no strict rule for the number of oxygen atoms that are associated with the *-ic acid* suffix; the names of these acids are best memorized. Table **1.11.1** lists some acids and bases and their names. Note that acids have hydrogen written first, as if it were the cation, while most bases have the negative hydroxide ion, if it appears in the formula, written last.

> *The name oxygen comes from the Latin meaning "acid producer" because its discoverer, Antoine Lavoisier, thought it was the essential element in acids. Lavoisier was wrong, but it is too late to change the name now.*

Example 1.11.1

Name each substance.

a. HF(aq)
b. $Sr(OH)_2$(aq)

Solution

a. This acid has only two elements in its formula, so its name includes the *hydro-* prefix. The stem of the other element's name, fluorine, is *fluor*, and we must also include the *-ic acid* ending. Its name is hydrofluoric acid.

b. This base is named as an ionic compound between the strontium ion and the hydroxide ion: strontium hydroxide.

Exercise 1.11.1

Name each substance.

a. $H_2Se(aq)$
b. $Ba(OH)_2(aq)$

Notice that one base listed in Table **1.11.1**—ammonia—does not have hydroxide as part of its formula. How does this compound increase the amount of hydroxide ion in aqueous solution? Instead of dissociating into hydroxide ions, ammonia molecules react with water molecules by taking a hydrogen ion from the water molecule to produce an ammonium ion and a hydroxide ion:

$$NH_{3(aq)} + H_2O_{(\ell)} \rightarrow NH^+_{4(aq)} + OH^-_{(aq)} \tag{1.11.3}$$

Because this reaction of ammonia with water causes an increase in the concentration of hydroxide ions in solution, ammonia satisfies the Arrhenius definition of a base. Many other nitrogen-containing compounds are bases because they too react with water to produce hydroxide ions in aqueous solution.

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1.12: Brønsted-Lowry Acids and Bases (Review)

learning objective

- recognize acids and bases

The Brønsted-Lowry Theory of Acids and Bases

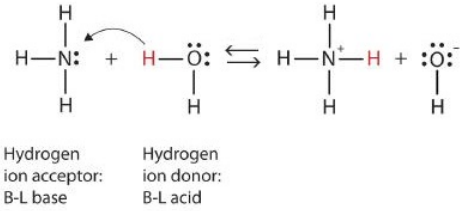
In 1923, Danish chemist Johannes Brønsted and English chemist Thomas Lowry independently proposed new definitions for acids and bases, ones that focus on proton transfer. A **Brønsted-Lowry acid** is any species that can donate a proton (H^+) to another molecule. A **Brønsted-Lowry base** is any species that can accept a proton from another molecule. In short, **a Brønsted-Lowry acid** is a **proton donor (PD)**, while **a Brønsted-Lowry base** is a **proton acceptor (PA)**.

> *A Brønsted-Lowry acid is a proton donor, while a Brønsted-Lowry base is a proton acceptor.*

Let us use the reaction of ammonia in water to demonstrate the Brønsted-Lowry definitions of an acid and a base. Ammonia and water molecules are reactants, while the ammonium ion and the hydroxide ion are products:

$$\mathbf{NH_3\,(aq) + H_2O\,(\ell) \rightleftharpoons NH_4^+\,(aq) + OH^-\,(aq)} \tag{1.12.1}$$

What has happened in this reaction is that the original water molecule has donated a hydrogen ion to the original ammonia molecule, which in turn has accepted the hydrogen ion. We can illustrate this as follows:

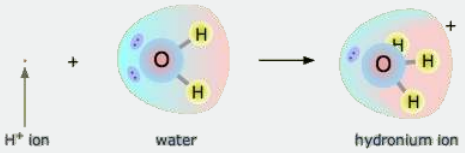


Because the water molecule donates a hydrogen ion to the ammonia, it is the Brønsted-Lowry acid, while the ammonia molecule—which accepts the hydrogen ion—is the Brønsted-Lowry base. Thus, ammonia acts as a base in both the Arrhenius sense and the Brønsted-Lowry sense.

Is an Arrhenius acid like hydrochloric acid still an acid in the Brønsted-Lowry sense? Yes, but it requires us to understand what really happens when HCl is dissolved in water. Recall that the hydrogen *atom* is a single proton surrounded by a single electron. To make the hydrogen *ion*, we remove the electron, leaving a bare proton. Do we *really* have bare protons floating around in aqueous solution? No, we do not. What really happens is that the H^+ ion attaches itself to H_2O to make H_3O^+, which is called the *hydronium ion*. For most purposes, H^+ and H_3O^+ represent the same species, but writing H_3O^+ instead of H^+ shows that we understand that there are no bare protons floating around in solution. Rather, these protons are actually attached to solvent molecules.

The Hydronium IOn

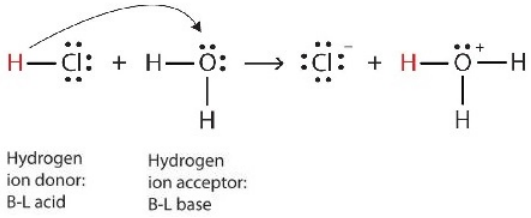
A proton in aqueous solution may be surrounded by more than one water molecule, leading to formulas like $\mathbf{H_5O_2^+}$ or $\mathbf{H_9O_4^+}$ rather than $\mathbf{H_3O^+}$. It is simpler, however, to use $\mathbf{H_3O^+}$ to represent the hydronium ion.



With this in mind, how do we define HCl as an acid in the Brønsted-Lowry sense? Consider what happens when HCl is dissolved in H_2O:

$$\mathrm{HCl\,(g) + H_2O\ (\ell)\ \rightarrow H_3O^+\,(aq) + Cl^-\,(aq)} \tag{1.12.2}$$

We can depict this process using Lewis electron dot diagrams:



Now we see that a hydrogen ion is transferred from the HCl molecule to the H_2O molecule to make chloride ions and hydronium ions. As the hydrogen ion donor, HCl acts as a Brønsted-Lowry acid; as a hydrogen ion acceptor, H_2O is a Brønsted-Lowry base. So HCl is an acid not just in the Arrhenius sense but also in the Brønsted-Lowry sense. Moreover, by the Brønsted-Lowry definitions, H_2O is a base in the formation of aqueous HCl. So the Brønsted-Lowry definitions of an acid and a base classify the dissolving of HCl in water as a reaction between an acid and a base—although the Arrhenius definition would not have labeled H_2O a base in this circumstance.

- A Brønsted-Lowry acid is a proton (hydrogen ion) donor.
- A Brønsted-Lowry base is a proton (hydrogen ion) acceptor.
- All Arrhenius acids and bases are Brønsted-Lowry acids and bases as well. However, not all Brønsted-Lowry acids and bases are Arrhenius acids and bases.

Example 1.12.1

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:

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

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.

Exercise 1.12.1

Identify the Brønsted-Lowry acid and the Brønsted-Lowry base in this chemical equation.

$$\mathrm{H_2PO_4^- + H_2O \rightleftharpoons HPO_4^{2-} + H_3O^+} \tag{1.12.3}$$

Answer:

Brønsted-Lowry acid: $H_2PO_4^-$; Brønsted-Lowry base: H_2O

Exercise 1.12.2

Which of the following compounds is a Bronsted-Lowry base?

a. HCl
b. HPO_4^{2-}
c. H_3PO_4
d. NH_4^+
e. $CH_3NH_3^+$

Answer:

A Brønsted-Lowry Base is a proton acceptor, which means it will take in an H^+. This eliminates $\mathbf{HCl}$, $\mathbf{H_3PO_4}$, $\mathbf{NH_4^+}$ and $\mathbf{CH_3NH_3^+}$ because they are Bronsted-Lowry acids. They all give away protons. In the case of $\mathbf{HPO_4^{2-}}$, consider the following equation:

$$\mathbf{HPO_4^{2-}(aq) + H_2O(l) \rightarrow PO_4^{3-}(aq) + H_3O^+(aq)}$$

Here, it is clear that HPO_4^{2-} is the acid since it donates a proton to water to make H_3O^+ and PO_4^{3-}. Now consider the following equation:

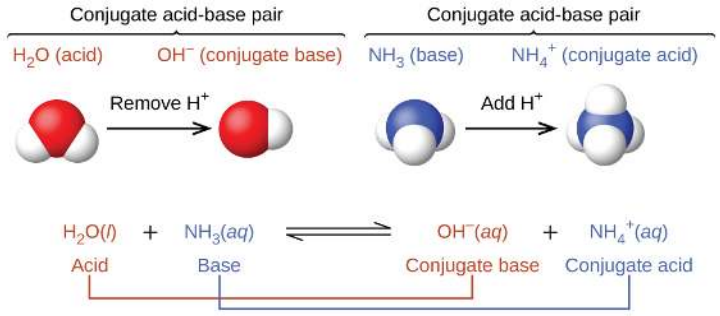
$$\mathbf{HPO_4^{2-}(aq) + H_2O(l) \rightarrow H_2PO_4^- + OH^-(aq)}$$

In this case, HPO_4^{2-} is the base since it accepts a proton from water to form $H_2PO_4^-$ and OH^-. Thus, HPO_4^{2-} is an acid and base together, making it amphoteric.

Since HPO_4^{2-} is the only compound from the options that can act as a base, the answer is **(b) $\mathbf{HPO_4^{2-}}$.**

Conjugate Acid-Base Pair

In reality, all acid-base reactions involve the transfer of protons between acids and bases. For example, consider the acid-base reaction that takes place when ammonia is dissolved in water. A water molecule (functioning as an acid) transfers a proton to an ammonia molecule (functioning as a base), yielding the conjugate base of water, $\mathbf{OH^-}$, and the conjugate acid of ammonia, $\mathbf{NH_4^+}$:



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 $\boldsymbol{NH_4^+/NH_3}$ and $\boldsymbol{H_2O/OH^-}$.

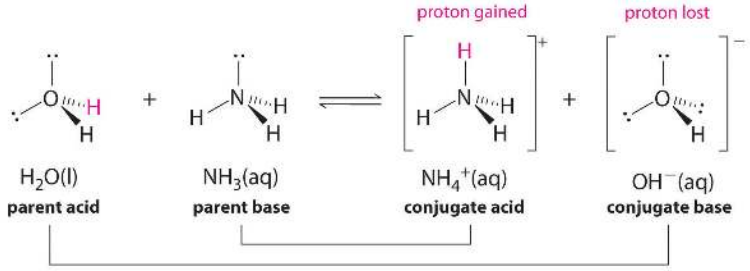


Figure **1.12.1**. The strongest acids are at the bottom left, and the strongest bases are at the top right. The conjugate base of a strong acid is a very weak base, and, conversely, the conjugate acid of a strong base is a very weak acid.

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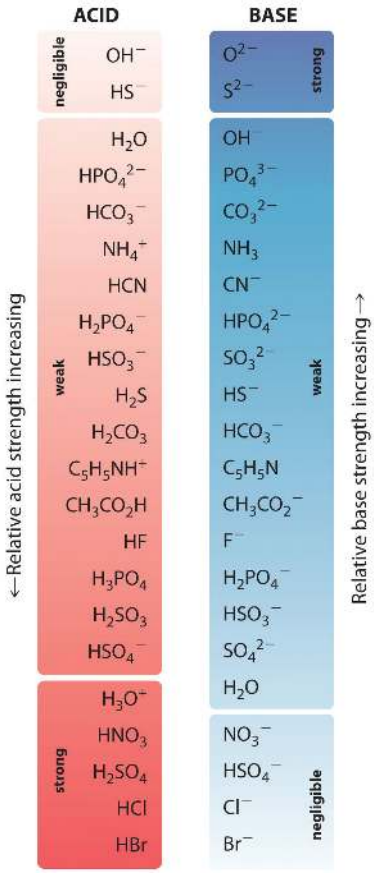


Figure **1.12.1**: The Relative Strengths of Some Common Conjugate Acid–Base Pairs

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.

Example 1.12.2

Identify the conjugate acid-base pairs in this equilibrium.

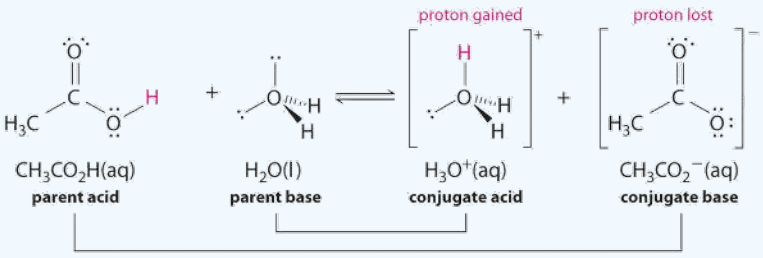
$$CH_3CO_2H + H_2O \rightleftharpoons H_3O^+ + CH_3CO_2^-$$

Solution

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).



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Example 1.12.3

Identify the conjugate acid-base pairs in this equilibrium.

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

Solution

One pair is H_2O and OH^-, where H_2O 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 $(CH_3)_3N$ and $(CH_3)_3NH^+$, where $(CH_3)_3NH^+$ is the conjugate acid (it has an additional proton) and $(CH_3)_3N$ is the conjugate base.

Exercise 1.12.3

Identify the conjugate acid-base pairs in this equilibrium.

$$NH_2^- + H_2O \rightleftharpoons NH_3 + OH^-$$

Answer:

H_2O (acid) and OH^- (base); NH_2^- (base) and NH_3 (acid)

Contributors and Attributions

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1.13: Lewis Acids and Bases

Learning Objective

- Use the definition of Lewis Acids and Bases to recognize electron movement in reactions

Acids and bases are an important part of chemistry. One of the most applicable theories is the Lewis acid/base motif that extends the definition of an acid and base beyond H^+ and OH^- ions as described by Brønsted-Lowry acids and bases.

Introduction

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.

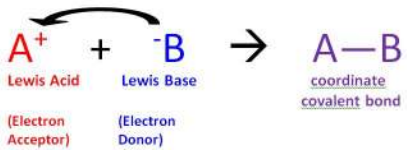


Figure **1.13.1**: Above: A Lewis Base (B) donates it electrons to a Lewis Acid (A) resulting in a coordinate covalently bonded compound, also known as an adduct.

The reaction of a Lewis acid and a Lewis base will produce a coordinate covalent bond, as shown in Figure **1.13.1** above. A coordinate covalent bond is just a type of covalent bond in which one reactant gives it electron pair to another reactant. In this case the lewis base donates its electrons to the lewis acid. When they do react this way the resulting product is called an addition compound, or more commonly an adduct.

- Lewis Acid: a species that accepts an electron pair (i.e., an electrophile) and will have vacant orbitals
- Lewis Base: a species that donates an electron pair (i.e., a nucleophile) and will have lone-pair electrons

Lewis Acids

Lewis acids accept an electron pair. Lewis Acids are Electrophilic meaning that they are electron attracting. When bonding with a base the acid uses its lowest unoccupied molecular orbital or LUMO (Figure 2).

- Various species can act as Lewis acids. All cations are Lewis acids since they are able to accept electrons. (e.g., Cu^{2+}, Fe^{2+}, Fe^{3+})
- An atom, ion, or molecule with an incomplete octet of electrons can act as an Lewis acid (e.g., BF_3, AlF_3).
- Molecules where the central atom can have more than 8 valence shell electrons can be electron acceptors, and thus are classified as Lewis acids (e.g., $SiBr_4$, SiF_4).
- Molecules that have multiple bonds between two atoms of different electronegativities (e.g., CO_2, SO_2)

Lewis Bases

Lewis Bases donate an electron pair. Lewis Bases are Nucleophilic meaning that they “attack” a positive charge with their lone pair. They utilize the highest occupied molecular orbital or HOMO (Figure 2). An atom, ion, or molecule with a lone-pair of electrons can thus be a Lewis base. Each of the following anions can "give up" their electrons to an acid, e.g., OH^-, CN^-, CH_3COO^-, $:NH_3$, $H_2O:$, $CO:$. Lewis base's HOMO (highest occupied molecular orbital) interacts with the Lewis acid's LUMO (lowest unoccupied molecular orbital) to create bonded molecular orbitals. Both Lewis Acids and Bases contain HOMO and LUMOs but only the HOMO is considered for Bases and only the LUMO is considered for Acids (Figure **1.13.2**).

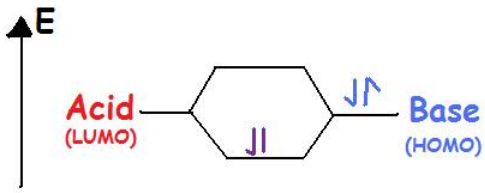


Figure **1.13.2**: Lewis Acids have vacant orbitals so they are in a lower energy level. While lewis bases have lone pair electrons to share and thus occupy a higher energy level.

Complex Ion / Coordination Compounds

Complex ions are polyatomic ions, which are formed from a central metal ion that has other smaller ions joined around it. While Brønsted theory can't explain this reaction Lewis acid-base theory can help. A Lewis Base is often the ligand of a coordination compound with the metal acting as the Lewis Acid (see Oxidation States of Transition Metals).

$$Al^{3+} + 6H_2O \rightleftharpoons [Al(H_2O)_6]^{3+} \tag{1.13.1}$$

The aluminum ion is the metal and is a cation with an unfilled valence shell, and it is a Lewis Acid. Water has lone-pair electrons and is an anion, thus it is a Lewis Base.

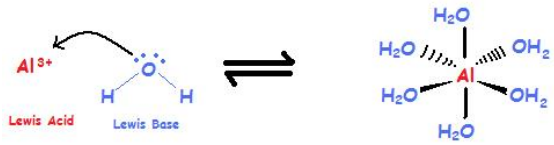


Figure **1.13.3**: Aluminum ion acts as a Lewis acid and accepts the electrons from water, which is acting as a Lewis base. This helps explain the resulting hexaaquaaluminum(III) ion.

The Lewis Acid accepts the electrons from the Lewis Base which donates the electrons. Another case where Lewis acid-base theory can explain the resulting compound is the reaction of ammonia with Zn^{2+}.

$$Zn^{2+} + 4NH_3 \rightarrow [Zn(NH_3)_4]^{4+} \tag{1.13.2}$$

Similarly, the Lewis Acid is the zinc Ion and the Lewis Base is NH_3. Note how Brønsted Theory of Acids and Bases will not be able to explain how this reaction occurs because there are no H^+ or OH^- ions involved. Thus, Lewis Acid and Base Theory allows us to explain the formation of other species and complex ions which do not ordinarily contain hydronium or hydroxide ions. One is able to expand the definition of an acid and a base via the Lewis Acid and Base Theory. The lack of H^+ or OH^- ions in many complex ions can make it harder to identify which species is an acid and which is a base. Therefore, by defining a species that donates an electron pair and a species that accepts an electron pair, the definition of a acid and base is expanded.

Amphoterism

As of now you should know that acids and bases are distinguished as two separate things however some substances can be both an acid and a base. You may have noticed this with water, which can act as both an acid or a base. This ability of water to do this makes it an amphoteric molecule. Water can act as an acid by donating its proton to the base and thus becoming its conjugate acid, OH-. However, water can also act as a base by accepting a proton from an acid to become its conjugate base, H_3O^+.

- Water acting as an Acid:

$$H_2O + NH_3 \rightarrow NH_4^+ + OH^- \tag{1.13.3}$$

- Water acting as a Base:

$$H_2O + HCl \rightarrow Cl^- + H_3O^+ \tag{1.13.4}$$

You may have noticed that the degree to which a molecule acts depends on the medium in which the molecule has been placed in. Water does not act as an acid in an acid medium and does not act as a base in a basic medium. Thus, the medium which a molecule is placed in has an effect on the properties of that molecule. Other molecules can also act as either an acid or a base. For example,

$$Al(OH)_3 + 3H^+ \rightarrow Al^{3+} + 3H_2O \tag{1.13.5}$$

- where $Al(OH)_3$ is acting as a Lewis Base.

$$Al(OH)_3 + OH^- \rightarrow Al(OH)_4^- \tag{1.13.6}$$

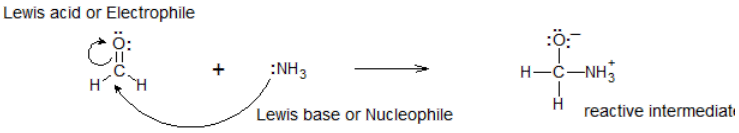
- where $Al(OH)_3$ is acting as an Lewis Acid.

Note how the amphoteric properties of the $Al(OH)_3$ depends on what type of environment that molecule has been placed in.

Lewis Bases & Acids as Nucleophiles & Electrophiles

The emphasis on electron flow in the Lewis Theory of acids and bases is an important foundation for learning and predicting reaction mechanisms. The electron rich Lewis base can be described as a nucleophile. Nucleophiles are attracted to and can react with compounds or ions that have full or partial positive charge (like the nucleus). The electron poor Lewis acids can be described as electrophiles. Electrophiles attract nucleophiles until orbital overlap occurs between them triggering a reaction. At this point in the course, we can indicate electron flow using curved arrows when both the reactant(s) and product(s) are given.

Example

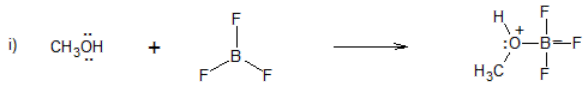


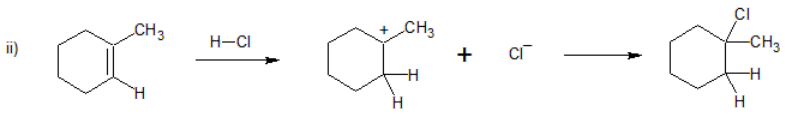
Exercises

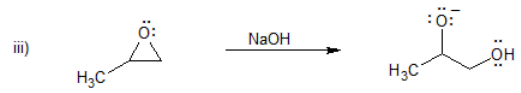
For the following reactions,

a) add curved arrows to indicate the electron flow

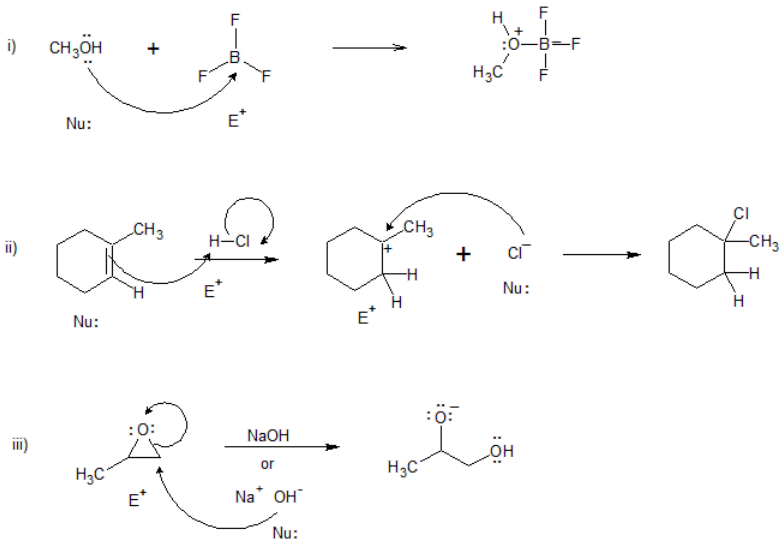
b) label each reactant as the Nu (nucleophile) or E^+ (electrophile).







Solutions



Outside Links

- Very Detailed review of Lewis Acids and Bases, covering all topics of this type of chemistry
- Very Complex and Detailed "Lewis Acid and Base Interaction Matrix"
- Youtube Video about Lewis Acids/Bases

References

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1.14: Distinguishing between pH and pKa

Learning Objective

- Determine relative strengths of acids and bases from their pK_a values
- Determine the form of an acid or base at a specified pH (given the pK_a)

The Henderson-Hasselbach Equation - a Quantitative View

We will use the general reaction for a weak acid to write the Ka expression.

$$HA_{(aq)} + H_2O_{(l)} \rightleftharpoons H_3O^+_{(aq)} + A^-_{(aq)} \tag{1.14.1}$$

$$K_a = \frac{[H_3O^+][A^-]}{[HA]} \tag{1.14.2}$$

pKa = -log Ka

where each bracketed term represents the concentration of that substance in solution.

The stronger an acid, the greater the ionization, the lower the pKa, and the lower the pH the compound will produce in solution.

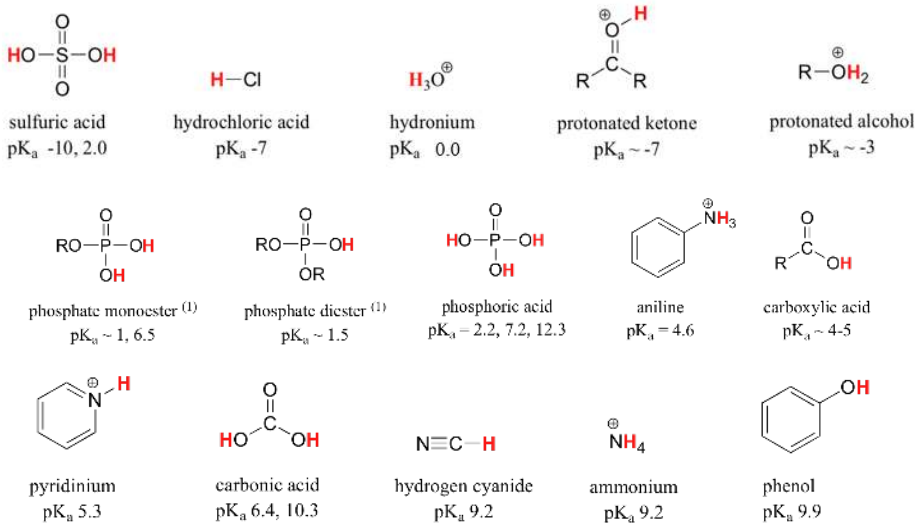
It is important to realize that pK_a is not at all the same thing as pH: the former is an inherent property of a compound or functional group, while the latter is the measure of the hydronium ion concentration in a particular aqueous solution:

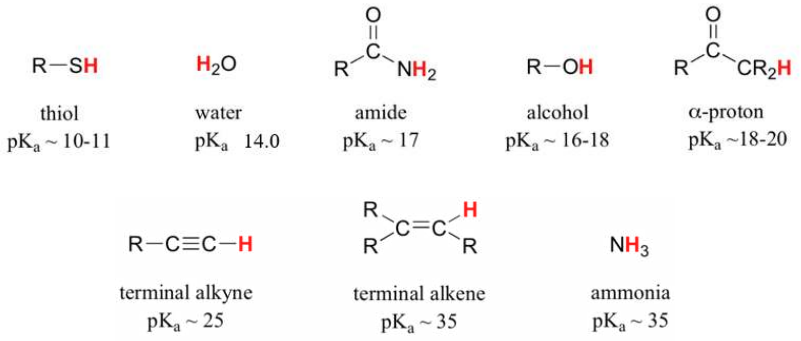
pH = -log $[H_3O^+]$

Additional reagents can be added to a reaction solution to change the pH of the reaction conditions beyond the effects of an individual compound.

Relative Acidity and pKa Values

An application of the Henderson-Hasselbach Equation is the ability to determine the relative acidity of compounds by comparing their pKa values. The stronger an acid, the greater the ionization, the lower the pKa, and the lower the pH the compound will produce in solution. Some selected pKa values for compounds in the study of organic chemistry are shown bellow. Since organic reactions can be performed in non-aqueous environments, the pH can exceed 14 and organic compounds can have pKa values above 16. It is a variation on that line from the Wizard of Oz, "We don't live in water anymore."



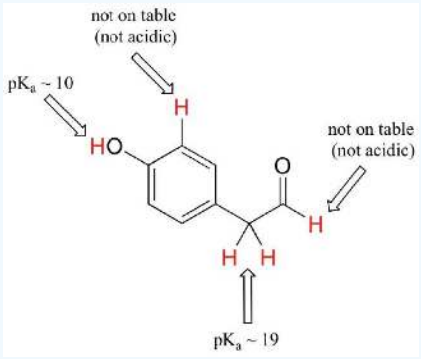


It is a very good idea to commit to memory the approximate pK_a ranges of the compounds above. A word of caution: when using the pK_a table, be absolutely sure that you are considering the correct conjugate acid/base pair. If you are asked to say something about the basicity of ammonia (NH_3) compared 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!)

* A note on the pKa of water: The pKa of water is 14. Biochemistry and organic chemistry texts often list the value as 15.7. These texts have incorrectly factored the molar value for the concentration of water into the equilibrium constant. The correct derivation of the equilibrium constant involves the **activity** of water, which has a value of 1.

Example

While this course begins with single functional groups, we will eventually work with interesting compounds containing multiple functional groups. Recognizing which hydrogens can be ionized as acidic protons and which hydrogens can NOT, is a useful skill. Notice in this example that we need to evaluate the potential acidity at *four* different locations on the molecule.



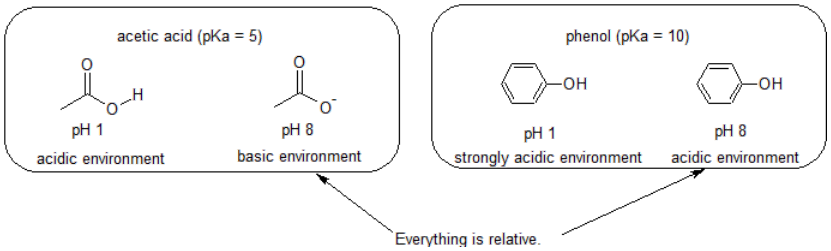
Aldehyde and aromatic protons are not at all acidic (pK_avalues are above 40 – not on our table). The two protons on the carbon next to the carbonyl are slightly acidic, with pK_a values around 19-20 according to the table. The most acidic proton is on the phenol group, so if the compound were to be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

Acidic & Basic Environments - Everything is Relative in Reactivity

Because our goal is understanding dynamic chemical reactivity, we do NOT need to know the specific amount of the protonated and unprotonated forms of a compound. We simply need to know which form is predominate. When the pH of the environment is less than the pKa of the compound, the environment is considered acidic and the compound will exist predominately in its

protonated form. When the pH of the environment is greater than the pKa of the compound, the environment is considered basic and the compound will exist predominately in its deprotonated form.

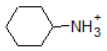
For example, the pKa of acetic acid is about 5. At a pH of 1, the environment is considered acidic and acetic acid exists predominately in its protonated form. At pH 8, the environment is considered basic, and acetic acid becomes deprotonated to form acetate ($CH_3CO_2^-$). Conversely, the pKa of phenol is 10. At pH 8, the environment is considered acidic for phenol and it remains primarily protonated.



It is also important to remember that organic chemistry does NOT have to occur in water so pKa values can be as high as 50.

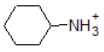
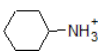
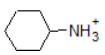
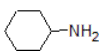
Exercise

1. Complete the table below to indicate whether each compound exists predominantly in its protonated (acidic environment) or deprotonated (basic environment) form.

compound (pKa)	pH 1 environment	pH 8 environment	pH 13 environment
pKa = 5.1			
 pKa = 10.7			
pKa = 16			
pKa = 20			

Answer

1.

compound (pKa)	pH 1 environment	pH 8 environment	pH 13 environment
pKa = 5.1			
 pKa = 10.7			
pKa = 16			
pKa = 20			

1.14: Distinguishing between pH and pKa is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

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1.15: Predicting Relative Acidity

Learning Objective

- Predict relative strengths of acids and bases from their structure, bonding and resonance

Since compounds are neutral, it can be difficult to evaluate and compare their overall stability without going through the tedious process of performing bond energy calculations.

When acidic compounds donate hydrogen ions or accepts electrons, they become ionized. It is much easier to compare ions because we can evaluate the charge density. The lower the charge density, the more stable the ion. Conversely, the higher the charge density, the less stable the ion. Charge density is analogous to density of matter. We place charge in the numerator, instead of mass, and volume can still be found in the denominator.

$$\text{charge density} = \frac{\text{charge}}{\text{volume}} \tag{1.15.1}$$

The six strong acids (HCl, HBr, HI, HNO_3, H_2SO_4, $HClO_4$) fully ionize to form the highly stable anions (Cl^-, Br^-, I^-, NO_3^-, SO_4^{2-}, ClO_4^-) respectively.

For the remaining weak acids (HA), we can determine their relative acidity by comparing the relative electron densities of their conjugate bases (A^-).

the lower the electron density, the more stable the conjugate base

Structural Effects on Electron Density - Four Considerations

There are four main considerations for evaluating electron density.

1. Identity of the element or atoms 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.

Identity of the Element

When comparing the identity of the elements, it depends on the positional relationship of the elements on the periodic table.

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 increases, the electron density decreases.

Figure **1.15.1** 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.

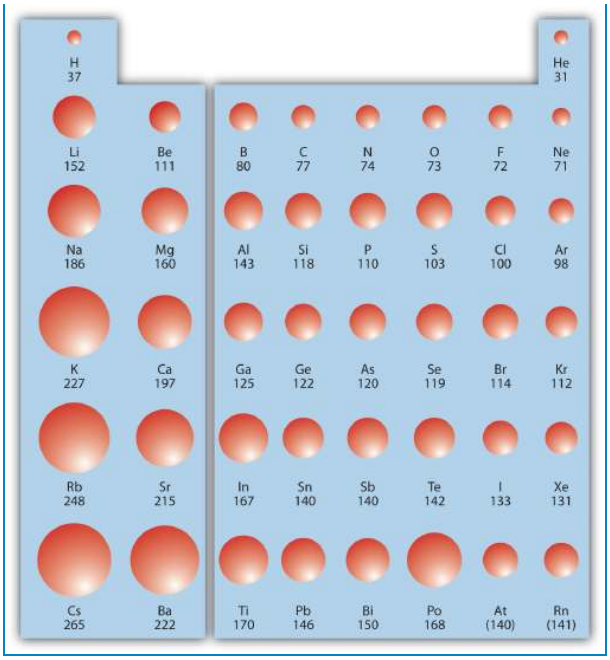
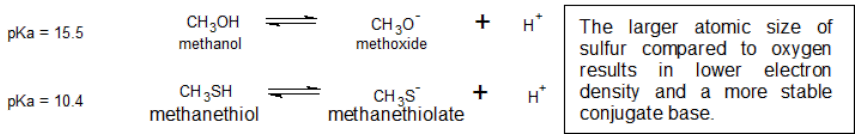


Figure **1.15.1**: Atomic Radii Trends on the Periodic Table. Although there are some reversals in the trend (e.g., see Po in the bottom row), atoms generally get smaller as you go across the periodic table and larger as you go down any one column. Numbers are the radii in pm.

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.



Across a Period (aka across a row) As we move across a period 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 methane, ammonia, water, and hydrofluoric acid reflects the relative electonegativities of the C < N < O < F.

Compound	pK_a	Reaction
methane	50	$CH_4 \rightleftharpoons CH_3^- + H^+$
ammonia	36	$NH_3 \rightleftharpoons NH_2^- + H^+$
water	14	$H_2O \rightleftharpoons OH^- + H^+$
hydrofluoric acid	3	$HF \rightleftharpoons F^- + H^+$

Periodic trends

First, we will focus on individual atoms, and think about trends associated with the position of an element on the periodic table. We'll use as our first models the simple organic compounds ethane, methylamine, and ethanol, but the concepts apply equally to more complex biomolecules, such as the side chains of alanine, lysine, and serine.

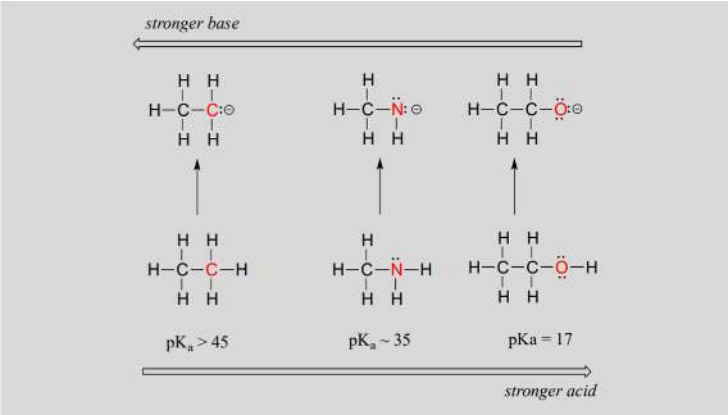


Figure 1.15.2: Horizontal periodic trend in acidity and basicity. (CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

We can see a clear trend in acidity as we move from left to right along the second row of the periodic table from carbon to nitrogen to oxygen. The key to understanding this trend is to consider the hypothetical conjugate base in each case*: the more stable (weaker) the conjugate base, the stronger the acid*. Look at where the negative charge ends up in each conjugate base. In the ethyl anion, the negative charge is borne by carbon, while in the methylamine anion and ethoxide anion the charges are located on a nitrogen and an oxygen, respectively. Remember the periodic trend in electronegativity (section 2.3A): it also increases as we move from left to right along a row, meaning that oxygen is the most electronegative of the three, and carbon the least. *The more electronegative an atom, the better it is able to bear a negative charge*. Thus, the ethoxide anion is the most stab = 0.00le (lowest energy, least basic) of the three conjugate bases, and the ethyl anion is the least stable (highest energy, most basic).

We can use the same set of ideas to explain the difference in basicity between water and ammonia.

$$pK_a = 0.00 \quad H_3O^+ \rightleftharpoons H_2O + H^+$$

$$pK_a = 9.26 \quad NH_4^+ \rightleftharpoons NH_3 + H^+$$

By looking at the pK$_a$values for the appropriate conjugate acids, we know that ammonia is more basic than water. Oxygen, as the more electronegative element, holds more tightly to its lone pair than the nitrogen. The nitrogen lone pair, therefore, is more likely to break away and form a new bond to a proton - it is, in other words, more basic. Once again, a more reactive (stronger) conjugate base means a less reactive (weaker) conjugate acid.

When moving vertically within a given column of the periodic table, we again observe a clear periodic trend in acidity. This is best illustrated with the halides: basicity, like electronegativity, increases as we move up the column.

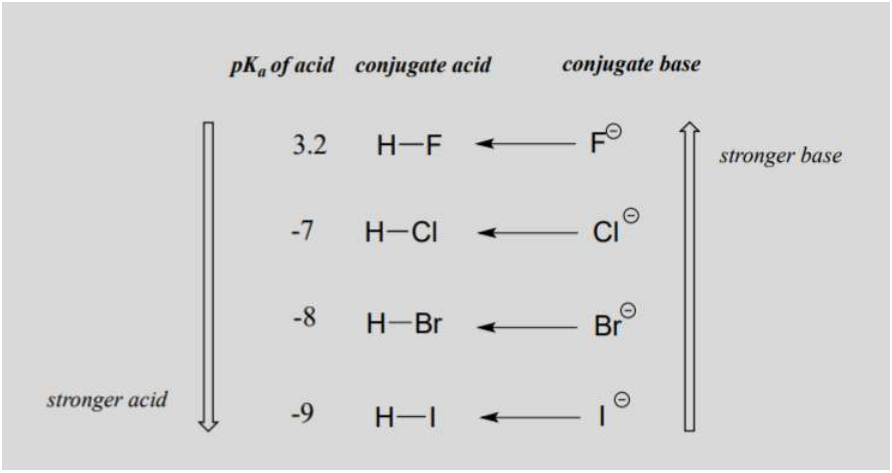


Figure 1.15.4: Vertical periodic trend in acidity and basicity. (CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

Conversely, acidity in the haloacids increases as we move *down* the column.

In order to make sense of this trend, we will once again consider the stability of the conjugate bases. Because fluorine is the most electronegative halogen element, we might expect fluoride to also be the least basic halogen ion. But in fact, it is the *least* stable, and the most basic! It turns out that when moving vertically in the periodic table, the *size* of the atom trumps its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodine ion, the negative charge is spread out over a significantly larger volume:

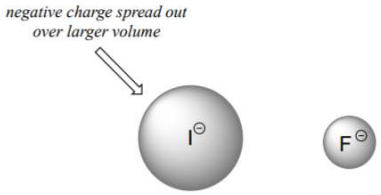


Figure **1.15.5**: In conjugate bases the size of the ion controls basicity. ()

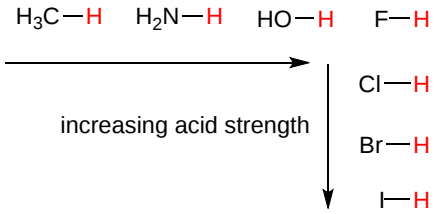
This illustrates a fundamental concept in organic chemistry that is important enough to put in red:

Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one atom.

We will see this idea expressed again and again throughout our study of organic reactivity, in many different contexts. For now, the concept is applied only to the influence of atomic radius on anion stability. Because fluoride is the least stable (most basic) of the halide conjugate bases, HF is the least acidic of the haloacids, only slightly stronger than acetic acid. HI, with a pK_a of about -9, is one the strongest acids known.

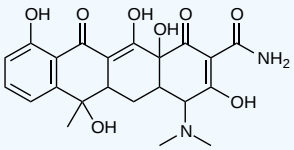
More importantly to the study of biological organic chemistry, this trend tells us that thiols are more acidic than alcohols. The pK_a of the thiol group on the cysteine side chain, for example, is approximately 8.3, while the pK_a for the hydroxyl on the serine side chain is on the order of 17.

To reiterate: acid strength increases as we move to the right along a row of the periodic table, and as we move down a column.



Example 1.15.1:

Draw the structure of the conjugate base that would form if the compound below were to react with 1 molar equivalent of sodium hydroxide:



Solution

Is resonance possible to localize the charge?

In the previous section we focused our attention on periodic trends - the differences in acidity and basicity between groups where the exchangeable proton was bound to different elements. Now, it is time to think about how the structure of different organic groups contributes to their relative acidity or basicity, even when we are talking about the same element acting as the proton donor/acceptor. When evaluating conjugate bases for the presence of the resonance contributors, remember to look for movable electrons as described in section 1.10 of this chapter. Delocalizing electrons over two or more atoms lowers the electron density.

The first model pair we will consider is 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. What makes a carboxylic acid so much more acidic than an alcohol? As before, we begin by considering the conjugate bases.

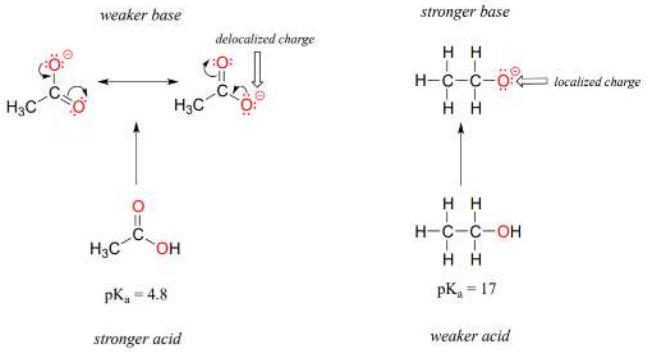


Figure **1.15.8**: (CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

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 localized 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 2.2C). What this means, you may recall, 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 – it has nowhere else to go.

Now is the time to think back to that statement from the previous section that was so important that it got printed in bold font in its own paragraph – in fact, it is so important that we'll just say it again: "Electrostatic charges, whether positive or negative, are more stable when they are 'spread out' than when they are confined to one atom." Now, we are seeing this concept in another context, where a charge is being 'spread out' (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

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 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 that much more stable than the ethoxide ion, all due to the effects of resonance delocalization.

The resonance effect also nicely explains why a nitrogen atom is basic when it is in an amine, but *not* basic when it is part of an amide group. Recall that in an amide, there is significant double-bond character to the carbon-nitrogen bond, due to a second resonance contributor in which the nitrogen lone pair is part of a p bond.

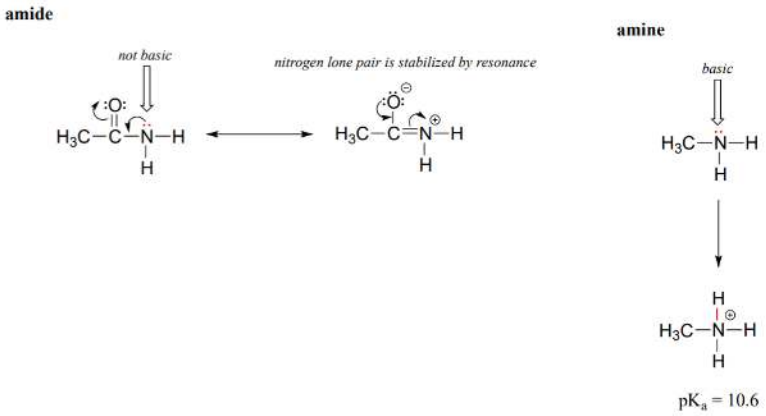
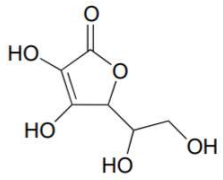


Figure **1.15.9**: (CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

While the electron lone pair of an amine nitrogen is 'stuck' in one place, the lone pair on an amide nitrogen is delocalized by resonance. Notice that in this case, we are extending our central statement to say that 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 available for bonding with a proton – these two electrons are too 'comfortable' being part of the delocalized pi-bonding system. The lone pair on an amine nitrogen, by contrast, is not part of a delocalized p system, and is very ready to form a bond with any acidic proton that might be nearby.

Often it requires some careful thought to predict the most acidic proton on a molecule. Ascorbic acid, also known as Vitamin C, has a pK_a of 4.1.

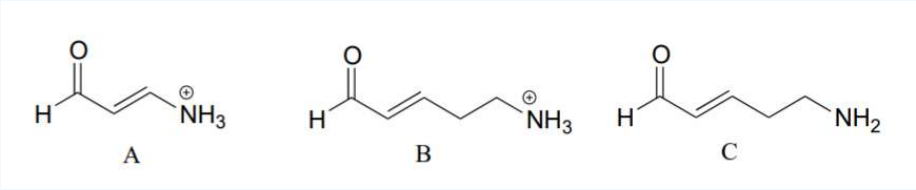


ascorbic acid
(Vitamin C)

There are four hydroxyl groups on this molecule – which one is the most acidic? If we consider all four possible conjugate bases, we find that there is only one for which we can delocalized the negative charge over *two* oxygen atoms.

Example 1.15.1:

Rank the compounds below from most acidic to least acidic, and explain your reasoning.

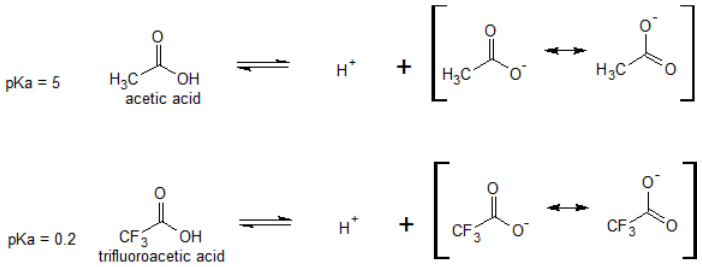


(CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

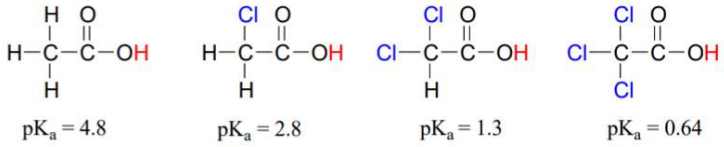
Inductive Effects

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. Inductive effects decrease quickly with distance. The inductive effect can be electron donating which helps stabilize positive charge. Alkyl groups (hydrocarbons) are inductive electron donators. The inductive effect can also be electron withdrawing. Electronegativity indicates the strength of electron withdrawing induction. Halogens are inductive electron withdrawing groups.

The effects of induction on relative acidity can also be seen when comparing acetic acid with trifluoroacetic acid. The difference in acidity does not have to do with resonance delocalization because no additional resonance structures can be drawn for the fluorinated molecule. The fluorine atoms inductively pull some of the electron density away from the carboxylate ion to further delocalize the negative charge of the conjugate base.



Compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:

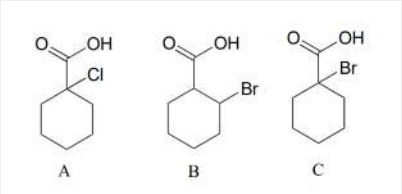


(CC-NC-SA; Timothy Soderberg via UMn Morris Digital Well)

The presence of the chlorines clearly increases the acidity of the carboxylic acid group. A chlorine atom is more electronegative than a hydrogen, and thus is able to 'induce', or 'pull' electron density towards itself, away from the carboxylate group. In helping to further spread out the electron density of the conjugate base, which as we know 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*. The inductive electron-withdrawing effect of the chlorines 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.

Exercise

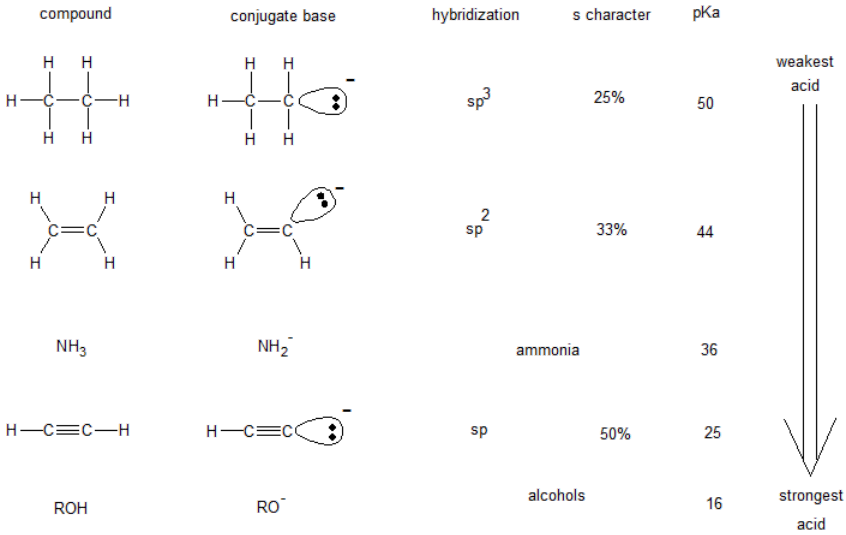
Rank the compounds below from most acidic to least acidic, and explain your reasoning.



Solution

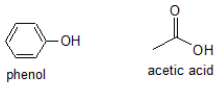
Orbital Hybridization

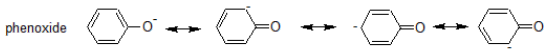
The hybridization of an orbital affects its electronegativity. Within a shell, the s orbitals occupy the region closer to the nucleus than the p orbitals. Therefore, the spherical s orbitals are more electronegative than the lobed p orbitals. The relative electronegativity of hybridized orbitals is sp > sp^2 > sp^3. This trend indicates the sp hybridized orbitals are more stable with a -1 charge than sp^3 hybridized orbitals. The table below shows how orbital hybridization compares with the identity of the atom when predicting relative acidity.

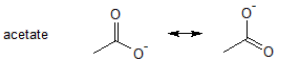


Guided Practice

Let's practice by comparing the relative acidity of phenol with acetic acid.







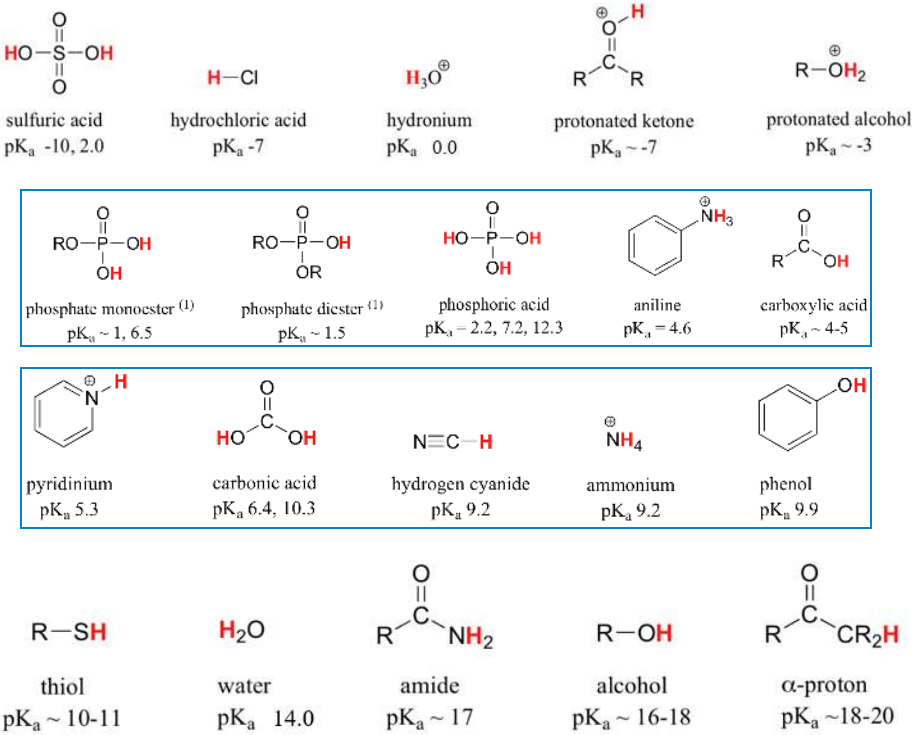
Which compound is the stronger acid - phenol or acetic acid?

To answer this question, we draw all the relevant resonance contributors for each conjugate base, phenoxide and acetate, respectively.

Phenoxide has four resonance contributors, but three of the contributors have a negative charge on a carbon atom while both resonance contributors for acetate have a negative charge on the more electronegative element oxygen. There are no inductive effects or orbital hybridization differences to consider in this example, so we would predict acetic acid to be the stronger acid. The acetate ion is more stable than the phenoxide ion, so we would expect acetic acid to be the stronger acid.

The pKa table below supports our prediction. Acetic acid has a pKa of 4.7 while phenol has a pKa of 9.9.

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!)



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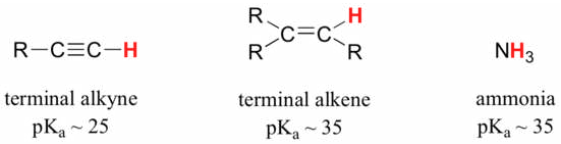

Contributors and Attributions

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1.16: Molecular Formulas and Empirical Formulas (Review)

Learning objective

- Determine the empirical and molecular formulas from combustion data

Molecular formulas tell you how many atoms of each element are in a compound, and empirical formulas tell you the simplest or most reduced ratio of elements in a compound. If a compound's molecular formula cannot be reduced any more, then the empirical formula is the same as the molecular formula. Combustion analysis can determine the empirical formula of a compound, but cannot determine the molecular formula (other techniques can though). Once known, the molecular formula can be calculated from the empirical formula.

Empirical Formulas

An empirical formula tells us the relative ratios of different atoms in a compound. The ratios hold true on the *molar* level as well. Thus, H_2O is composed of two atoms of hydrogen and 1 atom of oxygen. Likewise, **1.0 mole of H_2O** is composed **of 2.0 moles of hydrogen** and **1.0 mole of oxygen**. We can also work backwards from molar ratios since *if we know the molar amounts of each element in a compound we can determine the empirical formula*.

Example 1.16.1: Mercury Chloride

Mercury forms a compound with chlorine that is 73.9% mercury and 26.1% chlorine by mass. What is the empirical formula?

Let's say we had a 100 gram sample of this compound. The sample would therefore contain 73.9 grams of mercury and 26.1 grams of chlorine. How many moles of each atom do the individual masses represent?

For Mercury:

$$(73.9\ g) \times \left(\frac{1\ mol}{200.59\ g}\right) = 0.368\ moles \tag{1.16.1}$$

For Chlorine:

$$(26.1\ g) \times \left(\frac{1\ mol}{35.45\ g}\right) = 0.736\ mol \tag{1.16.2}$$

What is the molar ratio between the two elements?

$$\frac{0.736\ mol\ Cl}{0.368\ mol\ Hg} = 2.0 \tag{1.16.3}$$

Thus, we have twice as many moles (i.e. atoms) of Cl as Hg. The empirical formula would thus be (remember to list cation first, anion last):

$$HgCl_2 \tag{1.16.4}$$

Molecular Formula from Empirical Formula

The chemical formula for a compound obtained by composition analysis is always the empirical formula. We can obtain the chemical formula from the empirical formula if we know the molecular weight of the compound. The chemical formula will always be some *integer multiple* of the empirical formula (i.e. integer multiples of the subscripts of the empirical formula). The general flow for this approach is shown in Figure **1.16.1** and demonstrated in Example **1.16.2**.

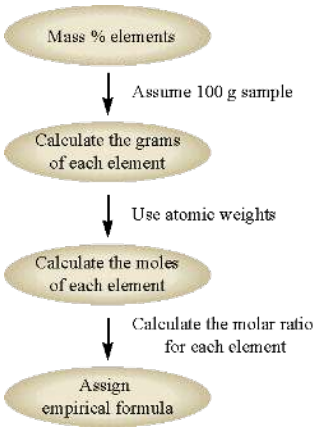


Figure **1.16.1**: The general flow chart for solving empirical formulas from known mass percentages.

Example 1.16.2: Ascorbic Acid

Vitamin C (ascorbic acid) contains 40.92 % C, 4.58 % H, and 54.50 % O, by mass. The experimentally determined molecular mass is 176 amu. What is the empirical and chemical formula for ascorbic acid?

Solution

Consider an arbitrary amount of 100 grams of ascorbic acid, so we would have:

- 40.92 grams C
- 4.58 grams H
- 54.50 grams O

This would give us how many moles of each element?

- Carbon

$$(40.92\ \cancel{g\,C}) \times \left(\frac{1\ mol\ C}{12.011\ \cancel{g\,C}}\right) = 3.407\ mol\ C \tag{1.16.5}$$

- Hydrogen

$$(4.58\ \cancel{g\,H}) \times \left(\frac{1\ mol\ H}{1.008\ \cancel{g\,H}}\right) = 4.544\ mol\ H \tag{1.16.6}$$

- Oxygen

$$(54.50\ \cancel{g\,O}) \times \left(\frac{1\ mol\ O}{15.999\ \cancel{g\,O}}\right) = 3.406\ mol\ O \tag{1.16.7}$$

Determine the simplest whole number ratio by dividing by the smallest molar amount (3.406 moles in this case - see oxygen):

- Carbon

$$C = \frac{3.407\ mol}{3.406\ mol} \approx 1.0 \tag{1.16.8}$$

- Hydrogen

$$C = \frac{4.5.44\ mol}{3.406\ mol} = 1.0 \tag{1.16.9}$$

- Oxygen

$$C = \frac{3.406\ mol}{3.406\ mol} = 1.0 \tag{1.16.10}$$

The relative molar amounts of carbon and oxygen appear to be equal, but the relative molar amount of hydrogen is higher. Since we cannot have "fractional" atoms in a compound, we need to normalize the relative amount of hydrogen to be equal to an integer. 1.333 would appear to be 1 and 1/3, so if we multiply the relative amounts of each atom by '3', we should be able to get integer values for each atom.

C = (1.0)*3 = 3

H = (1.333)*3 = 4

O = (1.0)*3 = 3

or

$C_3H_4O_3$

This is our ***empirical formula*** for ascorbic acid.

What about the chemical formula? We are told that the experimentally determined molecular mass is **176 *amu***. What is the molecular mass of our empirical formula?

(3*12.011) + (4*1.008) + (3*15.999) = 88.062 *amu*

The molecular mass from our empirical formula is significantly lower than the experimentally determined value. What is the ratio between the two values?

(176 *amu*/88.062 *amu*) = 2.0

Thus, it would appear that our empirical formula is essentially one half the mass of the actual molecular mass. If we multiplied our empirical formula by '2', then the molecular mass would be correct. Thus, the actual molecular formula is:

2* $C_3H_4O_3$ = **$C_6H_8O_6$**

Combustion Analysis

When a compound containing carbon and hydrogen is subject to combustion with oxygen in a special combustion apparatus all the carbon is converted to CO_2 and the hydrogen to H_2O (Figure **1.16.2**). The amount of carbon produced can be determined by measuring the amount of CO_2 produced. This is trapped by the sodium hydroxide, and thus we can monitor the mass of CO_2 produced by determining the increase in mass of the CO_2 trap. Likewise, we can determine the amount of H produced by the amount of H_2O trapped by the magnesium perchlorate.

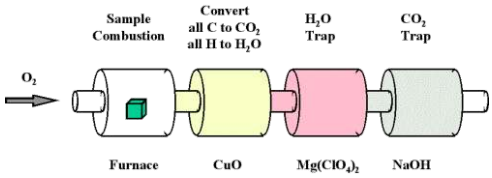


Figure **1.16.2**: Combustion analysis apparatus

One of the most common ways to determine the elemental composition of an unknown hydrocarbon is an analytical procedure called combustion analysis. A small, carefully weighed sample of an unknown compound that may contain carbon, hydrogen, nitrogen, and/or sulfur is burned in an oxygen atmosphere,Other elements, such as metals, can be determined by other methods. and the quantities of the resulting gaseous products (CO_2, H_2O, N_2, and SO_2, respectively) are determined by one of several possible methods. One procedure used in combustion analysis is outlined schematically in Figure **1.16.3** and a typical combustion analysis is illustrated in Examples **1.16.3** and **1.16.4**.

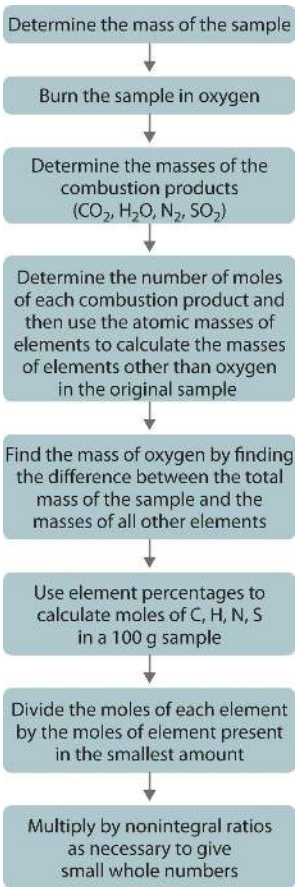


Figure **1.16.3**: Steps for Obtaining an Empirical Formula from Combustion Analysis

Example 1.16.3: Combustion of Isopropyl Alcohol

What is the empirical formulate for isopropyl alcohol (which contains only C, H and O) if the combustion of a 0.255 grams isopropyl alcohol sample produces 0.561 grams of CO_2 and 0.306 grams of H_2O?

Solution

From this information quantitate the amount of C and H in the sample.

$$(0.561\ \cancel{g\ CO_2}) \left(\frac{1\ mol\ CO_2}{44.0\ \cancel{g\ CO_2}} \right) = 0.0128\ mol\ CO_2 \tag{1.16.11}$$

Since one mole of CO_2 is made up of one mole of C and two moles of O, if we have 0.0128 moles of CO_2 in our sample, then we know we have 0.0128 moles of C in the sample. How many grams of C is this?

$$(0.0128\ \cancel{mol\ C}) \left(\frac{12.011\ g\ C}{1\ \cancel{mol\ C}} \right) = 0.154\ g\ C \tag{1.16.12}$$

How about the hydrogen?

$$(0.306\ \cancel{g\ H_2O}) \left(\frac{1\ mol\ H_2O}{18.0\ \cancel{g\ H_2O}} \right) = 0.017\ mol\ H_2O \tag{1.16.13}$$

Since one mole of H_2O is made up of one mole of oxygen and ***two*** moles of hydrogen, if we have 0.017 moles of H_2O, then we have 2*(0.017) = 0.034 moles of hydrogen. Since hydrogen is about 1 gram/mole, we must have **0.034 grams of hydrogen** in our original sample.

When we add our carbon and hydrogen together we get:

0.154 grams (C) + 0.034 grams (H) = **0.188 grams**

But we know we combusted *0.255 grams* of isopropyl alcohol. The 'missing' mass must be from the oxygen atoms in the isopropyl alcohol:

0.255 grams - 0.188 grams = 0.067 grams oxygen

This much oxygen is how many moles?

$$(0.067\ \cancel{g O})\left(\frac{1\ mol\ O}{15.994\ \cancel{g O}}\right) = 0.0042\ mol\ O \tag{1.16.14}$$

Overall therefore, we have:

- 0.0128 moles Carbon
- 0.0340 moles Hydrogen
- 0.0042 moles Oxygen

Divide by the smallest molar amount to normalize:

- C = 3.05 atoms
- H = 8.1 atoms
- O = 1 atom

Within experimental error, the most likely empirical formula for propanol would be C_3H_8O

Example 1.16.4: Combustion of Naphalene

Naphthalene, the active ingredient in one variety of mothballs, is an organic compound that contains carbon and hydrogen only. Complete combustion of a 20.10 mg sample of naphthalene in oxygen yielded 69.00 mg of CO_2 and 11.30 mg of H_2O. Determine the empirical formula of naphthalene.

Given: mass of sample and mass of combustion products

Asked for: empirical formula

Strategy:

A. Use the masses and molar masses of the combustion products, CO_2 and H_2O, to calculate the masses of carbon and hydrogen present in the original sample of naphthalene.
B. Use those masses and the molar masses of the elements to calculate the empirical formula of naphthalene.

Solution:

A Upon combustion, 1 mol of $\mathbf{CO_2}$ is produced for each mole of carbon atoms in the original sample. Similarly, 1 mol of H_2O is produced for every 2 mol of hydrogen atoms present in the sample. The masses of carbon and hydrogen in the original sample can be calculated from these ratios, the masses of CO_2 and H_2O, and their molar masses. Because the units of molar mass are grams per mole, we must first convert the masses from milligrams to grams:

$$\underset{mass\ of\ C}{} = 69.00\,mg\,CO_2 \times \frac{1\,g}{1000\,mg} \times \frac{1\,mol\,CO_2}{44.010\,g\,CO_2} \times \frac{1\,molC}{1\,mol\,CO_2} \times \frac{12.011\,g}{1\,mol\,C} \tag{1.16.15}$$

$$= 1.883 \times 10^{-2}\,g\,C \tag{1.16.16}$$

$$\underset{mass\ of\ H}{} = 11.30\,mg\,H_2O \times \frac{1\,g}{1000\,mg} \times \frac{1\,mol\,H_2O}{18.015\,g\,H_2O} \times \frac{2\,molH}{1\,mol\,H_2O} \times \frac{1.0079\,g}{1\,mol\,H} \tag{1.16.17}$$

$$= 1.264 \times 10^{-3}\,g\,H \tag{1.16.18}$$

B To obtain the relative numbers of atoms of both elements present, we need to calculate the number of moles of each and divide by the number of moles of the element present in the smallest amount:

$$moles\,C = 1.883 \times 10^{-2}\,g\,C \times \frac{1\,mol\,C}{12.011\,g\,C} = 1.568 \times 10^{-3}\,molC \tag{1.16.19}$$

$$moles\,H = 1.264 \times 10^{-3}\,g\,H \times \frac{1\,mol\,H}{1.0079\,g\,H} = 1.254 \times 10^{-3}\,molH \tag{1.16.20}$$

Dividing each number by the number of moles of the element present in the smaller amount gives

$$H: \frac{1.254 \times 10^{-3}}{1.254 \times 10^{-3}} = 1.000 \;\; C: \frac{1.568 \times 10^{-3}}{1.254 \times 10^{-3}} = 1.250 \tag{1.16.21}$$

Thus naphthalene contains a 1.25:1 ratio of moles of carbon to moles of hydrogen: $C_{1.25}H_{1.0}$. Because the ratios of the elements in the empirical formula must be expressed as small whole numbers, multiply both subscripts by 4, which gives C_5H_4 as the empirical formula of naphthalene. In fact, the molecular formula of naphthalene is $C_{10}H_8$, which is consistent with our results.

Exercise 1 1.16.4

a. Xylene, an organic compound that is a major component of many gasoline blends, contains carbon and hydrogen only. Complete combustion of a 17.12 mg sample of xylene in oxygen yielded 56.77 mg of CO_2 and 14.53 mg of H_2O. Determine the empirical formula of xylene.

b. The empirical formula of benzene is CH (its molecular formula is C_6H_6). If 10.00 mg of benzene is subjected to combustion analysis, what mass of CO_2 and H_2O will be produced?

Answer a

The empirical formula is C_4H_5. (The molecular formula of xylene is actually C_8H_{10}.)

Answer b

33.81 mg of CO_2; 6.92 mg of H_2O

Exercise 2

Elemental analysis of an organic compound indicates its composition to be 37.82% carbon, 6.36% hydrogen, and 55.82% chlorine.

a. What is the empirical formula for this compound?

b. Mass spectral analysis indicates a molar mass of 129 g/mol. What is the molecular formula for this compound?

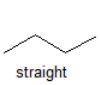
c. Draw all the possible bond-line structures with this molecular formula.

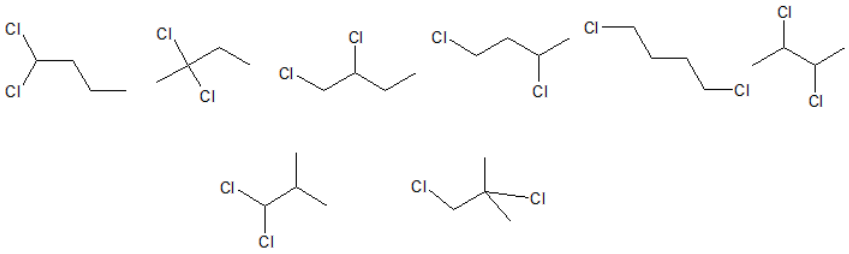
Solutions to Exercise 2

a. C_2H_5Cl with a molar mass of 64.5 g/mol

b. $C_4H_{10}Cl_2$

c. There 8 possible structures with the molecular formula $C_4H_{10}Cl_2$. It can help to start with the different carbon backbones and then systematically add any branches (substituents).

For $C_2H_{10}Cl_2$, there are two ways to bond the carbon atoms.  straight or branched



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1.17: Additional Exercises

Bond Formation: The Octet Rule

1-1 Identify the number of valence electrons for each of the following elements. Then, identify the maximum number of covalent bonds it can form with other atoms while keeping a neutral net charge.

a) Oxygen

b) Carbon

c) Chlorine

d) Sulfur

e) Hydrogen

f) Boron

1-2 Which of the following atoms can bond with Br - to satisfy the octet rule?

a) Mg^{+2}

b) O^{-2}

c) Cl^{-}

d) K^{+}

1-3 Draw the Lewis dot structure of the correct answer from the previous problem **1-2 (a) - (d).**

1-4 Identify which of the following compounds could not form due to an unfilled octet.

a) NCl_3

b) NaOH

c) PCl

d) CF_4

Lewis Structures

1-5 Draw the Lewis structures for the following compounds.

a) H_2O

b) O_3

c) BH_3

d) $SOCl_2$

1-6 Name the element that corresponds to each electronic configuration and identify how many valence electrons it has.

a) $1s^2 2s^2 2p^6$

b) $1s^2 2s^2 2p^6 3s^2$

c) $1s^2 2s^2 2p^4$

d) $1s^2 2s^2 2p^6 3s^2 3p^6 4s^2 3d^{10} 4p5$

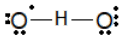
1-7 Draw the Lewis structures for PF_3 and PF_5.

1-8 Draw the Lewis structure for furan.

1-9 Identify the correct Lewis structure for hydroperoxyl, HO_2.

(a)

(b)



(c)

Electronegativity and Bond Polarity

1-10 For the indicated bond in each of the following compounds, identify which atom is more electronegative, if applicable.

(a) $H_3C—CH_3$ (b) $H—NH_2$ (c) $N\equiv CH$

(d) $H_2B—H$ (e) $H_3C—I$ (f) $H_2N—OH$

1-11 For each of the compounds in the previous problem, add a dipole moment arrow.

Formal Charges

1-12 For the following compounds, draw the structural formula. Then calculate the formal charge on each atom other than hydrogen.

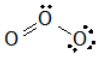
a) $N(CH_3)_4^+$

b) HSO_4^-

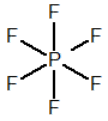
c) CH_3CC^-

1-13 Identify the formal charge for the following compounds.

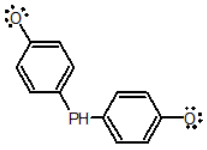
(a)



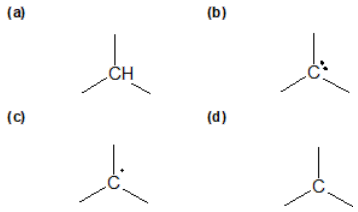
(b)



(c)



1-14 Identify the formal charges for the central carbon in each of the following compounds.



Ionic Structures

1-15 Identify the substituent ions that make up the following salts.

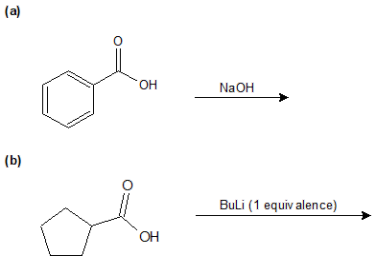
a) NaCl

b) $MgBr_2$

c) KNO_3

d) NaH_2PO_4

1-16 Identify the products of the following reactions.



1-17 Give the correct nomenclature or write the correct chemical formula for the following ionic compounds.

a) NaCN

b) calcium oxalate

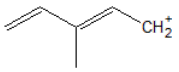
c) $Al(OH)_3$

d) tin (II) phosphate

e) potassium hypochlorite

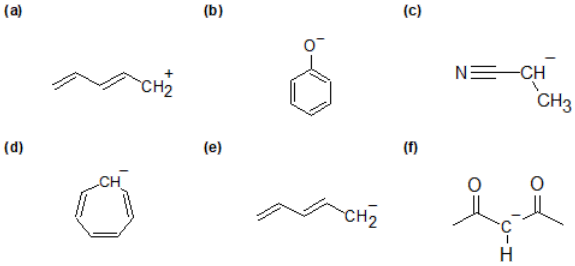
Resonance

1-18 For the following structure, draw its resonance structure(s).



1-19 Which resonance form from the previous problem has the most stable carbocation? Explain your answer.

1-20 Draw the important resonance forms to show the delocalization of charges in the following compounds.



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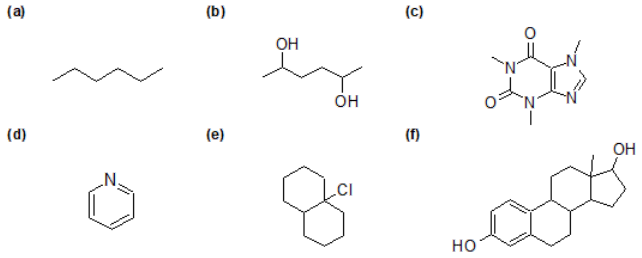
1-21 Explain how resonance contributes to the lower pKa of acetic acid CH_3CO_2H (pKa= 4.75) compared to the pKa of ethanol CH_3CH_2OH (pKa=15.9).

1-22 Draw the resonance structure(s) for fulminic acid (HCNO).

Structural, Molecular and Empirical Formulas

1-23 Identify the molecular and empirical formula for the following structures.



1-24 Draw all possible structural formulas for the following compounds.

a) C_4H_{10}

b) CHN

c) C_4H_9Cl

1-25 True or False: You can always calculate the exact molecular weight of a molecule from its empirical formula.

1-26 For the following molecular formulas, provide the empirical formula.

a) $C_4H_4O_2$

b) $C_8H_6N_2$

c) $C_9H_{21}N_3O_3$

Acids and Bases - Arrhenius, Bronsted-Lowry, and Lewis

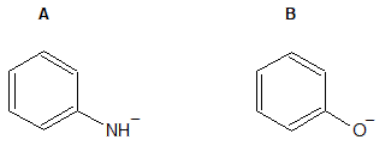
1-27 Briefly explain the three different definitions of acids and bases.

1-28 Calculate the Ka of nitric acid (HNO_3). pKa of nitric acid is -1.4.

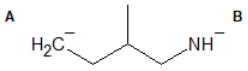
1-29 Rank the following in order of decreasing acidity: NH_4^+ HF H_3O^+ H_2O

1-30 Rank the following in order of decreasing basicity: HSO_4^- H_2O CH_3COO^- NH_2^-

1-31 Identify which compound is the stronger base. Identify which compound is the stronger acid.



1.32 Identify which group is more likely to grab a H^+.



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1.18: Solutions to Additional Exercises

Bond Formation: The Octet Rule

1-1:

a) 6 v.e. / 2 covalent bonds

b) 4 v.e. / 4 covalent bonds

c) 7 v.e. / 1 covalent bond

d) 6 v.e. / 2 covalent bonds (can also expand the octet to make 6 covalent bonds)

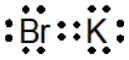
e) 1 v.e. / 1 covalent bond

f) 3 v.e. / 3 covalent bonds

1-2:

(d) K +

1-3:

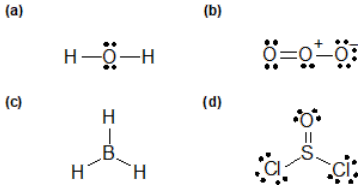


1-4:

(c) PCl

Lewis Structures

1-5:



1-6:

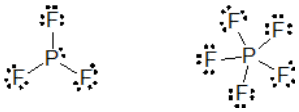
a) Neon, 8 valence electrons

b) Magnesium, 2 valence electrons

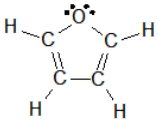
c) Oxygen, 6 valence electrons

d) Bromine, 7 valence electrons

1-7:



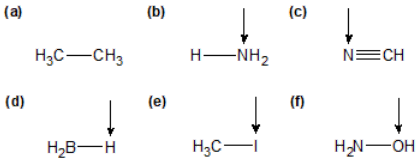
1-8:



1-9: C.

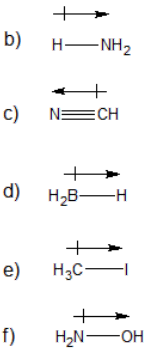
Electronegativity and Bond Polarity

1-10:



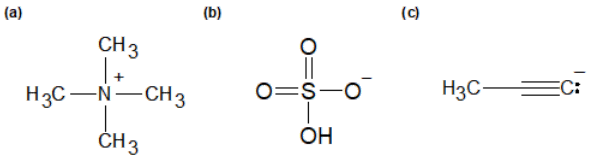
1-11:

a) no dipole moment arrow b/c non-polar



Formal Charges

1-12:



*all atoms have a formal charge of 0 unless otherwise noted.

1-13:

a) 0

b) -1

c) -2

1-14:

a) 0

b) -1

c) 0

d) +1

Ionic Structures

1-15:

a) Na^{+} and Cl^{-}

b) Mg^{+2} and 2 Br^{-}

c) K^{+} and NO_3^{-}

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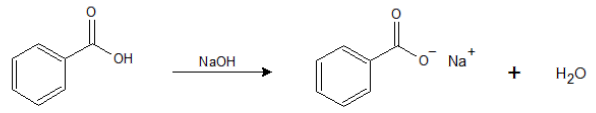
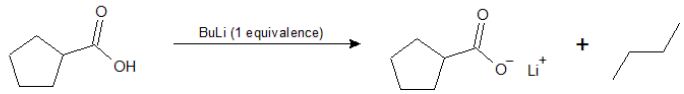
d) Na^+ and $H_2PO_4^-$

1-16:

(a)



(b)



1-17:

a) sodium cyanide

b) CaC_2O_4

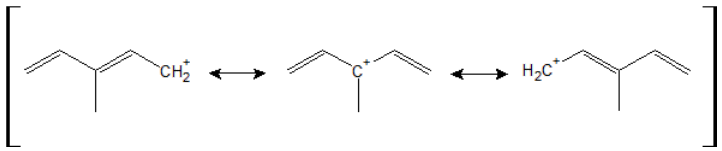
c) aluminum hydroxide

d) $Sn_3(PO_4)_2$

e) KClO

Resonance

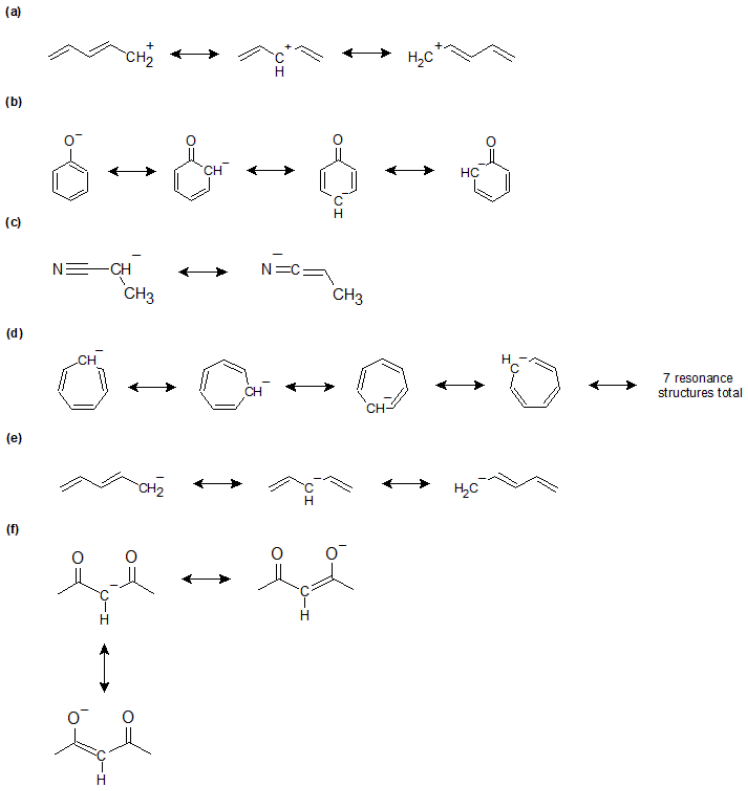
1-18:



1-19:

The resonance structure that is most stable has the tertiary carbocation. This tertiary carbocation is stabilized by hyperconjugation as well as two possible directions for resonance (compared to one immediate resonance structure for the other two carbocations).

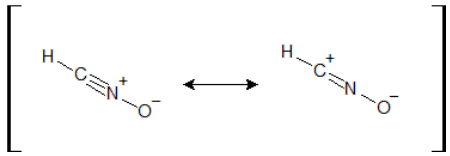
1-20:



1-21:

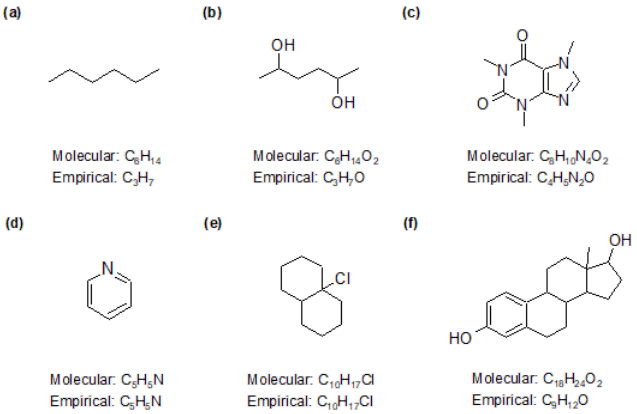
When comparing the deprotonated forms of acetic acid and ethanol, acetate and ethoxide respectively, you can observe that acetate delocalizes the negative charge over the entire carboxylate group. Ethoxide, however, can only hold the negative charge on the alkoxide, making it a better base, but worse as an acid.

1-22:

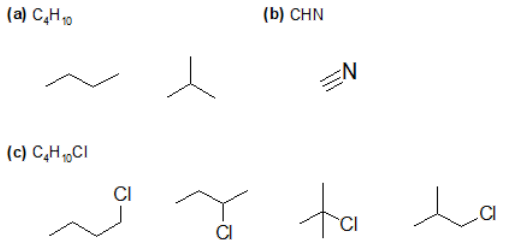


Structural, Molecular and Empirical Formulas

1-23:



1-24:



1-25:

False; empirical formulas are the simplest whole number ratios that are useful in calculating percent compositions of atoms in a molecule. However, as they do not give the absolute number of atoms in a molecule, they cannot be used to calculate the molecular weight of the molecule.

1-26:

a) C_2H_2O

b) C_4H_3N

c) C_9H_7NO

Acids and Bases - Arrhenius, Bronsted-Lowry, and Lewis

1-27:

Arrhenius: An Arrhenius acid is a species that will donate a H+ when dissolved in water. An Arrhenius base is a species that will break down to yield a OH- when dissolved in water.

Bronsted-Lowry: A Bronsted-Lowry acid is a species that will donate a H+ when dissolved in solution (not only in water). A Bronsted-Lowry base is a species that can accept a H+ in solution (not only in water).

Lewis: A Lewis acid is an electron pair acceptor. A Lewis base is an electron base donor.

1-28:

$Ka = 2.4 \times 10^{1}$

1-29:

$H_3O^+ > HF > NH_4^+ > H_2O$

1-30:

$NH_2^- > H_2O > CH_3COO^- > HSO_4^-$

1-31:

Compound A is the stronger base. Compound B is the stronger acid.

1-32:

Group A will want to grab the H^+ more than group B. Since C is less electronegative than N, it cannot stabilize the negative charge as well and will want to grab a H^+ in order to get rid of the charge. (grab = react with)

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CHAPTER OVERVIEW

2: Structure and Properties of Organic Molecules

Learning Objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- define the terms "sterics" and "electrostatics" - refer to section 2.1
- write and interpret molecular orbital (MO) diagrams - refer to section 2.2
- predict the hybridization and geometry of atoms in a molecule - refer to section 2.3
- draw accurate 3-D representations of molecules with approximate bond angles - refer to section 2.3
- recognize conjugated pi bond systems - refer to section 2.4
- recognize that benzene is aromatic - refer to section 2.4
- identify the orbitals occupied by lone pair electrons - refer to section 2.5
- distinguish between bonds that can rotate and those that cannot - refer to section 2.6
- recognize the relationships between constitutional (structural) isomers, conformational isomers, and geometric isomers - refer to section 2.7
- apply the homologous series to organic molecules with 1-10 carbons - refer to section 2.8
- classify hydrocarbons as saturated or unsaturated - refer to section 2.8
- classify hydrocarbons as alkanes, alkenes, alkynes, cycloalkanes, or aromatics (arenes) - refer to section 2.8
- recognize and classify the common functional groups of organic chemistry (alkanes, alkenes, alkynes, alkyl halides, alcohols, amines, ethers, aldehydes, ketones, carboxylic acids, esters, and amides - refer to section 2.9
- determine the dominant intermolecular forces (IMFs) of organic compounds - refer to section 2.10
- predict the relative boil points of organic compounds - refer to section 2.11
- predict whether a mixture of compounds will a form homogeneous or heterogeneous solution - refer to section 2.12
- distinguish between organic compounds that are H-bond donors versus H-bond acceptors - refer to section 2.13
- apply the terms sterics and electrostatics to organic compounds - refer to sections 2.1- 2.13

2.1: Pearls of Wisdom
2.2: Molecular Orbital (MO) Theory (Review)
2.3: Hybridization and Molecular Shapes (Review)
2.4: 2.4 Conjugated Pi Bond Systems
2.5: Lone Pair Electrons and Bonding Theories
2.6: Bond Rotation
2.7: Isomerism Introduction
2.8: Hydrocarbons
2.9: Organic Functional Groups
2.10: Intermolecular Forces (IMFs) - Review
2.11: Intermolecular Forces
2.12: Intermolecular Forces
2.13: Additional Practice Problems
2.14: Organic Functional Groups: H-bond donors
2.15: Additional Exercises
2.16: 2.15 Solutions to Additional Exercises

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2.1: Pearls of Wisdom

Learning Objective

- define the terms "sterics" and "electrostatics"

Introduction

Functional groups are the common bonding patterns found in organic compounds. Organic compounds are classified by their functional groups.

To talk about organic chemistry, we need to be able to

a) recognize and name the major organic functional groups (see chapter 3 for nomenclature)

b) apply bonding theories to the structure of functional groups

c) visual functional groups in three dimensions

d) determine the polarity & intermolecular forces of organic compounds

Ultimately, all of the information above will be integrated at the end of this chapter to predict solubilities and relative boiling points of organic compounds. In future chapters, these skills will help elucidate reaction mechanisms and pathways.

Sterics & Electrostatics - all roads lead to one or other

Sterics and electrostatics are primary considerations when learning the reactions of organic chemistry.

Sterics is the spatial arrangement (3-dimensional structure) of atoms in a molecule or ion.

Electrostatics is the the charge distribution within a molecule or ion.

Depending on the reaction mechanism, either sterics or electrostatics (charge stabilization) will play a dominant role in the rate determining step. For concerted (one-step) reactions, sterics will strongly influence the orientation of reactants in the transition state. For two-step reactions, there is typically a charged intermediate that requires stabilization for the reaction to proceed. The intermediate with the lowest charge distribution is the most stable and reacts preferentially.

Sterics can be predicted using bonding theories. Molecular orbital (MO) theory uses the combination of atomic orbitals to yield molecular orbitals that are delocalized over the entire molecule. In valence bond theory (VB) theory, atomic orbitals can be hybridized. VB theory assumes that all bonds are localized bonds formed between two atoms by the donation of an electron from each atom. As discussed in chapter 1, this assumption is invalid because some atoms can bond using delocalized electrons through resonance. VB theory does a good job of qualitatively describing the shapes of covalent compounds which is important in determining the sterics of the reactions. While Molecular Orbital (MO) theory is good for understanding bonding in general and the electrostatics of a reactant, intermediate, or product.

Electrostatics are determined by applying the same concepts used to determine the relative acidity of compounds by evaluating the electron density of their conjugate bases. The less charge, the more stable an ion is. The stability of ions is determined by the identity of the element being ionized, charge delocalization via resonance, inductive effects, and orbital hybridization. Inductive effects can be electron withdrawing (aka electronegative) or electron donating, such alkyl group stabilization of carbocations. These parameters are listed in order of importance with the overall character of an ion must be evaluated to determine its relative stability. Refer to section 1.15 of this text for the full explanation.

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2.2: Molecular Orbital (MO) Theory (Review)

Learning Objective

- write and interpret molecular orbital (MO) diagrams

Overview

Molecular orbital (MO) theory describes the behavior of electrons in a molecule in terms of combinations of the atomic wavefunctions. The resulting molecular orbitals may extend over all the atoms in the molecule. Bonding molecular orbitals are formed by in-phase combinations of atomic wavefunctions, and electrons in these orbitals stabilize a molecule. Antibonding molecular orbitals result from out-of-phase combinations and electrons in these orbitals make a molecule less stable.

Molecular orbital theory describes the distribution of electrons in molecules in much the same way that the distribution of electrons in atoms is described using atomic orbitals. Using quantum mechanics, the behavior of an electron in a molecule is still described by a wave function, Ψ, analogous to the behavior in an atom. Just like electrons around isolated atoms, electrons around atoms in molecules are limited to discrete (quantized) energies. The region of space in which a valence electron in a molecule is likely to be found is called a molecular orbital (Ψ^2). Like an atomic orbital, a molecular orbital is full when it contains two electrons with opposite spin.

We will consider the molecular orbitals in molecules composed of two identical atoms (H_2 or Cl_2, for example). Such molecules are called homonuclear diatomic molecules. In these diatomic molecules, several types of molecular orbitals occur.

The mathematical process of combining atomic orbitals to generate molecular orbitals is called the linear combination of atomic orbitals (LCAO). The wave function describes the wavelike properties of an electron. Molecular orbitals are combinations of atomic orbital wave functions. Combining waves can lead to constructive interference, in which peaks line up with peaks, or destructive interference, in which peaks line up with troughs (Figure **2.2.2**). In orbitals, the waves are three dimensional, and they combine with in-phase waves producing regions with a higher probability of electron density and out-of-phase waves producing nodes, or regions of no electron density.

Figure **2.2.2**: (a) When in-phase waves combine, constructive interference produces a wave with greater amplitude. (b) When out-of-phase waves combine, destructive interference produces a wave with less (or no) amplitude.

There are two types of molecular orbitals that can form from the overlap of two atomic *s* orbitals on adjacent atoms. The two types are illustrated in Figure 8.4.3. The in-phase combination produces a lower energy σ_s molecular orbital (read as "sigma-s") in which most of the electron density is directly between the nuclei. The out-of-phase addition (which can also be thought of as subtracting the wave functions) produces a higher energy σ_s^* molecular orbital (read as "sigma-s-star") molecular orbital in which there is a node between the nuclei. The asterisk signifies that the orbital is an antibonding orbital. Electrons in a σ_s orbital are attracted by both nuclei at the same time and are more stable (of lower energy) than they would be in the isolated atoms. Adding electrons to these orbitals creates a force that holds the two nuclei together, so we call these orbitals bonding orbitals. Electrons in the σ_s^* orbitals are located well away from the region between the two nuclei. The attractive force between the nuclei and these electrons pulls the two nuclei apart. Hence, these orbitals are called antibonding orbitals. Electrons fill the lower-energy bonding orbital before the higher-energy antibonding orbital, just as they fill lower-energy atomic orbitals before they fill higher-energy atomic orbitals.

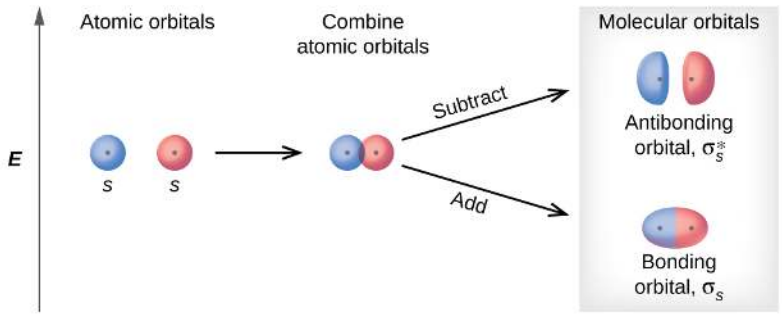


Figure **2.2.3**: Sigma (σ) and sigma-star (σ*) molecular orbitals are formed by the combination of two s atomic orbitals. The plus (+) signs indicate the locations of nuclei.

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 (Figure **2.2.4**). If two atoms are located along the *x*-axis in a Cartesian coordinate system, the two p_x orbitals overlap end to end and form σ_{px} (bonding) and σ^*_{px} (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.

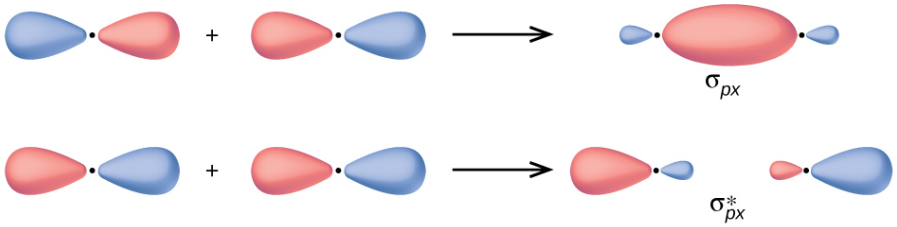


Figure **2.2.4**: Combining wave functions of two *p* atomic orbitals along the internuclear axis creates two molecular orbitals, σ_p and σ^*_p.

The side-by-side overlap of two *p* orbitals gives rise to a pi (π) bonding molecular orbital and a π* antibonding molecular orbital, as shown in Figure **2.2.5**. In valence bond theory, we describe π bonds as containing a nodal plane containing the internuclear axis and perpendicular to the lobes of the *p* orbitals, with electron density on either side of the node. In molecular orbital theory, we describe the π orbital by this same shape, and a π bond exists when this orbital contains electrons. Electrons in this orbital interact with both nuclei and help hold the two atoms together, making it a bonding orbital. For the out-of-phase combination, there are two nodal planes created, one along the internuclear axis and a perpendicular one between the nuclei.

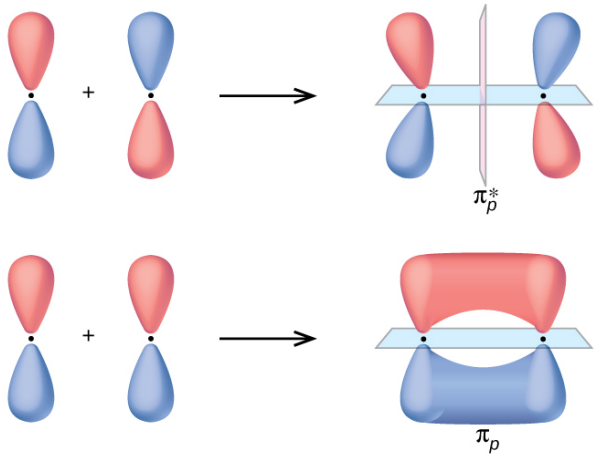
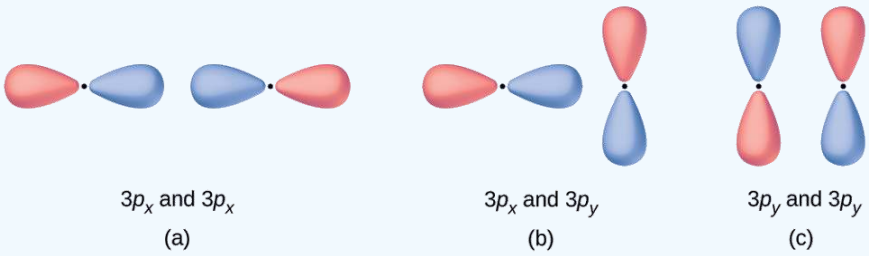


Figure **2.2.5**: Side-by-side overlap of each two p orbitals results in the formation of two π molecular orbitals. Combining the out-of-phase orbitals results in an antibonding molecular orbital with two nodes. One contains the internuclear axis, and one is perpendicular to the axis. Combining the in-phase orbitals results in a bonding orbital. There is a node (blue plane) containing the internuclear axis with the two lobes of the orbital located above and below this node.

In the molecular orbitals of diatomic molecules, each atom also has two sets of *p* orbitals oriented side by side (p_y and p_z), so these four atomic orbitals combine pairwise to create two π orbitals and two π* orbitals. The π_{py} and π^*_{py} orbitals are oriented at right angles to the π_{pz} and π^*_{pz} orbitals. Except for their orientation, the π_{py} and π_{pz} orbitals are identical and have the same energy; they are degenerate orbitals. The π^*_{py} and π^*_{pz} antibonding orbitals are also degenerate and identical except for their orientation. A total of six molecular orbitals results from the combination of the six atomic *p* orbitals in two atoms: σ_{px} and σ^*_{px}, π_{py} and π^*_{py}, π_{pz} and π^*_{pz}.

Example 2.2.1

Molecular Orbitals Predict what type (if any) of molecular orbital would result from adding the wave functions so each pair of orbitals shown overlap. The orbitals are all similar in energy.



Solution

a. This is an in-phase combination, resulting in a σ_{3p} orbital
b. This will not result in a new orbital because the in-phase component (bottom) and out-of-phase component (top) cancel out. Only orbitals with the correct alignment can combine.
c. This is an out-of-phase combination, resulting in a π^*_{3p} orbital.

Exercise 2.2.1

Label the molecular orbital shown as σ or π, bonding or antibonding and indicate where the node occurs.

Answer

The orbital is located along the internuclear axis, so it is a σ orbital. There is a node bisecting the internuclear axis, so it is an antibonding orbital.

Molecular Orbital Energy Diagrams

The relative energy levels of atomic and molecular orbitals are typically shown in a molecular orbital diagram (Figure **2.2.7**). For a diatomic molecule, the atomic orbitals of one atom are shown on the left, and those of the other atom are shown on the right. Each horizontal line represents one orbital that can hold two electrons. The molecular orbitals formed by the combination of the atomic orbitals are shown in the center. Dashed lines show which of the atomic orbitals combine to form the molecular orbitals. For each pair of atomic orbitals that combine, one lower-energy (bonding) molecular orbital and one higher-energy (antibonding) orbital result. Thus we can see that combining the six 2*p* atomic orbitals results in three bonding orbitals (one σ and two π) and three antibonding orbitals (one σ* and two π*).

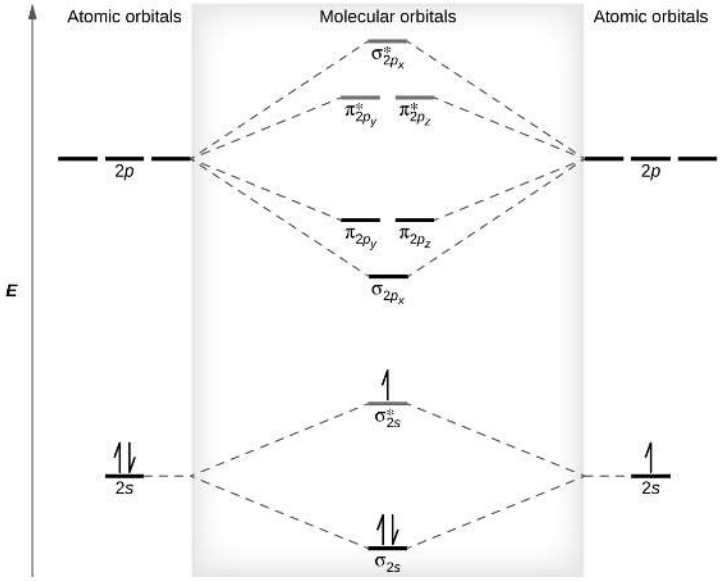


Figure **2.2.7**: This is the molecular orbital diagram for the homonuclear diatomic $\mathbf{Be_2^+}$, *showing the molecular orbitals of the valence shell only. The molecular orbitals are filled in the same manner as atomic orbitals, using the Aufbau principle and Hund's rule.*

We predict the distribution of electrons in these molecular orbitals by filling the orbitals in the same way that we fill atomic orbitals, by the Aufbau principle. Lower-energy orbitals fill first, electrons spread out among degenerate orbitals before pairing, and each orbital can hold a maximum of two electrons with opposite spins (Figure **2.2.7**). Just as we write electron configurations for atoms, we can write the molecular electronic configuration by listing the orbitals with superscripts indicating the number of electrons present. For clarity, we place parentheses around molecular orbitals with the same energy. In this case, each orbital is at a different energy, so parentheses separate each orbital. Thus we would expect a diatomic molecule or ion containing seven electrons (such as $\mathbf{Be_2^+}$) would have the molecular electron configuration $(\sigma_{1s})^2(\sigma_{1s}^*)^2(\sigma_{2s})^2(\sigma_{2s}^*)^1$. It is common to omit the core electrons from molecular orbital diagrams and configurations and include only the valence electrons.

Bond Order

The filled molecular orbital diagram shows the number of electrons in both bonding and antibonding molecular orbitals. The net contribution of the electrons to the bond strength of a molecule is identified by determining the bond order that results from the filling of the molecular orbitals by electrons.

When using Lewis structures to describe the distribution of electrons in molecules, we define bond order as the number of bonding pairs of electrons between two atoms. Thus a single bond has a bond order of 1, a double bond has a bond order of 2, and a triple bond has a bond order of 3. We define bond order differently when we use the molecular orbital description of the distribution of

electrons, but the resulting bond order is usually the same. The MO technique is more accurate and can handle cases when the Lewis structure method fails, but both methods describe the same phenomenon.

In the molecular orbital model, an electron contributes to a bonding interaction if it occupies a bonding orbital and it contributes to an antibonding interaction if it occupies an antibonding orbital. The bond order is calculated by subtracting the destabilizing (antibonding) electrons from the stabilizing (bonding) electrons. Since a bond consists of two electrons, we divide by two to get the bond order. We can determine bond order with the following equation:

$$\text{bond order} = \frac{(\text{number of bonding electrons}) - (\text{number of antibonding electrons})}{2} \tag{2.2.1}$$

The order of a covalent bond is a guide to its strength; a bond between two given atoms becomes stronger as the bond order increases. If the distribution of electrons in the molecular orbitals between two atoms is such that the resulting bond would have a bond order of zero, a stable bond does not form. We next look at some specific examples of MO diagrams and bond orders.

Bonding in Diatomic Molecules

A dihydrogen molecule (H_2) forms from two hydrogen atoms. When the atomic orbitals of the two atoms combine, the electrons occupy the molecular orbital of lowest energy, the σ_{1s} bonding orbital. A dihydrogen molecule, H_2, readily forms because the energy of a H_2 molecule is lower than that of two H atoms. The σ_{1s} orbital that contains both electrons is lower in energy than either of the two 1*s* atomic orbitals.

A molecular orbital can hold two electrons, so both electrons in the H_2 molecule are in the σ_{1s} bonding orbital; the electron configuration is $(\sigma_{1s})^2$. We represent this configuration by a molecular orbital energy diagram (Figure **2.2.8**) in which a single upward arrow indicates one electron in an orbital, and two (upward and downward) arrows indicate two electrons of opposite spin.

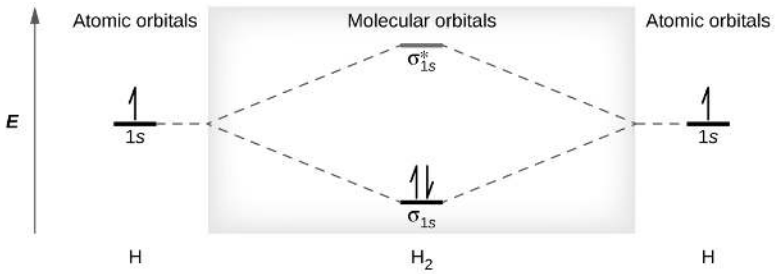


Figure **2.2.8**:*The molecular orbital energy diagram predicts that H_2 will be a stable molecule with lower energy than the separated atoms.*

A dihydrogen molecule contains two bonding electrons and no antibonding electrons so we have

$$\text{bond order in } H_2 = \frac{(2-0)}{2} = 1 \tag{2.2.2}$$

Because the bond order for the H–H bond is equal to 1, the bond is a single bond.

A helium atom has two electrons, both of which are in its 1*s* orbital. Two helium atoms do not combine to form a dihelium molecule, He_2, with four electrons, because the stabilizing effect of the two electrons in the lower-energy bonding orbital would be offset by the destabilizing effect of the two electrons in the higher-energy antibonding molecular orbital. We would write the hypothetical electron configuration of He_2 as $(\sigma_{1s})^2(\sigma^*_{1s})^2$ as in Figure **2.2.9** . The net energy change would be zero, so there is no driving force for helium atoms to form the diatomic molecule. In fact, helium exists as discrete atoms rather than as diatomic molecules. The bond order in a hypothetical dihelium molecule would be zero.

$$\text{bond order in } He_2 = \frac{(2-2)}{2} = 0 \tag{2.2.3}$$

A bond order of zero indicates that no bond is formed between two atoms.

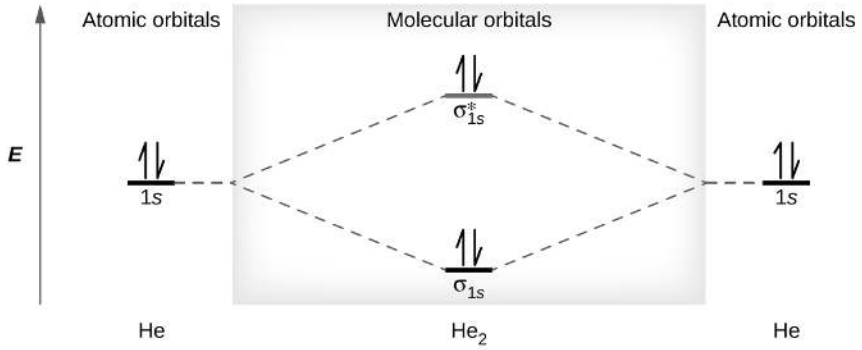


Figure **2.2.9**: *The molecular orbital energy diagram predicts that He_2 will not be a stable molecule, since it has equal numbers of bonding and antibonding*

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- Paul Flowers (University of North Carolina - Pembroke), Klaus Theopold (University of Delaware) and Richard Langley (Stephen F. Austin State University) with contributing authors. Textbook content produced by OpenStax College is licensed under a Creative Commons Attribution License 4.0 license. Download for free at http://cnx.org/contents/85abf193-2bd...a7ac8df6@9.110).

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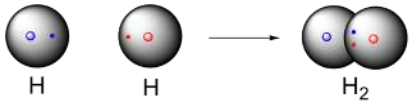
2.3: Hybridization and Molecular Shapes (Review)

Learning Objectives

- predict the hybridization and geometry of atoms in a molecule - refer to section 2.3
- draw accurate 3-D representations of molecules with approximate bond angles

Formation of sigma bonds: the H_2 molecule

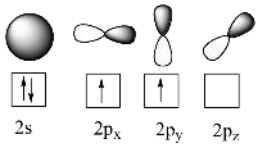
The simplest case to consider is the hydrogen molecule, H_2. When we say that the two electrons from each of the hydrogen atoms are shared to form a covalent bond between the two atoms, what we mean in valence bond theory terms is that the two spherical 1*s* orbitals overlap, allowing the two electrons to form a pair within the two overlapping orbitals.



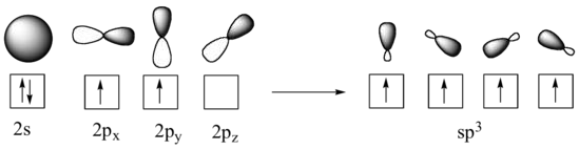
These two electrons are now attracted to the positive charge of *both* of the hydrogen nuclei, with the result that they serve as a sort of 'chemical glue' holding the two nuclei together.

Bonding in Methane

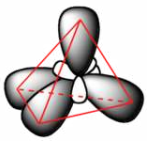
Now let's turn to methane, the simplest organic molecule. Recall the valence electron configuration of the central carbon:



This picture, however, is problematic. How does the carbon form four bonds if it has only two half-filled *p* orbitals available for bonding? A hint comes from the experimental observation that the four C-H bonds in methane are arranged with tetrahedral geometry about the central carbon, and that each bond has the same length and strength. 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.



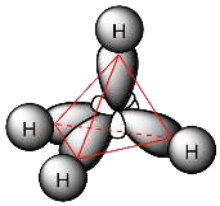
The sp^3 hybrid orbitals, like the *p* orbitals of which they are partially composed, are oblong in shape, and have two lobes of opposite sign. Unlike the *p* orbitals, however, the two lobes are of very different size. The larger lobes of the sp^3 hybrids are directed towards the four corners of a tetrahedron, meaning that the angle between any two orbitals is 109.5°.



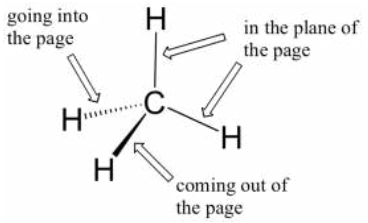
This geometric arrangement makes perfect sense if you consider that it is precisely this angle that allows the four orbitals (and the electrons in them) to be as far apart from each other as possible.This is simply a restatement of the Valence Shell Electron Pair

Repulsion (VSEPR) theory that you learned in General Chemistry: electron pairs (in orbitals) will arrange themselves in such a way as to remain as far apart as possible, due to negative-negative electrostatic repulsion.

Each C-H bond in methane, then, can be described as an overlap between a half-filled 1*s* orbital in a hydrogen atom and the larger lobe of one of the four half-filled sp^3 hybrid orbitals in the central carbon. The length of the carbon-hydrogen bonds in methane is 1.09 Å (1.09×10^{-10} m).



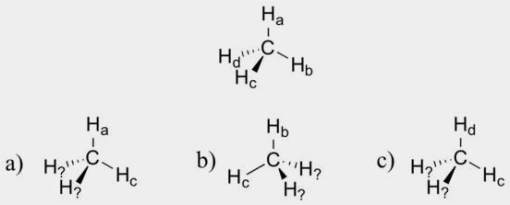
While previously we drew a Lewis structure of methane in two dimensions using lines to denote each covalent bond, we can now draw a more accurate structure in three dimensions, showing the tetrahedral bonding geometry. To do this on a two-dimensional page, though, we need to introduce a new drawing convention: the solid / dashed wedge system. In this convention, a solid wedge simply represents a bond that is meant to be pictured emerging from the plane of the page. A dashed wedge represents a bond that is meant to be pictured pointing into, or behind, the plane of the page. Normal lines imply bonds that lie in the plane of the page.



This system takes a little bit of getting used to, but with practice your eye will learn to immediately 'see' the third dimension being depicted.

Example

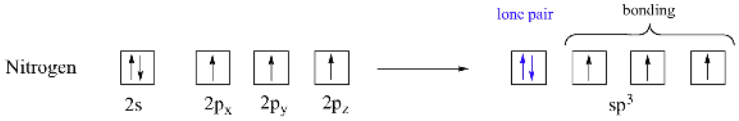
Imagine that you could distinguish between the four hydrogens in a methane molecule, and labeled them H_a through H_d. In the images below, the *exact same* methane molecule is rotated and flipped in various positions. Draw the missing hydrogen atom labels. (It will be much easier to do this if you make a model.)



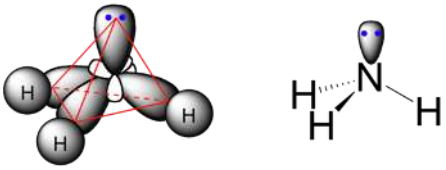
Exercise

Describe, with a picture and with words, the bonding in chloroform, $CHCl_3$.

Solutions

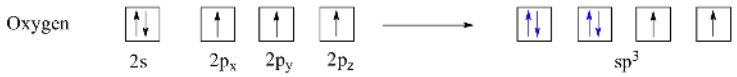


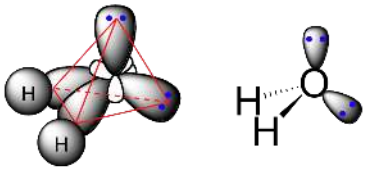
The bonding arrangement here is also tetrahedral: the three N-H bonds of ammonia can be pictured as forming the base of a trigonal pyramid, with the fourth orbital, containing the lone pair, forming the top of the pyramid.



Recall from your study of VSEPR theory in General Chemistry that the lone pair, with its slightly greater repulsive effect, 'pushes' the three N-H sbonds away from the top of the pyramid, meaning that the H-N-H bond angles are slightly less than tetrahedral, at 107.3˚ rather than 109.5˚.

VSEPR theory also predicts, accurately, that a water molecule is 'bent' at an angle of approximately 104.5˚. It would seem logical, then, to describe the bonding in water as occurring through the overlap of sp^3-hybrid orbitals on oxygen with 1sorbitals on the two hydrogen atoms. In this model, the two nonbonding lone pairs on oxygen would be located in sp^3 orbitals.





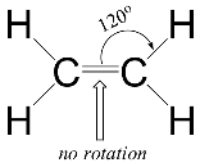
Some experimental evidence, however, suggests that the bonding orbitals on the oxygen are actually unhybridized 2*p* orbitals rather than sp^3 hybrids. Although this would seem to imply that the H-O-H bond angle should be 90˚ (remember that *p* orbitals are oriented perpendicular to one another), it appears that electrostatic repulsion has the effect of distorting this *p*-orbital angle to 104.5˚. Both the hybrid orbital and the nonhybrid orbital models present reasonable explanations for the observed bonding arrangement in water, so we will not concern ourselves any further with the distinction.

Exercise
Draw, in the same style as the figures above, an orbital picture for the bonding in methylamine. Solution

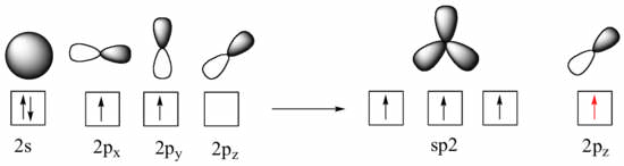
Formation of π bonds - sp^2 and sp hybridization

The valence bond theory, along with the hybrid orbital concept, does a very good job of describing double-bonded compounds such as ethene. Three experimentally observable characteristics of the ethene molecule need to be accounted for by a bonding model:

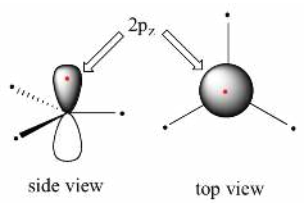
1. Ethene is a planar (flat) molecule.
2. Bond angles in ethene are approximately 120°, and the carbon-carbon bond length is 1.34 Å, significantly shorter than the 1.54 Å single carbon-carbon bond in ethane.
3. There is a significant barrier to rotation about the carbon-carbon double bond.



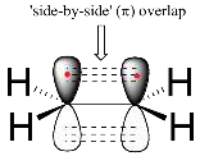
Clearly, these characteristics are not consistent with an sp^3 hybrid bonding picture for the two carbon atoms. Instead, the bonding in ethene is described by a model involving the participation of a different kind of hybrid orbital. Three atomic orbitals on each carbon – the 2*s*, $2p_x$ and $2p_y$ orbitals – combine to form three sp^2 hybrids, leaving the $2p_z$ orbital unhybridized.



The three sp^2 hybrids are arranged with trigonal planar geometry, pointing to the three corners of an equilateral triangle, with angles of 120°between them. The unhybridized $2p_z$ orbital is *perpendicular* to this plane (in the next several figures, sp^2 orbitals and the sigma bonds to which they contribute are represented by lines and wedges; only the $2p_z$ orbitals are shown in the 'space-filling' mode).

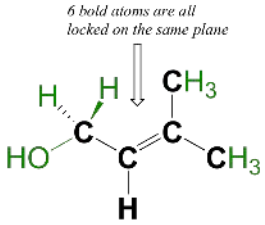


The carbon-carbon double bond in ethene consists of one sbond, formed by the overlap of two sp^2 orbitals, and a second bond, calleda **π (pi) bond**, which is formed by the *side-by-side* overlap of the two unhybridized $2p_z$ orbitals from each carbon.

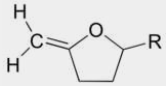


spacefilling image of bonding in ethene

The pi bond does *not* have symmetrical symmetry. 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. The presence of the pi bond thus ‘locks’ the six atoms of ethene into the same plane. This argument extends to larger alkene groups: in each case, the six atoms of the group form a single plane.

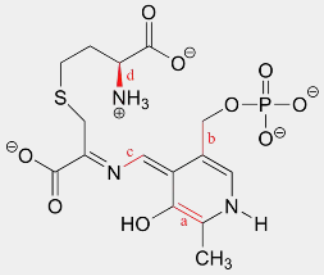


Conversely, sbonds such as the carbon-carbon single bond in ethane (CH_3CH_3) exhibit free rotation, and can assume many different conformations, or shapes - this is one of the main subjects of Chapter 3.

Exercise
Circle the six atoms in the molecule below that are ‘locked’ into the same plane. 

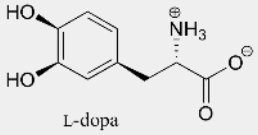
Exercise

What kinds of orbitals are overlapping in bonds a-d indicated below?



Exercise

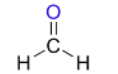
What is wrong with the way the following structure is drawn?



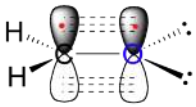
L-dopa

Solutions

A similar picture can be drawn for the bonding in carbonyl groups, such as formaldehyde. In this molecule, the carbon is sp^2-hybridized, and we will assume that the oxygen atom is also sp^2 hybridized. The carbon has three sigma bonds: two are formed by overlap between two of its sp^2 orbitals with the 1sorbital from each of the hydrogens, and the third sigma bond is formed by overlap between the remaining carbon sp^2 orbital and an sp^2 orbital on the oxygen. The two lone pairs on oxygen occupy its other two sp^2 orbitals.



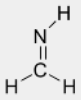
formaldehyde



The pi bond is formed by side-by-side overlap of the unhybridized $2p_z$ orbitals on the carbon and the oxygen. Just like in alkenes, the $2p_z$ orbitals that form the pi bond are perpendicular to the plane formed by the sigma bonds.

Exercise

Describe and draw the bonding picture for the imine group shown below. Use the drawing of formaldehyde above as your guide.



Solution

Contributors and Attributions

- **Organic Chemistry With a Biological Emphasis** by Tim Soderberg (University of Minnesota, Morris)

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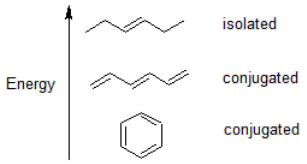
2.4: 2.4 Conjugated Pi Bond Systems

Learning Objective

- recognize conjugated pi bond systems
- recognize that benzene is aromatic

Introduction

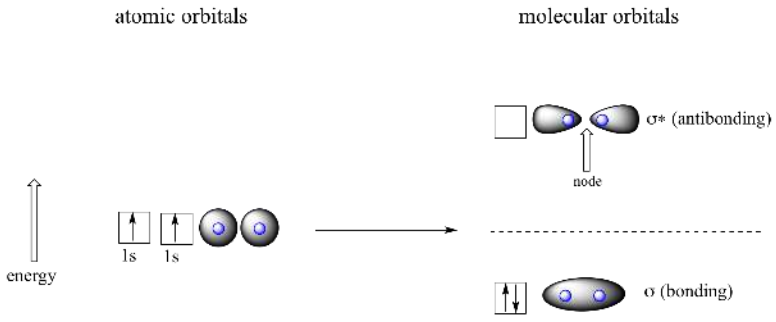
It is important to train our eye to recognize structural features that have stabilizing effects. Alternating single and double bonds create a conjugated pi bond system across multiple atoms that lowers the energy and stabilizes the molecule or ion. When we look at carbon-carbon double bonds (C=C), we need to look and see if they are isolated or conjugated.



To understand the source of this stabilization we will use molecular orbital (MO) theory. Valence bond theory does a remarkably good job at explaining the bonding geometry of many of the functional groups in organic compounds, however, it fails to adequately account for the stability contained in alternating double and single bonds. In order to understand these properties, we will use the ideas of MO theory.

Let's go back and 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 mathematically combine to form two new orbitals. Recall that an atomic orbital (such as the 1s orbital of a hydrogen atom) describes a region of space around a single atom inside which electrons are likely to be found. *A molecular orbital describes a region of space around two or more atoms inside which electrons are likely to be found.*

Mathematical principles tell us that when orbitals combine, the number of orbitals before the combination takes place must equal the number of new orbitals that result from the combination – 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* **sigma (σ) orbitals**.



Molecular orbitals for H_2

According to MO theory, one sigma orbital is lower in energy than either of the two isolated atomic 1*s* orbitals –this lower sigma orbital is referred to as a **bonding molecular orbital**. The second, **'sigma star' orbital** is higher in energy than the two atomic 1*s* orbitals, and is referred to as an **antibonding molecular 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, antibonding sigma*

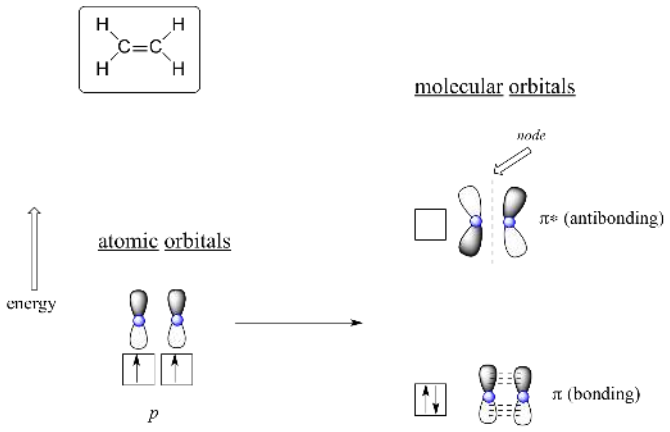
orbital can be visualized as a pair of droplets, with areas of higher electron density near each nucleus and a ‘node’, (area of zero electron density) midway between the two nuclei.

Remember that we are thinking here about electron behavior as *wave behavior*. When two separate waves combine, they can do so with **constructive interference**, where the two amplitudes build up and reinforce one another, or **destructive interference**, where the two amplitudes cancel one another out. Bonding MOs 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. Antibonding MO’s are the consequence of destructive interference which results in a repulsive interaction and a region of zero electron density between the nuclei (in other words, a node).

Following the same *aufbau* ('building up') principle you learned in General Chemistry for writing out electron configurations, we place the two electrons in the H_2 molecule in the lowest energy molecular orbital, which is the (bonding) sigma orbital. The bonding (attracting) MO is full, and the antibonding (repulsing) MO is empty.

MO theory and conjugated pi bonds

The advantage of using MO theory to understand bonding in organic molecules becomes more apparent when we think about pi bonds. Let’s first consider the pi bond in ethene from an MO theory standpoint (in this example we will be disregarding the s bonds in the molecule, and thinking *only* about the π bond). We start with two atomic orbitals: one unhybridized 2p orbital from each carbon. Each contains a single electron. In MO theory, the two atomic combine mathematically to form two **pi molecular orbitals**, one a low-energy pi bonding orbital and one a high-energy pi* antibonding orbital.



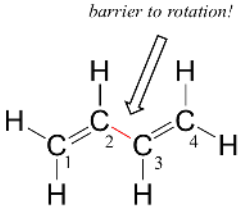
Molecular orbitals for ethene (ethylene)

In the bonding pi orbital, the two shaded lobes of the *p* orbitals interact *constructively* with each other, as do the two unshaded lobes (remember, the arbitrary shading choice represents mathematical (+) and (-) signs for the mathematical wavefunction describing the orbital). There is increased electron density between the two carbon nuclei in the molecular orbital - it is a bonding interaction.

In the higher-energy antibonding pi* orbital, the shaded lobe of one *p* orbital interacts *destructively* with the unshaded lobe of the second *p* orbital, leading to a node between the two nuclei and overall repulsion between the carbon nuclei.

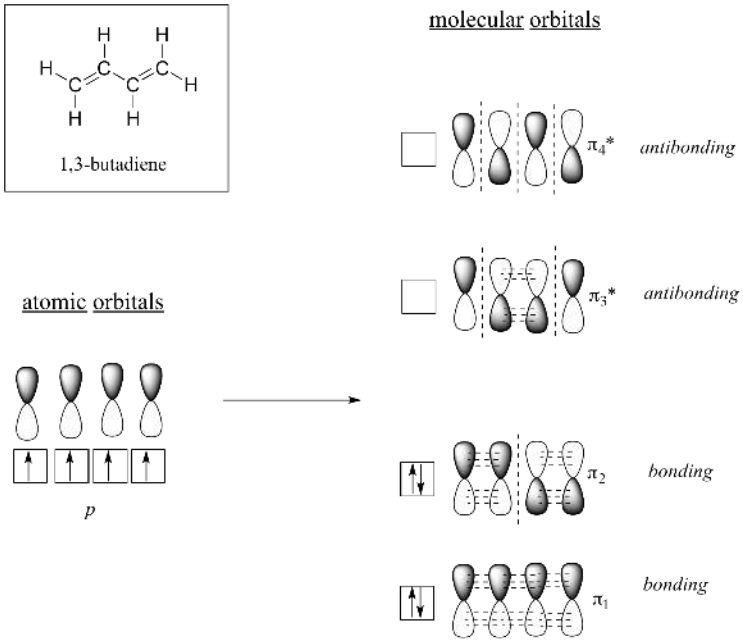
Again using the 'building up' principle, we place the two electrons in the lower-energy, bonding pi molecular orbital. The antibonding pi* orbital remains empty.

Next, we'll consider the 1,3-butadiene molecule. From valence orbital theory alone we might expect that the C_2-C_3 bond in this molecule, because it is a sigma bond, would be able to rotate freely.



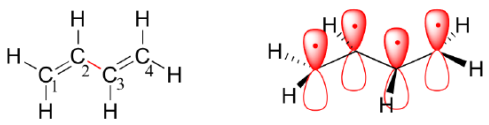
Experimentally, however, it is observed that there is a significant barrier to rotation about the C_2-C_3 bond, and that the entire molecule is planar. In addition, the C_2-C_3 bond is 148 pm long, shorter than a typical carbon-carbon single bond (about 154 pm), though longer than a typical double bond (about 134 pm).

Molecular orbital theory accounts for these observations with the concept of **delocalized pi bonds**. In this picture, the four *2p* atomic orbitals combine mathematically to form four pi molecular orbitals of increasing energy. Two of these - the bonding pi orbitals - are lower in energy than the *p* atomic orbitals from which they are formed, while two - the antibonding pi* orbitals - are higher in energy.



The lowest energy molecular orbital, pi_1, has only constructive interaction and zero nodes. Higher in energy, but still lower than the isolated *p* orbitals, the pi_2 orbital has one node but two constructive interactions - thus it is still a bonding orbital overall. Looking at the two antibonding orbitals, pi_3* has two nodes and one constructive interaction, while pi_4* has three nodes and zero constructive interactions.

By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding pi_1 and pi_2 MO's. Because pi_1 includes constructive interaction between C_2 and C_3, there is a degree, in the 1,3-butadiene molecule, of pi-bonding interaction between these two carbons, which accounts for its shorter length and the barrier to rotation. The valence bond picture of 1,3-butadiene shows the two pi bonds as being isolated from one another, with each pair of pi electrons 'stuck' in its own pi bond. However, molecular orbital theory predicts (accurately) that the four pi electrons are to some extent delocalized, or 'spread out', over the whole pi system.



1,3-butadiene

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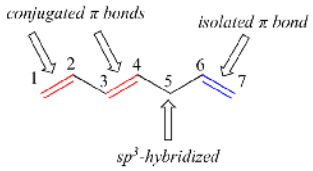
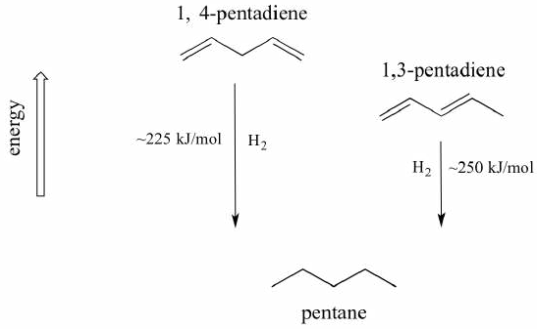
space-filling view

1,3-butadiene is the simplest example of a system of **conjugated pi bonds**. To be considered conjugated, two or more pi bonds must be separated by only one single bond – in other words, there cannot be an intervening sp^3-hybridized carbon, because this would break up the overlapping system of parallel *p* orbitals. In the compound below, for example, the C_1-C_2 and C_3-C_4 double bonds are conjugated, while the C_6-C_7 double bond is **isolated** from the other two pi bonds by sp^3-hybridized C_5.

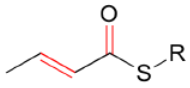


A very important concept to keep in mind is that *there is an inherent thermodynamic stability associated with conjugation.* This stability can be measured experimentally by comparing the **heat of hydrogenation** of two different dienes. (Hydrogenation is a reaction type that we will learn much more about in chapter 15: essentially, it is the process of adding a hydrogen molecule - two protons and two electrons - to a p bond). When the two *conjugated* double bonds of 1,3-pentadiene are 'hydrogenated' to produce pentane, about 225 kJ is released per mole of pentane formed. Compare that to the approximately 250 kJ/mol released when the two *isolated* double bonds in 1,4-pentadiene are hydrogenated, also forming pentane.

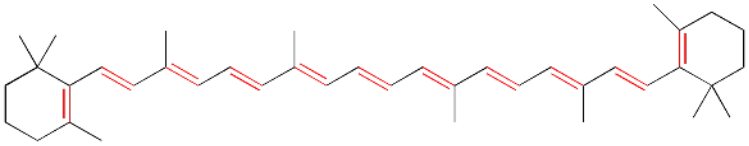


The conjugated diene is lower in energy: in other words, it is more stable. In general, conjugated pi bonds are more stable than isolated pi bonds.

Conjugated pi systems can involve oxygen and nitrogen atoms as well as carbon. In the metabolism of fat molecules, some of the key reactions involve alkenes that are conjugated to carbonyl groups.



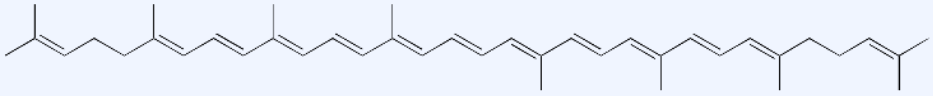
In chapter 4, we will see that MO theory is very useful in explaining why organic molecules that contain extended systems of conjugated pi bonds often have distinctive colors. beta-carotene, the compound responsible for the orange color of carrots, has an extended system of 11 conjugated pi bonds.



beta-carotene

Exercise: Identify all conjugated and isolated double bonds in the structures below. For each conjugated pi system, specify the number of overlapping *p* orbitals, and how many pi electrons are shared among them.

Exercise: 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?

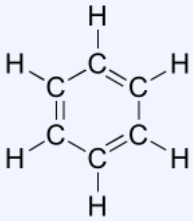


lycopene

Solutions to exercises

Aromaticity - The Ultimate Conjugated System

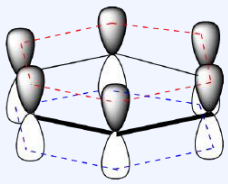
Molecular orbital theory is especially helpful in explaining the unique properties of **aromatic** compounds such as benzene:



3D interactive model of benzene

Although benzene is most often drawn with three double bonds and three single bonds, in fact all of the carbon-carbon bonds iare exactly the same length (138 pm). In addition, the pi bonds in benzene are significantly less reactive than 'normal' pi bonds, either isolated or conjugated. Something about the structure of benzene makes its pi bonding arrangement especially stable. This ‘something’ has a name: it is called ‘aromaticity’.

What exactly is this ‘aromatic’ property that makes the pi bonds in benzene so stable? In large part, the answer to this question lies in the fact that benzene is a *cyclic* molecule in which all of the ring atoms are sp^2-hybridized. This allows the pi electrons to be delocalized in molecular orbitals that extend all the way around the ring, above and below the plane. For this to happen, of course, the ring must be planar – otherwise the *p* orbitals couldn’t overlap properly. Benzene is indeed known to be a flat molecule.

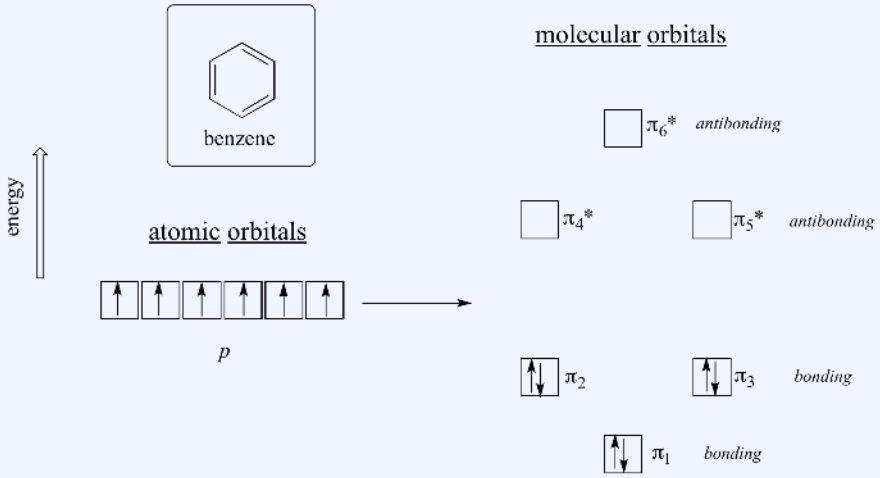


π electrons delocalized around the ring, above and below the plane

Do all cyclic molecules with alternating single and double bonds have this same aromatic stability? The answer, in fact, is ‘no’. The eight-membered cyclooctatetraene ring shown below is *not* flat, and its π bonds react like 'normal' alkenes.

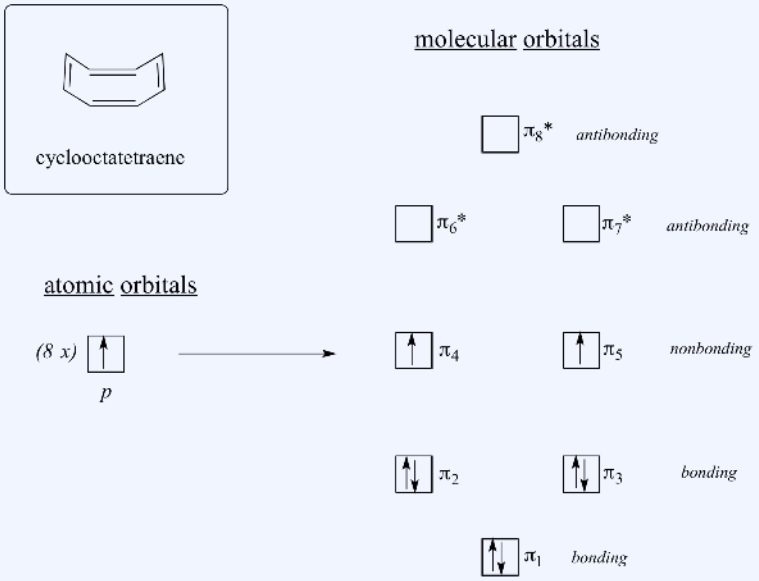
cyclooctatetraene
(not aromatic)

Clearly it takes something more to be aromatic, and this can best be explained with molecular orbital theory. Let’s look at an energy diagram of the pi molecular orbitals in benzene.



Quantum mechanical calculations tell us that the six pi molecular orbitals in benzene, formed from six atomic *p* orbitals, occupy four separate energy levels. pi_1 and pi_6* have unique energy levels, while the pi_2 - pi_3 and pi_4*- pi_5* pairs are **degenerate**, meaning they are at the same energy level. When we use the *aufbau* principle to fill up these orbitals with the six pi electrons in benzene, we see that the bonding orbitals are completely filled, and the antibonding orbitals are empty. This gives us a good clue to the source of the special stability of benzene: a full set of bonding MO's is similar in many ways to the 'full shell' of electrons in the atomic orbitals of the stable noble gases helium, neon, and argon.

Now, let's do the same thing for cyclooctatetraene, which we have already learned is *not* aromatic.



The result of molecular orbital calculations tells us that the lowest and highest energy MOs (pi_1 and pi_8*) have unique energy levels, while the other six form degenerate pairs. Notice that pi_4 and pi_5 are at the same energy level as the isolated $2p_z$ atomic orbitals: these are therefore neither bonding nor antibonding, rather they are referred to as **nonbonding MOs**. Filling up the MOs with the eight pi electrons in the molecule, we find that the last two electrons are unpaired and fall into the two degenerate nonbonding orbitals. Because we don't have a perfect filled shell of bonding MOs, our molecule is not aromatic. As a consequence, each of the double bonds in cyclooctatetraene acts more like an *isolated* double bond.

For now, the important learning objective is to recognize conjugated pi bonds systems and understand the benzene is exceptionally stable exhibiting a property called aromaticity. Aromaticity and chemistry of aromatic compounds is relatively complex and is discussed in greater detail in subsequent chapters of this text.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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2.5: Lone Pair Electrons and Bonding Theories

Learning Objective

- identify the orbitals occupied by lone pair electrons

Valence Bond and Molecular Orbital Theories

The table below summarizes the main points of the two complementary bonding theories. Both theories provide different, useful ways of describing molecular structure. We will use both theories and often blend them to analyze and predict chemical structure and reactivity. The bonding theories are reviewed in greater detail in the next two sections.

Comparison of Bonding Theories

Valence Bond Theory	Molecular Orbital Theory
considers bonds as localized between one pair of atoms	considers electrons delocalized throughout the entire molecule
creates bonds from overlap of atomic orbitals (*s*, *p*, *d*…) and hybrid orbitals (*sp*, sp^2, sp^3…)	combines atomic orbitals to form molecular orbitals (σ, σ*, π, π*)
forms σ or π bonds	creates bonding and antibonding interactions based on which orbitals are filled
predicts molecular shape based on the number of regions of electron density	predicts the arrangement of electrons in molecules
needs multiple structures to describe resonance	

Orbitals of Lone Pair Electrons

There are situations in which we will want to integrate molecular orbital and valence bond theories. Identifying the orbitals of lone pair electrons is one situation. Hybridized orbitals create sigma bonds and hold lone pairs. The sigma bonds create the "framework" that holds all the atoms together as a molecule or ion. Un-hybridized p orbitals create pi bonds perpendicular to this sigma framework. In the future, we will learn that some lone pair electrons on heteroatoms of rings can occupy p orbitals to create aromaticity. Stay tuned for upcoming attractions. For the first ten chapters of this text, we will only focus on non-aromatic compounds.

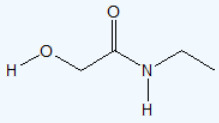
To identify the orbitals of the lone pair electrons in non-aromatic compounds, we can follow a two-step approach.

Step 1: Add any missing lone pair electrons to the heteroatoms (atoms other than carbon and hydrogen).

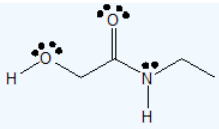
Step 2: Determine the hybridization of any atoms with lone pairs (heteroatoms). Lone pairs occupy the hybridized orbitals.

Example

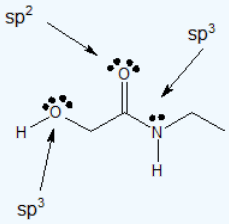
To identify the orbitals of the lone pair electrons in the compound below, we will follow the approach above.



Step 1: Add lone pairs.



Step 2: Determine the hybridization of any atom with lone pairs.



The lone pairs on each heteroatom occupy the indicated hybridized orbital.

NOTE: These guidelines only apply for non-aromatic compounds. There can be exceptions to these guidelines for some heterocyclic aromatic compounds. These exceptions are fully explained in a later chapter of this text.

Exercise

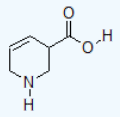
1. For the compound below:

a) add the lone pair electrons

b) label the hybridization and electron geometry for all non-hydrogen atoms

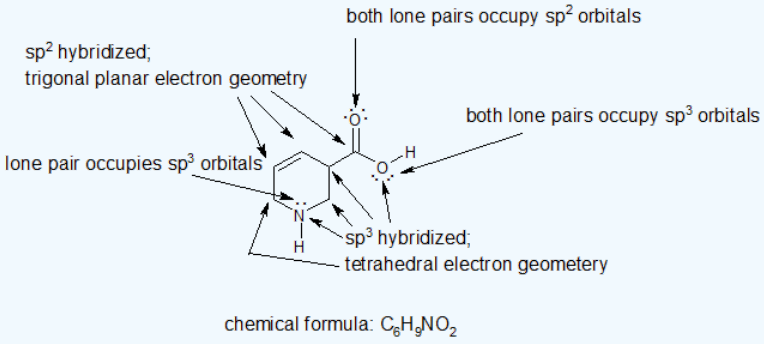
c) specify the hybridization of the orbital for each lone pair

d) What is the chemical formula of this compound?



Answer

1.



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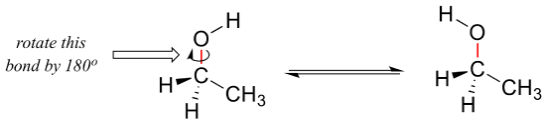
2.6: Bond Rotation

Learning Objective

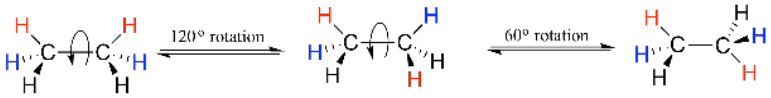
- distinguish between bonds that can rotate and those that cannot

Sigma Bonds can Rotate

We learned in section 2.1 that single bonds in organic molecules are free to rotate, due to the 'end-to-end' (sigma) nature of their orbital overlap. Consider the carbon-oxygen bond in ethanol, for example: with a 180° rotation about this bond, the shape of the molecule would look quite different:

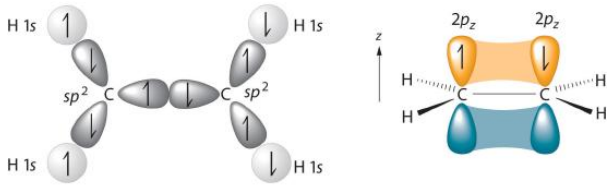


For ethane, rotation about the carbon-carbon sigma bond results in many different possible three-dimensional arrangements of the atoms.



Pi Bonds are rigid

Pi bonds are created from overlapping p orbitals. The lobes of the p orbitals prevent the atoms sharing pi bonds from rotating as shown in the diagram below.

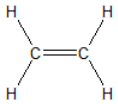


(a) C_2H_4 σ-bonded framework (b) C_2H_4 π bonding

Double and Triple Bonds cannot Rotate

The pi bonds in double and triple bonds prevent these bonds from rotating. This rigidity has an effect on the physical structure of compounds and can influence chemical reactivity. For now, we want to build the habit of looking at static drawings and diagrams of organic compounds and visualizing their dynamic nature.

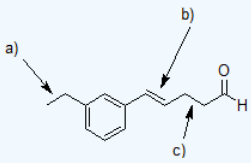
For ethene, there is no rotation about the carbon-carbon double bond because of the pi bond.



No rotation is possible between
the two carbon atoms sharing a double bond.

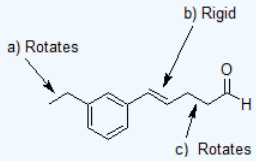
Exercise

1. Label the selected bonds in the compound below as "Rotates" or "Rigid."



Answer

1. Arrows for (a) and (c) are pointing to single bonds that can rotate. Arrow (b) is pointing to a double bond that is rigid because of the pi bond.



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2.7: Isomerism Introduction

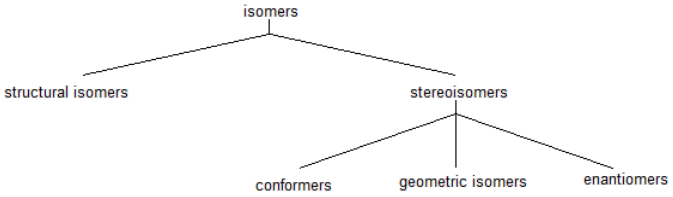
Learning Objective

- recognize the relationships between constitutional (structural) isomers, conformational isomers, and geometric isomers

Isomers

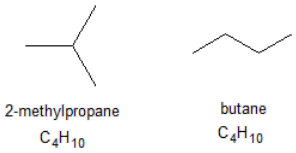
Isomers always have the same chemical formula. When the chemical formulae are different, then the compounds are completely different. Important information can be gained from the chemical formulas when comparing compounds.

Structural (constitutional) isomers have the same molecular formula but a different bonding arrangement among the atoms. Stereoisomers have identical molecular formulas and arrangements of atoms. They differ from each other only in the spatial orientation of groups in the molecule. For organic chemistry, there are several types of stereoisomers: enantiomers, diasteriomers, geometric isomers, and conformers. These stereoisomers will be introduced and explained throughout several chapters.



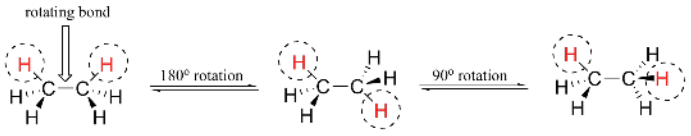
Structural (Constitutional) Isomers

Because carbon forms four bonds, there can be multiple ways to form molecules that follow the octet rule. Even with only four carbon atoms, there are two possible structures for the carbon backbone. The carbon atoms can be bonded to make a four carbon chain (butane) or there can be a one carbon branch from a three carbon chain (2-methylpropane). Butane and 2-methylpropane are structural isomers because they both have the chemical formula C_4H_{10}.



Identical vs Conformer

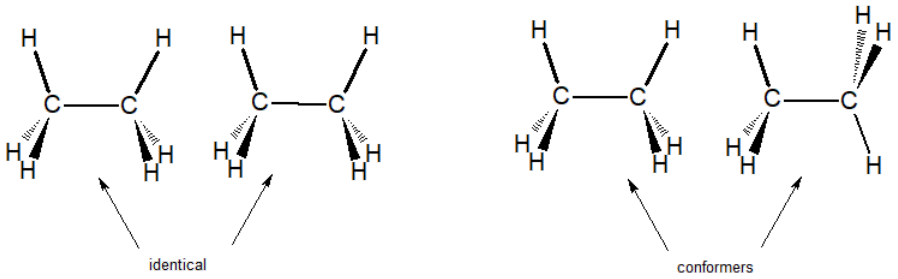
The rotation about single bonds creates dynamic molecules. When drawing and discussing molecules, it is important to be aware that our drawing are static while the molecule themselves are rotating. Although there are seven sigma bonds in the ethane molecule, rotation about the six carbon-hydrogen bonds 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. Conformers are the simplest example of stereoisomerism.



Identical compounds are the same compound shown with ALL atoms in the same spatial orientation.

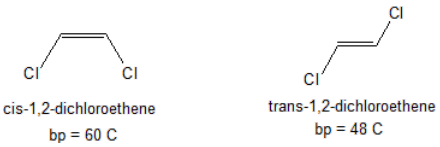
Conformers are the same compound shown with different rotations about single bonds.

In the example below, we can compare two identical structures for ethane with two conformers of ethane.

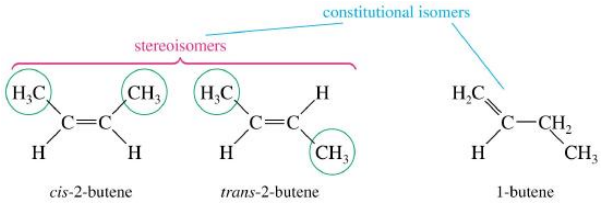


Geometric Isomers - an example of stereoisomerism

The rigidity of the pi bonds in double bonds can create geometric isomerism. Without rotation, there are two different orientations possible across the carbon-carbon double bond (C=C). The rigidity of the double bond creates a line of reference for spatial orientation. The prefixes cis and trans are used to distinguish between geometric isomers. The cis-stereoisomer has both non-hydrogen atoms on the same side of the double bond. Whereas, the trans-stereoisomer has the non-hydrogen atoms across the double bond. In the same way, we cross the ocean an a trans-Atlantic journey. This small difference may seem insignificant, but geometric isomers are different chemical compounds with different physical properties as shown in the example below.

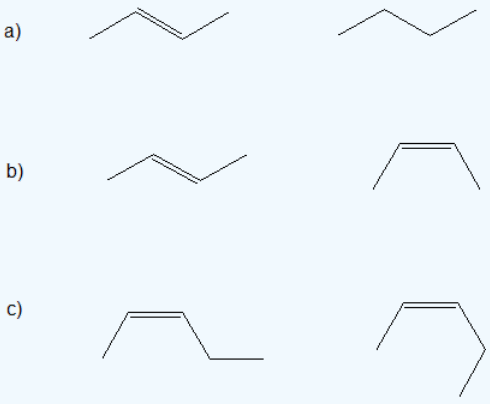


For now, it is important to distinguish between structural differences and spatial differences when comparing compounds. In the future, we will look more closely at isomerism.



Example

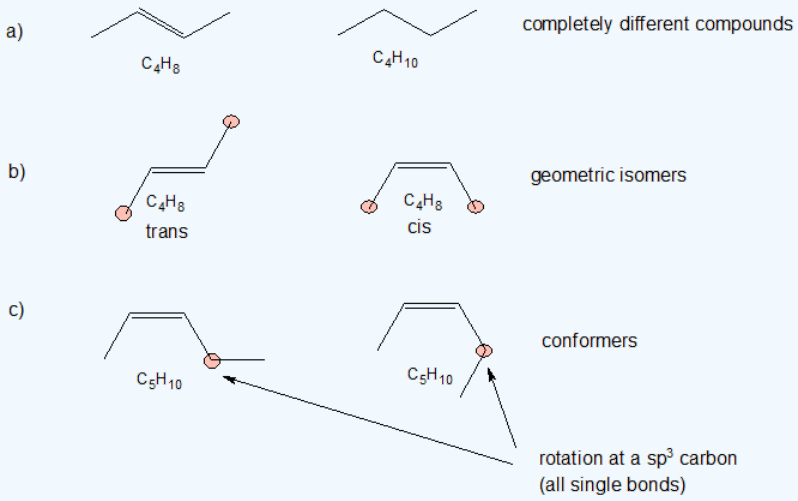
Let's look ate the bond-line structures below and determine the relationships between the following pairs of compounds: identical, conformers, structural isomers, geometric isomers, or completely different compounds.



The first important step (that is often skipped) is to determine the chemical formula of each compound. If the chemical formulas are different, then the compounds are completely different and there is NO isomeric relationship. If the chemical formulas are the same, then we identify the difference between to the compounds to determine their relatioship. If there are structural differences in the bonding patterns, then the compounds are constitutional (structural isomers). If the compounds have the same structural connections, but the spatial orientations are different, then the compounds are stereoisomers. For now,

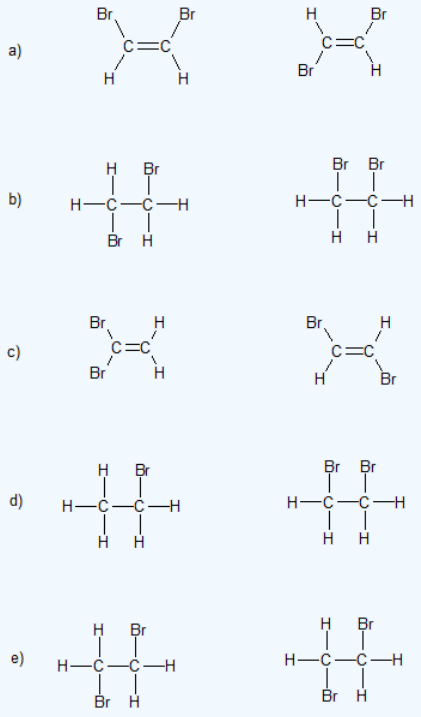
the possible stereoisomers are conformers showing the same compound with different carbon-carbon single bond rotations or geometric isomers of compounds with different orientations at the carbon-carbon double bonds.

Applying the logic above to our example, we determine the following.



Exercise

1. What is the relationship between the following pairs of compounds: identical, conformers, structural isomers, geometric isomers, or completely different compounds?



Answer

1.

a) geometric isomers

b) conformers

c) structural isomers

d) completely different compounds

e) identical

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2.8: Hydrocarbons

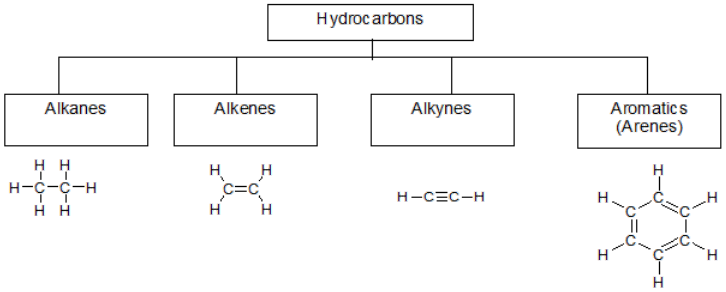
Learning Objective

- classify hydrocarbons as saturated or unsaturated
- classify hydrocarbons as alkanes, alkenes, alkynes, cycloalkanes, or aromatics (arenes)
- apply the homologous series to organic molecules with 1-10 carbons

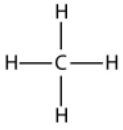
Hydrocarbon Classifications

Hydrocarbons are organic compounds that contain **only** carbon and hydrogen. The inherent ability of hydrocarbons to bond to themselves is known as catenation, and allows hydrocarbon to form more complex molecules, such as cyclohexane and benzene. Catenation comes from the fact that the bond character between carbon atoms is entirely non-polar.

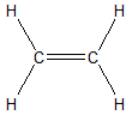
The four general classes of hydrocarbons are: alkanes, alkenes, alkynes and arenes. Aromatic compounds derive their names from the fact that many of these compounds in the early days of discovery were grouped because they were oils with fragrant odors. The classifications for hydrocarbons are summarized below.



Saturated hydrocarbons (alkanes) are the simplest of the hydrocarbon species. They are composed entirely of single bonds and are saturated with hydrogen. The general formula for saturated hydrocarbons is C_nH_{2n+2} (assuming non-cyclic structures). Saturated hydrocarbons are the basis of petroleum fuels and are found as either linear or branched species.The simplest alkanes have their C atoms bonded in a straight chain; these are called *normal* alkanes. They are named according to the number of carbon atoms in the chain. The smallest alkane is methane:



Unsaturated hydrocarbons have double and/or triple bonds between carbon atoms. Those with double bond are called alkenes and have the general formula C_nH_{2n} (assuming non-cyclic structures). Those containing triple bonds are called alkynes and have general formula C_nH_{2n-2}. The smallest alkene—ethene—has two C atoms and is also known by its common name ethylene and the smallest alkyne is ethyne, also known as acetylene.

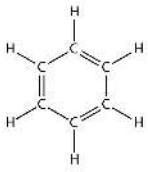


ethene
C_2H_4

ethyne (acetylene)
C_2H_2

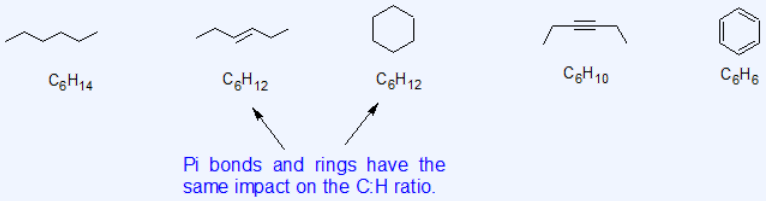
Cycloalkanes are hydrocarbons containing one or more carbon rings to which hydrogen atoms are attached. The prefix "cyclo" is added to the name to communicate the ring structure. The general formula for a saturated hydrocarbon containing one ring is C_nH_{2n}.

Aromatic hydrocarbons, also known as arenes, are hydrocarbons that have at least one aromatic ring. Aromatic compounds contain the benzene unit. Benzene itself is composed of six C atoms in a ring, with alternating single and double C–C bonds:



For most compounds, information beyond the chemical formula will be needed to elucidate their structure. However, the ratio of C:H in a chemical formula can provide insights into the chemical structure.

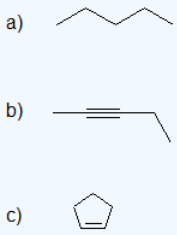
For example, let's look at some of the possible structures and chemical formulas for hydrocarbons containing six carbon atoms.



The saturated alkane has the highest ratio of hydrogen to carbon. The unsaturated alkene and the six membered alkane ring share the same chemical formula. It is important to remember this relationship. The unsaturated alkyne has a lower ratio of hydrogen to carbon than alkenes with a second pi bond. Benzene rings have the lowest hydrogen ratio to carbon at 1:1.

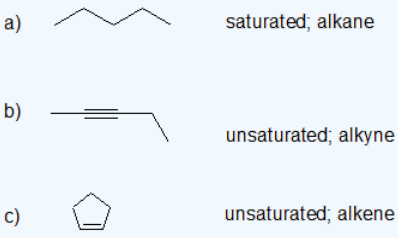
Exercise

1. Classify the following compounds are saturated or unsaturated. For unsaturated hydrocarbons, refine the classification by indicating whether the compound is an alkene, alkyne, or arene.



Answer

1.



The number of carbons continuously bonded together is an important structural feature and is described using the Homologous Series. In first year organic chemistry, the first ten names of the Homologous Series are usually all that need to be memorized.

Of course, your professor will set the standard. Most of the prefixes are familiar from the Greek prefixes for binary covalent compounds. It is the prefixes for the first four carbon chain lengths that may be unfamiliar. Interestingly, three of these hydrocarbons frequently appear in every day life. Methane gas is a primary component of flatulence and is the ingredient that ignites when farts are lit - don't try this at home. Propane and butane are gases at room temperature. They are stored under pressure to create the liquid state. Propane is the fuel for bbqs, while butane is used in lighters. The suffix "ane" is used to distinguish between the longest continuous carbon chain, while the shorter carbon branches (substituents) are indicated with "yl" as the suffix.

THE HOMOLOGOUS SERIES

# C's	Alkane Structure	Parent name	Substituent name
1	CH_4	methane	methyl
2	CH_3CH_3	ethane	ethyl
3	$CH_3CH_2CH_3$	propane	propyl
4	$CH_3CH_2CH_2CH_3$	butane	butyl
5	$CH_3CH_2CH_2CH_2CH_3$	pentane	pentyl
6	$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane	hexyl
7	$CH_3CH_2CH_2CH_2CH_2CH_2CH_3$	heptane	heptyl
8	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	octane	octyl
9	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	nonane	nonyl
10	$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$	decane	decyl

Exercise

2. Complete the table below.

Condensed Structural Formula	Chemical Name
	propane
C_6H_6	
$CH_3CH_2CH_2CH_2CH_2CH_3$	

Answer

2.

Condensed Structural Formula	Chemical Name
$CH_3CH_2CH_3$	propane
C_6H_6	benzene
$CH_3CH_2CH_2CH_2CH_2CH_3$	hexane

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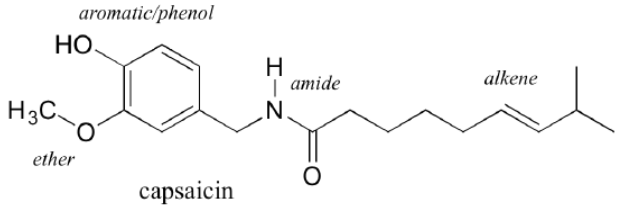
2.9: Organic Functional Groups

Learning Objective

- recognize and classify the common functional groups of organic chemistry (alkanes, alkenes, alkynes, alkyl halides, alcohols, amines, ethers, aldehydes, ketones, carboxylic acids, esters, and amides

Functional groups in organic compounds

Functional groups are structural units within organic compounds that are defined by specific bonding arrangements between specific atoms. The structure of capsaicin, the compound responsible for the heat in peppers, incorporates several functional groups, labeled in the figure below and explained throughout this section.

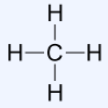


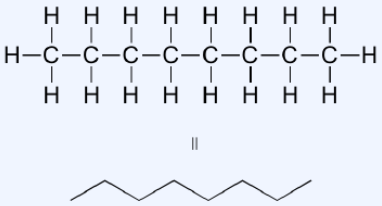
capsaicin

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 behave in organic reactions.

The 'default' in organic chemistry (essentially, the *lack* of any functional groups) is given the term **alkane**, characterized by single bonds between carbon and carbon, or between carbon and hydrogen. Methane, CH_4, is the natural gas you may burn in your furnace. Octane, C_8H_{18}, is a component of gasoline.

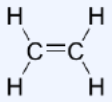
Alkanes

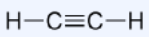

methane


octane

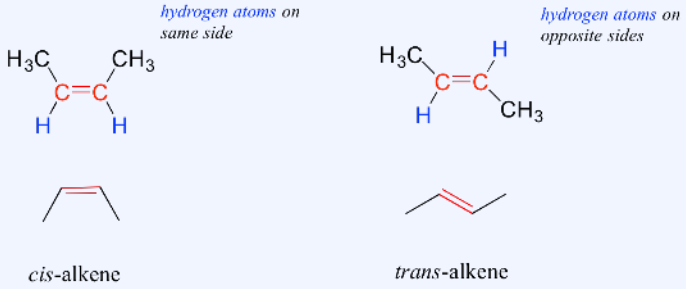
Alkenes (sometimes called **olefins**) have carbon-carbon double bonds, and **alkynes** have carbon-carbon triple bonds. Ethene, the simplest alkene example, is a gas that serves as a cellular signal in fruits to stimulate ripening. (If you want bananas to ripen quickly, put them in a paper bag along 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


ethene
(an alkene)


ethyne
(an alkyne)

Alkenes have trigonal planar electron geometry while alkynes have linear geometry. Furthermore, many alkenes can take two geometric forms: ***cis*** or ***trans***. 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.

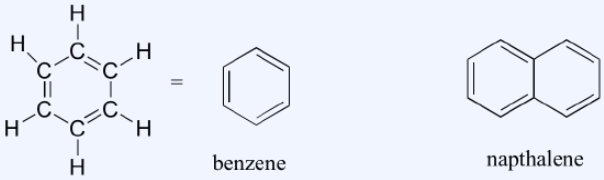


cis-alkene *trans*-alkene

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 15, 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 chapters 2 and 14.

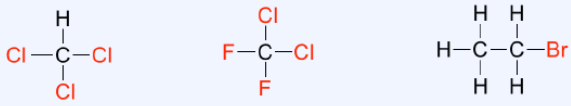
Aromatics



benzene napthalene

When the carbon of an alkane is bonded to one or more halogens, the group is referred to as a **alkyl halide** or **haloalkane**. 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.

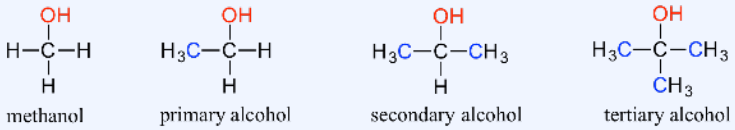
Haloalkanes

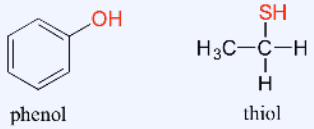


trichloromethane (chloroform) dichlorodifluoromethane (Freon-12) bromoethane

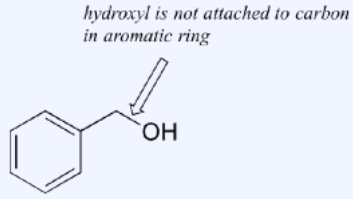
In the **alcohol** functional group, a carbon is single-bonded to an OH group (the OH group, by itself, is referred to as a **hydroxyl**). Except for methanol, all alcohols can be classified as primary, secondary, or tertiary. In a **primary alcohol**, the carbon bonded to the OH group is also bonded 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**. The sulfur analog of an alcohol is called a **thiol** (from the Greek *thio*, for sulfur).

Alcohols, phenols, and thiols





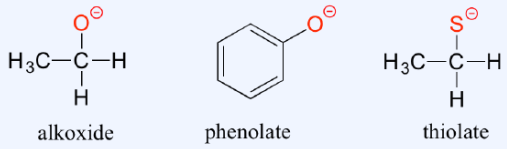
Note that the definition of a phenol states that the hydroxyl oxygen must be *directly* attached to one of the carbons of the aromatic ring. The compound below, therefore, is *not* a phenol - it is a primary alcohol.

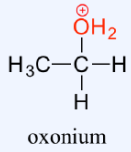


primary alcohol
(*not* a phenol)

The distinction is important, because as we will see later, there is a significant difference in the reactivity of alcohols and phenols.

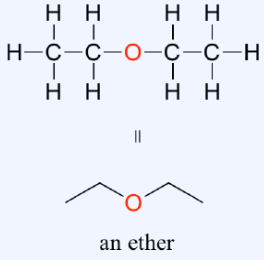
The deprotonated forms of alcohols, phenols, and thiols are called **alkoxides**, **phenolates**, and **thiolates**, respectively. A protonated alcohol is an **oxonium** ion.





In an **ether** functional group, a central oxygen is bonded to two carbons. Below is the structure of diethyl ether, a common laboratory solvent and also one of the first compounds to be used as an anesthetic during operations. The sulfur analog of an ether is called a **thioether** or **sulfide**.

Ethers and sulfides

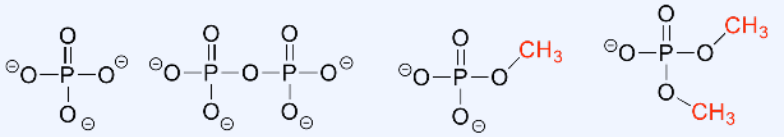


an ether

a sulfide

Phosphate and its derivative functional groups are ubiquitous in biomolecules. Phosphate linked to a single organic group is called a **phosphate ester**; when it has two links to organic groups it is called a **phosphate diester**. A linkage between two phosphates creates a **phosphate anhydride**.

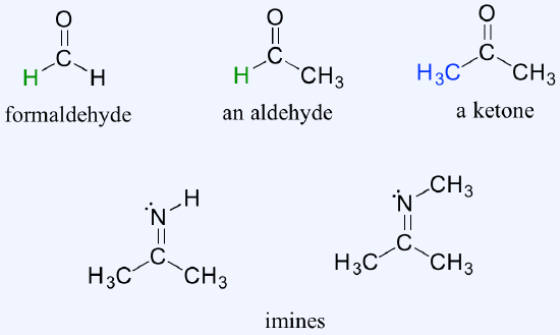
Organic phosphates



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.

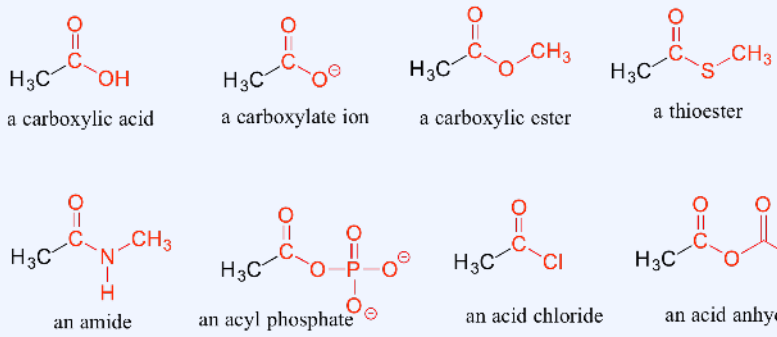
A group with a carbon-nitrogen double bond is called an **imine**, or sometimes a **Schiff base** (in this book we will use the term 'imine'). The chemistry of aldehydes, ketones, and imines will be covered in chapter 10.

Aldehydes, ketones, and imines

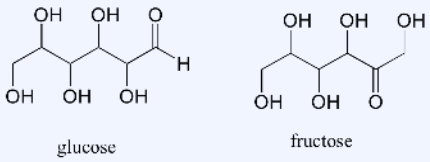


When a carbonyl carbon is bonded on one side to a carbon (or hydrogen) and on the other side to an oxygen, nitrogen, or sulfur, the functional group is considered to be one of the '**carboxylic acid derivatives**', a designation that describes a set of related functional groups. The eponymous member of this family is the **carboxylic acid** functional group, in which the carbonyl is bonded to a hydroxyl group. The conjugate base of a carboxylic acid is a **carboxylate**. Other derivatives are carboxylic esters (usually just called '**esters**'), **thioesters**, **amides**, **acyl phosphates**, **acid chlorides**, and **acid anhydrides**. With the exception of acid chlorides and acid anhydrides, the carboxylic acid derivatives are very common in biological molecules and/or metabolic pathways, and their structure and reactivity will be discussed in detail in chapter 11.

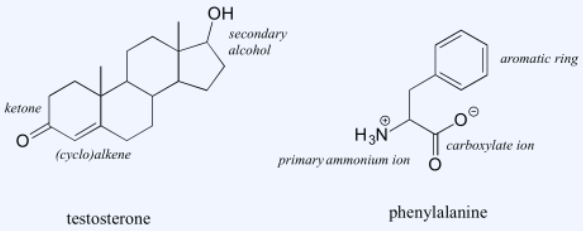
Carboxylic acid derivatives

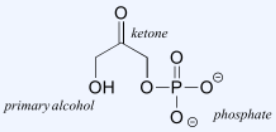


A single compound often contains several functional groups, particularly in biological organic chemistry. The six-carbon sugar molecules glucose and fructose, for example, contain aldehyde and ketone groups, respectively, and both contain five alcohol groups (a compound with several alcohol groups is often referred to as a '**polyol**').



The hormone testosterone, the amino acid phenylalanine, and the glycolysis metabolite dihydroxyacetone phosphate all contain multiple functional groups, as labeled below.



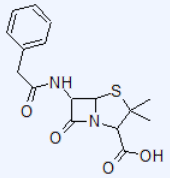


dihydroxyacetone phosphate
(DHAP)

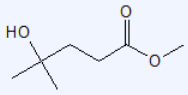
While not in any way a complete list, this section has covered most of the important functional groups that we will encounter in biological organic chemistry.

Exercise:

1. Identify the functional groups (other than alkanes) in the following organic compounds. State whether alcohols and amines are primary, secondary, or tertiary.



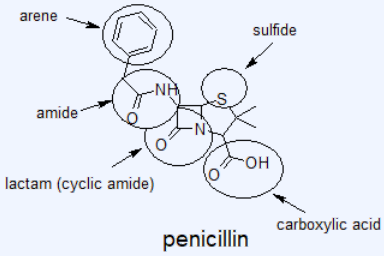
penicillin



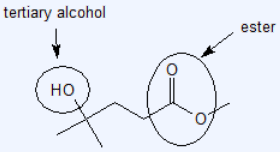
pyruvic acid

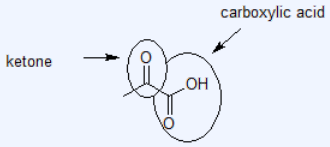
Solution

1.

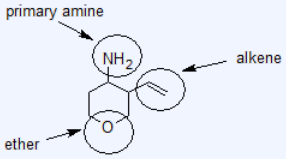


penicillin





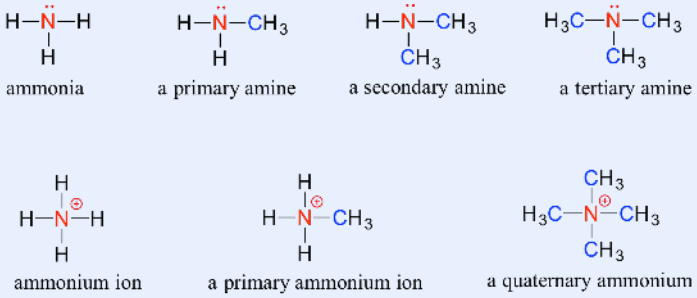
pyruvic acid



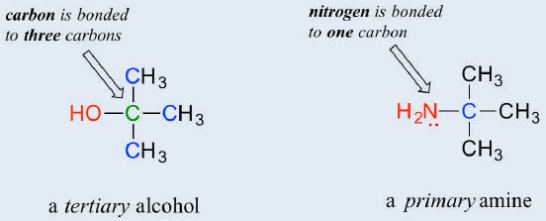
Amines are characterized by nitrogen atoms with single bonds to hydrogen and carbon. Just as there are primary, secondary, and tertiary alcohols, there are primary, secondary, and tertiary amines. Ammonia is a special case with no carbon atoms.

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.

Amines

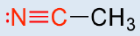


Note: Do not be confused by how the terms 'primary', 'secondary', and 'tertiary' are applied to alcohols and amines - the definitions are different. In alcohols, what matters is how many other carbons the alcohol *carbon* is bonded to, while in amines, what matters is how many carbons the *nitrogen* is bonded to.



Finally, a **nitrile** group is characterized by a carbon triple-bonded to a nitrogen.

Nitriles



acetonitrile

Exercise

2. Draw one example of each compound that includes the specified structural features. Be sure to designate the location of all non-zero formal charges. All atoms should have complete octets (phosphorus may exceed the octet rule). There are many possible correct answers for these, so be sure to check your structures with your instructor or tutor.

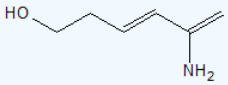
a) a compound with molecular formula $C_6H_{11}NO$ that includes alkene, secondary amine, and primary alcohol functional groups

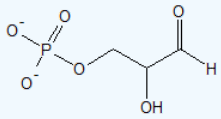
b) an ion with molecular formula $C_3H_5O_6P^{2-}$ that includes aldehyde, secondary alcohol, and phosphate functional groups.

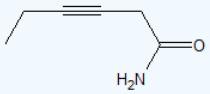
c) A compound with molecular formula C_6H_9NO that has an amide functional group, and does *not* have an alkene group.

Answer

2.

a) 

b) 

c) 

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2.10: Intermolecular Forces (IMFs) - Review

learning objective

- determine the dominant intermolecular forces (IMFs) of organic compounds

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*.

> *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 at high pressures. (For more information on the behavior of real gases and deviations from the ideal gas law,.)

In this section, we explicitly consider three kinds of intermolecular 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. The first two are often described collectively as van der Waals forces.

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 **2.10.1*a***.

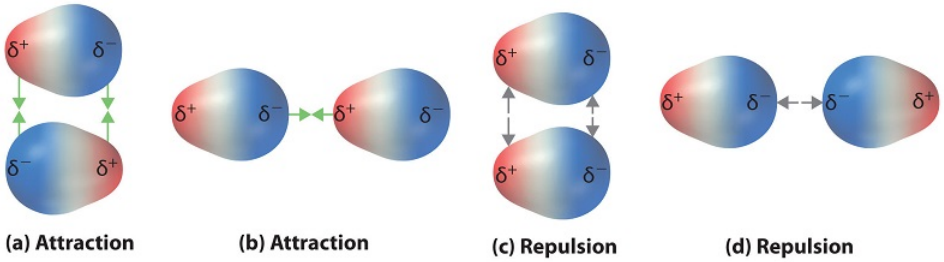


Figure **2.10.1**: Attractive and Repulsive Dipole–Dipole Interactions. (a and b) Molecular orientations in which the positive end of one dipole (δ^+) is near the negative end of another (δ^-) (and vice versa) produce attractive interactions. (c and d) Molecular orientations that juxtapose the positive or negative ends of the dipoles on adjacent molecules produce repulsive interactions.

These arrangements are more stable than arrangements in which two positive or two negative ends are adjacent (Figure **2.10.1***c*). Hence dipole–dipole interactions, such as those in Figure **2.10.1***b*, are *attractive intermolecular interactions*, whereas those in Figure **2.10.1***d* are *repulsive intermolecular 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 **2.10.2**. On average, however, the attractive interactions dominate.

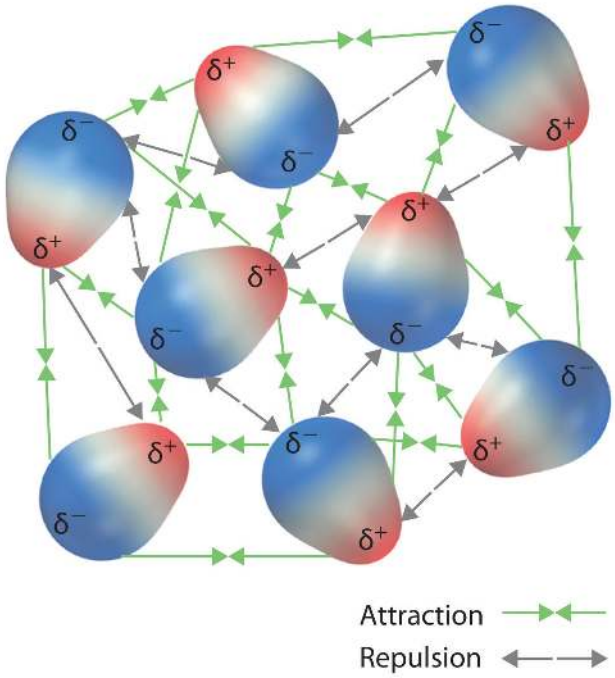


Figure **2.10.2**: Both Attractive and Repulsive Dipole–Dipole Interactions Occur in a Liquid Sample with Many Molecules

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 the 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 $1/r^3$, so doubling the distance between the dipoles decreases the strength of the interaction by 2^3, or 8-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 interionic 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 **2.10.1**.

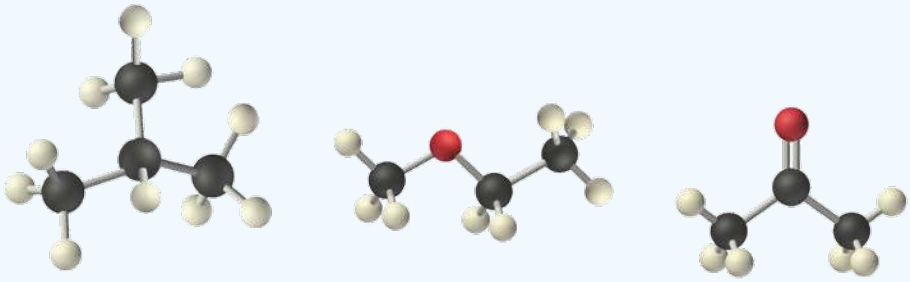
Table **2.10.1**: Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

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

> *The attractive energy between two ions is proportional to 1/r, whereas the attractive energy between two dipoles is proportional to 1/r6.*

Example

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:



2-Methylpropane Ethyl methyl ether Acetone

Given: compounds

Asked for: order of increasing boiling points

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 electronegativities. 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

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 (Table **2.10.2**).

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 **2.10.2**: 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 **2.10.3**, 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.

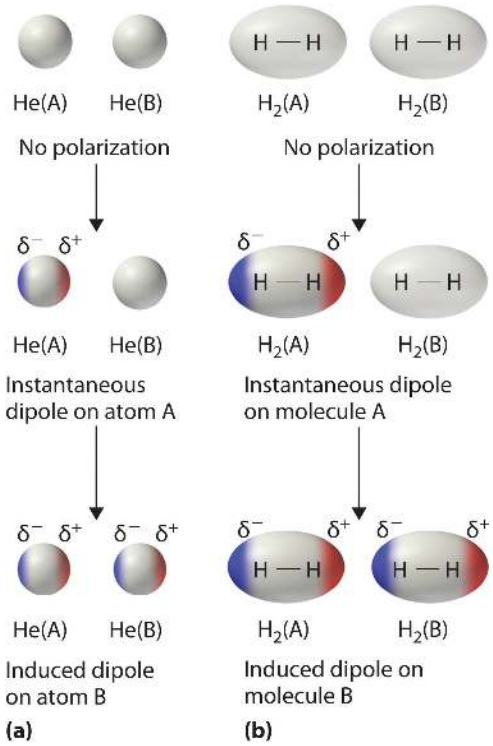


Figure **2.10.3**: Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

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 **2.10.3**, tends to become more pronounced as atomic and molecular masses increase (Table **2.10.2**). 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.

> *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 **2.10.4**). 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 **2.10.4** 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).

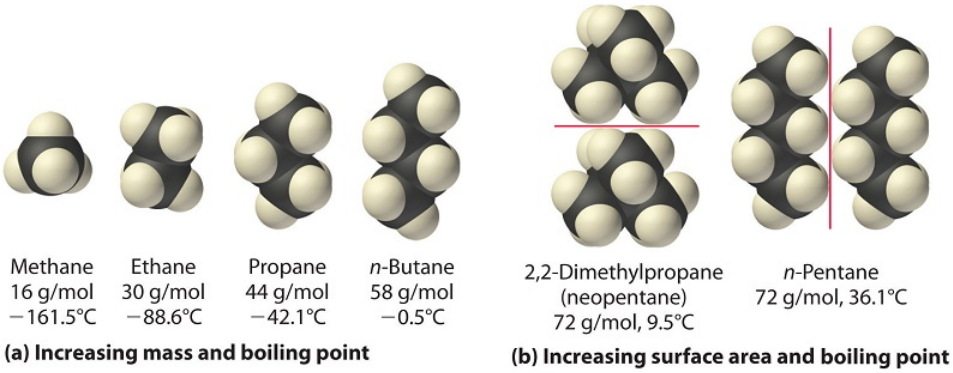


Figure **2.10.4**: Mass and Surface Area Affect the Strength of London Dispersion Forces. (a) In this series of four simple alkanes, larger molecules have stronger London forces between them than smaller molecules and consequently higher boiling points. (b) Linear *n*-pentane molecules have a larger 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

Arrange *n*-butane, propane, 2-methylpropane [isobutene, $(CH_3)_2CHCH_3$], and *n*-pentane in order of increasing boiling points.

Given: compounds

Asked for: 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

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 **2.10.5**. 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.

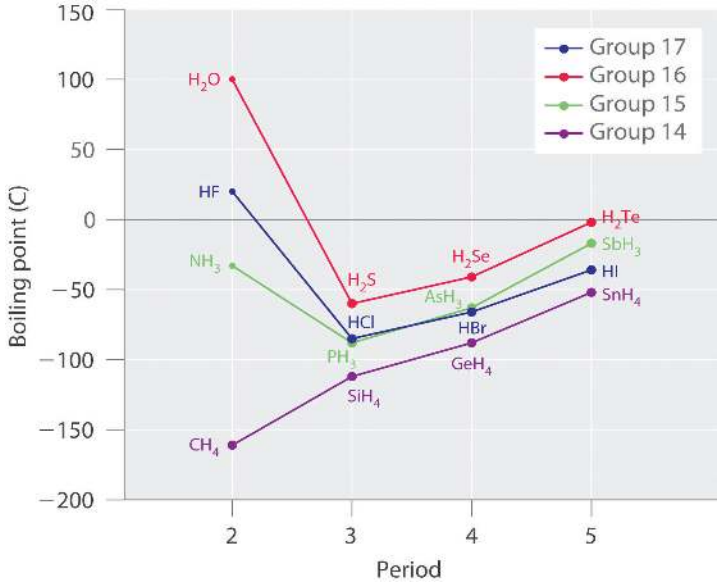


Figure **2.10.5**: The Effects of Hydrogen Bonding on Boiling Points. These plots of the boiling points of the covalent hydrides of the elements of groups 14–17 show that the boiling points of the lightest members of each series for which hydrogen bonding is possible (HF, NH_3, and H_2O) are anomalously 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 **2.10.6**. 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.

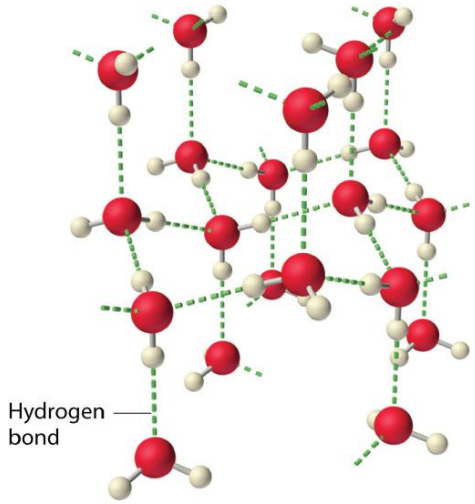


Figure **2.10.6**: The Hydrogen-Bonded Structure of Ice.

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, cagelike 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.

> *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.

Example

Considering CH_3OH, C_2H_6, Xe, and $(CH_3)_3N$, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Given: compounds

Asked for: formation of hydrogen bonds and structure

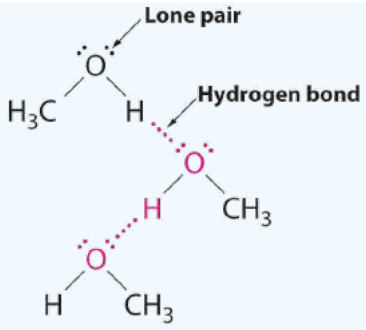
Strategy:

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:



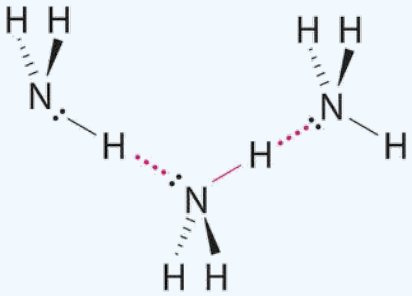
Hydrogen bonding in methanol

Exercise

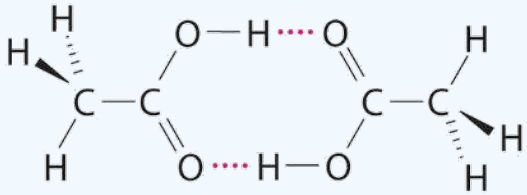
Considering CH_3CO_2H, $(CH_3)_3N$, NH_3, and CH_3F, which can form hydrogen bonds with themselves? Draw the hydrogen-bonded structures.

Answer

CH_3CO_2H and NH_3;



Hydrogen bonding in ammonia



Hydrogen bonding in acetic acid

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: Buckyballs

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:

$$\text{He } (-269°C) < \text{Ar } (-185.7°C) < N_2O\ (-88.5°C) < C_{60}\ (>280°C) < \text{NaCl } (1465°C).$$

Exercise

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)

Example

Identify the most significant intermolecular force in each substance.

a. C_3H_8
b. CH_3OH
c. H_2S

Solution

a. Although C–H bonds are polar, they are only minimally polar. The most significant intermolecular force for this substance would be dispersion forces.

b. This molecule has an H atom bonded to an O atom, so it will experience hydrogen bonding.

c. Although this molecule does not experience hydrogen bonding, the Lewis electron dot diagram and VSEPR indicate that it is bent, so it has a permanent dipole. The most significant force in this substance is dipole-dipole interaction.

Exercise

Identify the most significant intermolecular force in each substance.

a. HF
b. HCl

Answer a

hydrogen bonding

Answer b

dipole-dipole interactions

More complex examples of hydrogen bonding

The hydration of negative ions

When an ionic substance dissolves in water, water molecules cluster around the separated ions. This process is called hydration. Water frequently attaches to positive ions by co-ordinate (dative covalent) bonds. It bonds to negative ions using hydrogen bonds.

> *If you are interested in the bonding in hydrated positive ions, you could follow this link to co-ordinate (dative covalent) bonding.*

The diagram shows the potential hydrogen bonds formed to a chloride ion, Cl-. Although the lone pairs in the chloride ion are at the 3-level and would not normally be active enough to form hydrogen bonds, in this case they are made more attractive by the full negative charge on the chlorine.

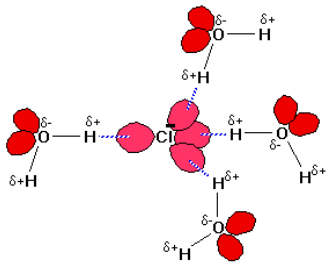


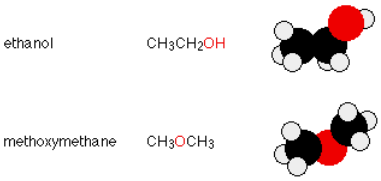
Figure 5: Hydrogen bonding between chloride ions and water.

However complicated the negative ion, there will always be lone pairs that the hydrogen atoms from the water molecules can hydrogen bond to.

Hydrogen bonding in alcohols

An alcohol is an organic molecule containing an -OH group. Any molecule which has a hydrogen atom attached directly to an oxygen or a nitrogen is capable of hydrogen bonding. Such molecules will always have higher boiling points than similarly sized molecules which don't have an -O-H or an -N-H group. The hydrogen bonding makes the molecules "stickier", and more heat is necessary to separate them.

Ethanol, CH_3CH_2OH, and methoxymethane, CH_3OCH_3, are structural isomers with the same molecular formula, C_2H_6O.

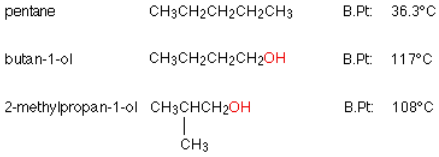


They have the same number of electrons, and a similar length to the molecule. The van der Waals attractions (both dispersion forces and dipole-dipole attractions) in each will be much the same. However, ethanol has a hydrogen atom attached directly to an oxygen - and that oxygen still has exactly the same two lone pairs as in a water molecule. Hydrogen bonding can occur between ethanol molecules, although not as effectively as in water. The hydrogen bonding is limited by the fact that there is only one hydrogen in each ethanol molecule with sufficient $\delta+$ charge.

In methoxymethane, lone pairs on the oxygen are still there, but the hydrogens are not sufficiently $\delta+$ for hydrogen bonds to form. Except in some rather unusual cases, the hydrogen atom has to be attached directly to the very electronegative element for hydrogen bonding to occur. The boiling points of ethanol and methoxymethane show the dramatic effect that the hydrogen bonding has on the stickiness of the ethanol molecules:

ethanol (with hydrogen bonding)	78.5°C
methoxymethane (without hydrogen bonding)	-24.8°C

The hydrogen bonding in the ethanol has lifted its boiling point about 100°C. It is important to realize that hydrogen bonding exists in addition to van der Waals attractions. For example, all the following molecules contain the same number of electrons, and the first two are much the same length. The higher boiling point of the butan-1-ol is due to the additional hydrogen bonding.



Comparing the two alcohols (containing -OH groups), both boiling points are high because of the additional hydrogen bonding due to the hydrogen attached directly to the oxygen - but they are not the same. The boiling point of the 2-methylpropan-1-ol isn't as

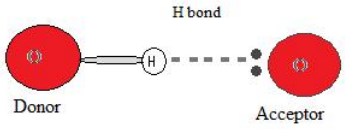
high as the butan-1-ol because the branching in the molecule makes the van der Waals attractions less effective than in the longer butan-1-ol.

Hydrogen bonding in organic molecules containing nitrogen

Hydrogen bonding also occurs in organic molecules containing N-H groups - in the same sort of way that it occurs in ammonia. Examples range from simple molecules like CH_3NH_2 (methylamine) to large molecules like proteins and DNA. The two strands of the famous double helix in DNA are held together by hydrogen bonds between hydrogen atoms attached to nitrogen on one strand, and lone pairs on another nitrogen or an oxygen on the other one.

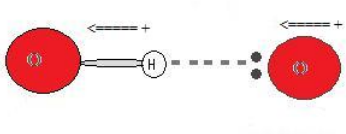
Donors and Acceptors

In order for a hydrogen bond to occur there must be both a hydrogen donor and an acceptor present. The donor in a hydrogen bond is the atom to which the hydrogen atom participating in the hydrogen bond is covalently bonded, and is usually a strongly electronegative atom such as N,O, or F. The hydrogen acceptor is the neighboring electronegative ion or molecule, and must posses a lone electron pair in order to form a hydrogen bond.



Why does a hydrogen bond occur?

Since the hydrogen donor is strongly electronegative, it pulls the covalently bonded electron pair closer to its nucleus, and away from the hydrogen atom. The hydrogen atom is then left with a partial positive charge, creating a dipole-dipole attraction between the hydrogen atom bonded to the donor, and the lone electron pair on the accepton. This results in a hydrogen bond.(see Interactions Between Molecules With Permanent Dipoles)

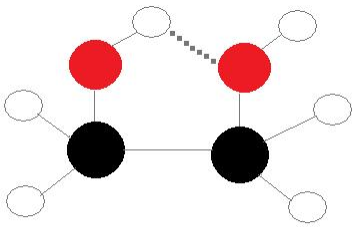


Types of hydrogen bonds

Hydrogen bonds can occur within one single molecule, between two like molecules, or between two unlike molecules.

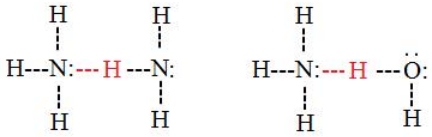
Intramolecular hydrogen bonds

Intramolecular hydrogen bonds are those which occur within one single molecule. This occurs when two functional groups of a molecule can form hydrogen bonds with each other. In order for this to happen, both a hydrogen donor an acceptor must be present within one molecule, and they must be within close proximity of each other in the molecule. For example, intramolecular hydrogen bonding occurs in ethylene glycol ($C_2H_4(OH)_2$) between its two hydroxyl groups due to the molecular geometry.


Intramolecular h-bonding in Ethylene Glycol molecule

Intermolecular hydrogen bonds

Intermolecular hydrogen bonds occur *between* separate molecules in a substance. They can occur between any number of like or unlike molecules as long as hydrogen donors and acceptors are present an in positions in which they can interact.For example, intermolecular hydrogen bonds can occur between NH_3 molecules alone, between H_2O molecules alone, or between NH_3 and H_2O molecules.



Properties and effects of hydrogen bonds

On Boiling Point

When we consider the boiling points of molecules, we usually expect molecules with larger molar masses to have higher normal boiling points than molecules with smaller molar masses. This, without taking hydrogen bonds into account, is due to greater dispersion forces (see Interactions Between Nonpolar Molecules). Larger molecules have more space for electron distribution and thus more possibilities for an instantaneous dipole moment. However, when we consider the table below, we see that this is not always the case.

Compound	Molar Mass	Normal Boiling Point
H_2O	18 g/mol	373 K
HF	20 g/mol	292.5 K
NH_3	17 g/mol	239.8 K
H_2S	34 g/mol	212.9 K
HCl	36.4 g/mol	197.9 K
PH_3	34 g/mol	185.2 K

We see that H_2O, HF, and NH_3 each have higher boiling points than the same compound formed between hydrogen and the next element moving down its respective group, indicating that the former have greater intermolecular forces. This is because H_2O, HF, and NH_3 all exhibit hydrogen bonding, whereas the others do not. Furthermore, H_2O has a smaller molar mass than HF but partakes in more hydrogen bonds per molecule, so its boiling point is consequently higher.

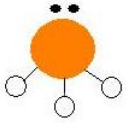
On Viscosity

The same effect that is seen on boiling point as a result of hydrogen bonding can also be observed in the viscosity of certain substances. Those substances which are capable of forming hydrogen bonds tend to have a higher viscosity than those that do not. Substances which have the possibility for multiple hydrogen bonds exhibit even higher viscosities.

Factors preventing Hydrogen bonding

Electronegativity

Hydrogen bonding cannot occur without significant electronegativity differences between hydrogen and the atom it is bonded to. Thus, we see molecules such as PH3, which no not partake in hydrogen bonding. PH3 exhibits a trigonal pyramidal molecular geometry like that of ammmonia, but unlike NH3 it cannot hydrogen bond. This is due to the similarity in the electronegativities of phosphorous and hydrogen. Both atoms have an electronegativity of 2.1, and thus, no dipole moment occurs. This prevents the hydrogen bonding from acquiring the partial positive charge needed to hydrogen bond with the lone electron pair in another molecule. (see Polarizability)



Atom Size

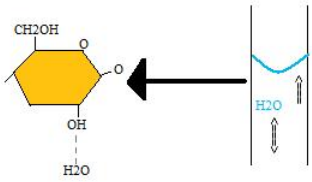
The size of donors and acceptors can also effect the ability to hydrogen bond. This can account for the relatively low ability of Cl to form hydrogen bonds. When the radii of two atoms differ greatly or are large, their nuclei cannot achieve close proximity when they interact, resulting in a weak interaction.

Hydrogen Bonding in Nature

Hydrogen bonding plays a crucial role in many biological processes and can account for many natural phenomena such as the Unusual properties of Water. In addition to being present in water, hydrogen bonding is also important in the water transport system of plants, secondary and tertiary protein structure, and DNA base pairing.

Plants

The cohesion-adhesion theory of transport in vascular plants uses hydrogen bonding to explain many key components of water movement through the plant's xylem and other vessels. Within a vessel, water molecules hydrogen bond not only to each other, but also to the cellulose chain which comprises the wall of plant cells. This creates a sort of capillary tube which allows for capillary action to occur since the vessel is relatively small. This mechanism allows plants to pull water up into their roots. Furthermore,hydrogen bonding can create a long chain of water molecules which can overcome the force of gravity and travel up to the high altitudes of leaves.



Proteins

Hydrogen bonding is present abundantly in the secondary structure of proteins, and also sparingly in tertiary conformation. The secondary structure of a protein involves interactions (mainly hydrogen bonds) between neighboring polypeptide backbones which contain Nitrogen-Hydrogen bonded pairs and oxygen atoms. Since both N and O are strongly electronegative, the hydrogen atoms bonded to nitrogen in one polypeptide backbone can hydrogen bond to the oxygen atoms in another chain and visa-versa. Though they are relatively weak,these bonds offer great stability to secondary protein structure because they repeat a great number of times.

In tertiary protein structure,interactions are primarily between functional R groups of a polypeptide chain; one such interaction is called a hydrophobic interaction. These interactions occur because of hydrogen bonding between water molecules around the hydrophobe and further reinforce conformation.

References

1. Chang, Raymond. General Chemistry:The Essential Concepts. 3rd ed. New York: Mcgraw Hill, 2003
2. Petrucci, et al. General Chemistry: Principles & Modern Applications. 9th ed. Upper Saddle River, New Jersey: Pearson/Prentice Hall, 2007.

Contributors

- Jose Pietri

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2.11: Intermolecular Forces

Learning Objective

- predict the relative boil points of organic compounds

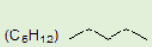
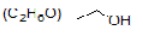
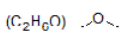
Intermolecular forces (IMFs) can be used to predict relative boiling points. The stronger the IMFs, the lower the vapor pressure of the substance and the higher the boiling point. Therefore, we can compare the relative strengths of the IMFs of the compounds to predict their relative boiling points.

H-bonding > dipole-dipole > London dispersion (van der Waals)

When comparing compounds with the same IMFs, we use size and shape as tie breakers since the London dispersion forces increase as the surface area increases. Since all compounds exhibit some level of London dispersion forces and compounds capable of H-bonding also exhibit dipole-dipole, we will use the phrase "dominant IMF" to communicate the IMF most responsible for the physical properties of the compound.

In the table below, we see examples of these relationships. When comparing the structural isomers of pentane (pentane, isopentane, and neopentane), they all have the same molecular formula C_5H_{12}. However, as the carbon chain is shortened to create the carbon branches found in isopentane and neopentane the overall surface area of the molecules decreases. The visual image of MO theory can be helpful in seeing each compound as a cloud of electrons in an all encompassing MO system. Branching creates more spherical shapes noting that the sphere allows the maximum volume with the least surface area. The structural isomers with the chemical formula C_2H_6O have different dominant IMFs. The H-bonding of ethanol results in a liquid for cocktails at room temperature, while the weaker dipole-dipole of the dimethylether results in a gas a room temperature. In the last example, we see the three IMFs compared directly to illustrate the relative strength IMFs to boiling points.

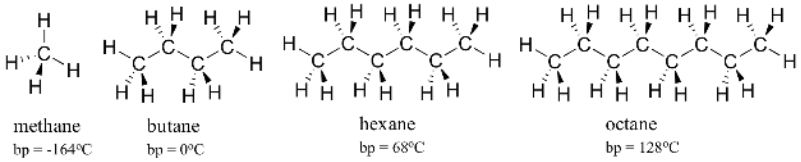
IMFs and Boiling Points

Compounds	bp	"dominant IMF"	
(C_6H_{12}) 	36°C	London dispersion	↑ branching ↓ surface area ↓ the London force ↓ the boiling points
(C_5H_{12})	28°C	London dispersion	
(C_5H_{12})	10°C	London dispersion	
(C_2H_6O) 	78°C	H-bonding	H-bond > dip-dip
(C_2H_6O) 	-25°C	dipole-dipole	
(methane) CH_4	-161°C	London dispersion	H-bond > dip-dip > London
(chloromethane) CH_3Cl	-24°C	dipole-dipole	
(methanol) CH_3OH	80°C	H-bonding	

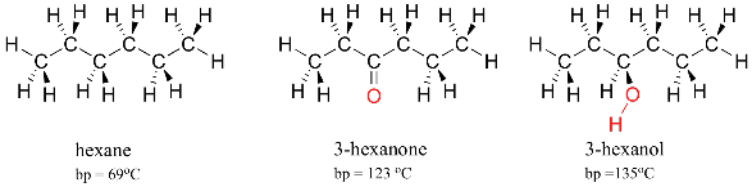
Boiling points and melting points

The observable melting and boiling points of different organic molecules provides an additional illustration of the effects of noncovalent interactions. The overarching principle involved is simple: the stronger the noncovalent interactions between molecules, the more energy that is required, in the form of heat, to break them apart. Higher melting and boiling points signify stronger noncovalent intermolecular forces.

Consider the boiling points of increasingly larger hydrocarbons. More carbons means a greater surface area possible for hydrophobic interaction, and thus higher boiling points.



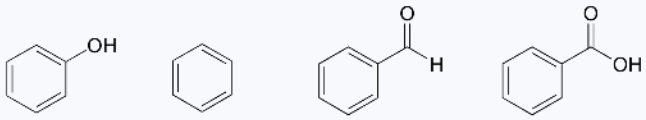
As you would expect, the strength of intermolecular hydrogen bonding and dipole-dipole interactions is reflected in higher boiling points. Just look at the trend for hexane (nonpolar London dispersion interactions only), 3-hexanone (dipole-dipole interactions), and 3-hexanol (hydrogen bonding).



Of particular interest to biologists (and pretty much anything else that is alive in the universe) is the effect of hydrogen bonding in water. Because it is able to form tight networks of intermolecular hydrogen bonds, water remains in the liquid phase at temperatures up to 100 ^{O}C, (slightly lower at high altitude). The world would obviously be a very different place if water boiled at 30 ^{O}C.

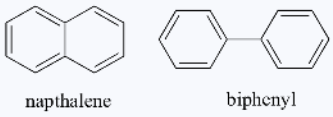
Exercise

1. Based on their structures, rank phenol, benzene, benzaldehyde, and benzoic acid in terms of lowest to highest boiling point.

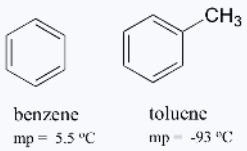


Solution

By thinking about noncovalent intermolecular interactions, we can also predict relative melting points. All of the same principles apply: stronger intermolecular interactions result in a higher melting point. Ionic compounds, as expected, usually have very high melting points due to the strength of ion-ion interactions (there are some ionic compounds, however, that are liquids at room temperature). The presence of polar and especially hydrogen-bonding groups on organic compounds generally leads to higher melting points. Molecular shape, and the ability of a molecule to pack tightly into a crystal lattice, has a very large effect on melting points. The flat shape of aromatic compounds such as napthalene and biphenyl allows them to stack together efficiently, and thus aromatics tend to have higher melting points compared to alkanes or alkenes with similar molecular weights.



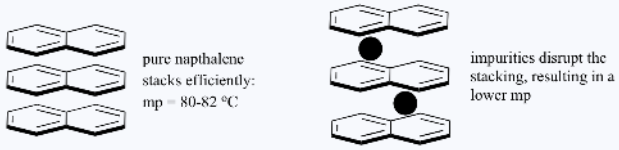
Comparing the melting points of benzene and toluene, you can see that the extra methyl group on toluene disrupts the molecule's ability to stack, thus decreasing the cumulative strength of intermolecular London dispersion forces.



Note also that the *boiling* point for toluene is 111 ^{o}C, well *above* the boiling point of benzene (80 ^{o}C). The key factor for the boiling point trend in this case is size (toluene has one more carbon), whereas for the melting point trend, shape plays a much

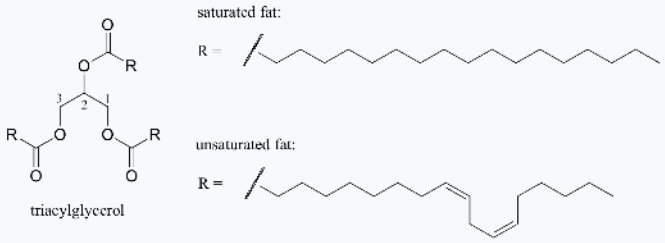
more important role. This makes sense when you consider that melting involves 'unpacking' the molecules from their ordered array, whereas boiling involves simply separating them from their already loose (liquid) association with each other.

If you are taking an organic lab course, you may have already learned that impurities in a crystalline substance will cause the observed melting point to be lower compared to a pure sample of the same substance. This is because impurities disrupt the ordered packing arrangement of the crystal, and make the cumulative intermolecular interactions weaker.



The melting behavior of lipid structures

An interesting biological example of the relationship between molecular structure and melting point is provided by the observable physical difference between animal fats like butter or lard, which are solid at room temperature, and vegetable oils, which are liquid. Both solid fats and liquid oils are based on a 'triacylglycerol' structure, where three hydrophobic hydrocarbon chains of varying length are attached to a glycerol backbone through an ester functional group (compare this structure to that of the membrane lipids discussed in section 2.4B).



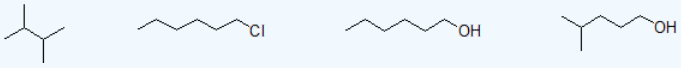
Interactive 3D image of a saturated triacylglycerol (BioTopics)

Saturated vs mono-unsaturated fatty acid (BioTopics)

In vegetable oils, the hydrophobic chains are **unsaturated**, meaning that they contain one or more double bonds. Solid animal fat, in contrast, contains **saturated** hydrocarbon chains, with no double bonds. The double bonds in vegetable oils cause those hydrocarbon chains to be more rigid, and 'bent' at an angle (remember that rotation is restricted around double bonds), with the result that they don't pack together as closely, and thus can be broken apart (*ie*. melted) more readily. Shown in the figure above is a polyunsaturated fatty acid chain (two double bonds), and you can click on the link to see interactive images of a saturated fatty acid compared to a monounsaturated fatty acid (one double bond).

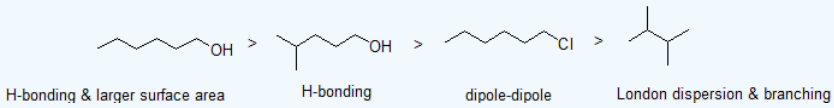
Exercise

2. Arrange the following compounds in order of decreasing boiling point.



Answer

2.



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2.12: Intermolecular Forces

Learning Objective

- predict whether a mixture of compounds will a form homogeneous or heterogeneous solution

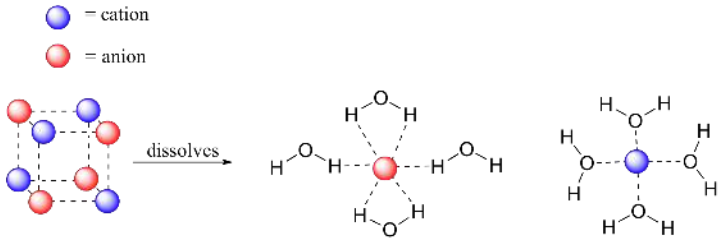
The type of intermolecular forces (IMFs) exhibited by compounds can be used to predict whether two different compounds can be mixed to form a homogeneous solution (soluble or miscible). Because organic chemistry can perform reactions in non-aqueous solutions using organic solvents. It is important to consider the solvent as a reaction parameter and the solubility of each reagent. With this said, solvent effects are secondary to the sterics and electrostatics of the reactants. Make sure that you do not drown in the solvent.

Solubility

Virtually all of the organic chemistry that you will see in this course takes place in the solution phase. In the organic laboratory, reactions are often run in nonpolar or slightly polar solvents such as toluene (methylbenzene), hexane, dichloromethane, or diethylether. In recent years, much effort has been made to adapt reaction conditions to allow for the use of 'greener' (in other words, more environmentally friendly) solvents such as water or ethanol, which are polar and capable of hydrogen bonding. In organic reactions that occur in the cytosolic region of a cell, the solvent is of course water. It is critical for any organic chemist to understand the factors which are involved in the solubility of different molecules in different solvents.

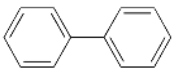
You probably remember the rule you learned in general chemistry regarding solubility: 'like dissolves like' (and even before you took any chemistry at all, you probably observed at some point in your life that oil does not mix with water). Let's revisit this old rule, and put our knowledge of covalent and noncovalent bonding to work.

Imagine that you have a flask filled with water, and a selection of substances that you will test to see how well they dissolve in the water. The first substance is table salt, or sodium chloride. As you would almost certainly predict, especially if you've ever inadvertently taken a mouthful of water while swimming in the ocean, this ionic compound dissolves readily in water. Why? Because water, as a very polar molecule, is able to form many ion-dipole interactions with both the sodium cation and the chloride anion, the energy from which is more than enough to make up for energy required to break up the ion-ion interactions in the salt crystal and some water-water hydrogen bonds.



The end result, then, is that in place of sodium chloride crystals, we have individual sodium cations and chloride anions surrounded by water molecules – the salt is now *in solution*. Charged species as a rule dissolve readily in water: in other words, they are very **hydrophilic** (water-loving).

Now, we'll try a compound called biphenyl, which, like sodium chloride, is a colorless crystalline substance (the two compounds are readily distinguishable by sight, however – the crystals look quite different).

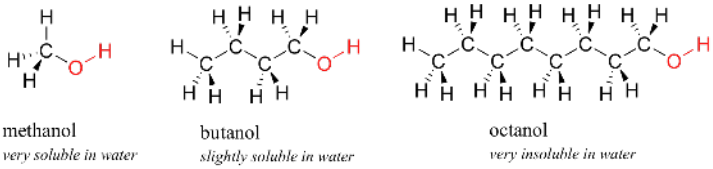


biphenyl

Biphenyl does not dissolve at all in water. Why is this? Because it is a very non-polar molecule, with only carbon-carbon and carbon-hydrogen bonds. It is able to bond to itself very well through nonpolar (London dispersion) interactions, but it is not able to form significant attractive interactions with the very polar solvent molecules. Thus, the energetic cost of breaking up the biphenyl-

to-biphenyl interactions in the solid is high, and very little is gained in terms of new biphenyl-water interactions. Water is a terrible solvent for nonpolar hydrocarbon molecules: they are very **hydrophobic** ('water-fearing').

Next, you try a series of increasingly large alcohol compounds, starting with methanol (1 carbon) and ending with octanol (8 carbons).



methanol
very soluble in water

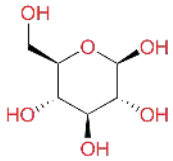
butanol
slightly soluble in water

octanol
very insoluble in water

You find that the smaller alcohols - methanol, ethanol, and propanol - dissolve easily in water. This is because the water is able to form hydrogen bonds with the hydroxyl group in these molecules, and the combined energy of formation of these water-alcohol hydrogen bonds is more than enough to make up for the energy that is lost when the alcohol-alcohol hydrogen bonds are broken up. When you try butanol, however, you begin to notice that, as you add more and more to the water, it starts to form its own layer on top of the water.

The longer-chain alcohols - pentanol, hexanol, heptanol, and octanol - are increasingly non-soluble. What is happening here? Clearly, the same favorable water-alcohol hydrogen bonds are still possible with these larger alcohols. The difference, of course, is that the larger alcohols have larger nonpolar, hydrophobic regions in addition to their hydrophilic hydroxyl group. At about four or five carbons, the hydrophobic effect begins to overcome the hydrophilic effect, and water solubility is lost.

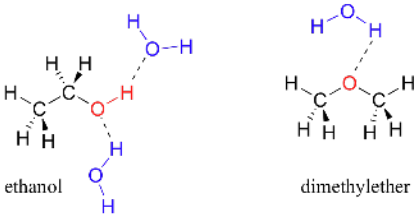
Now, try dissolving glucose in the water – even though it has six carbons just like hexanol, it also has five hydrogen-bonding, hydrophilic hydroxyl groups in addition to a sixth oxygen that is capable of being a hydrogen bond acceptor.



glucose

We have tipped the scales to the hydrophilic side, and we find that glucose is quite soluble in water.

We saw that ethanol was very water-soluble (if it were not, drinking beer or vodka would be rather inconvenient!) How about dimethyl ether, which is a constitutional isomer of ethanol but with an ether rather than an alcohol functional group? We find that diethyl ether is much less soluble in water. Is it capable of forming hydrogen bonds with water? Yes, in fact, it is –the ether oxygen can act as a hydrogen-bond acceptor. The difference between the ether group and the alcohol group, however, is that the alcohol group is both a hydrogen bond donor *and* acceptor.

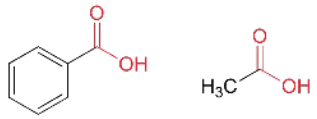


ethanol

dimethylether

The result is that the alcohol is able to form more energetically favorable interactions with the solvent compared to the ether, and the alcohol is therefore more soluble.

Here is another easy experiment that can be done (with proper supervision) in an organic laboratory. Try dissolving benzoic acid crystals in room temperature water – you'll find that it is not soluble. As we will learn when we study acid-base chemistry in a later chapter, carboxylic acids such as benzoic acid are relatively weak acids, and thus exist mostly in the acidic (protonated) form when added to pure water.

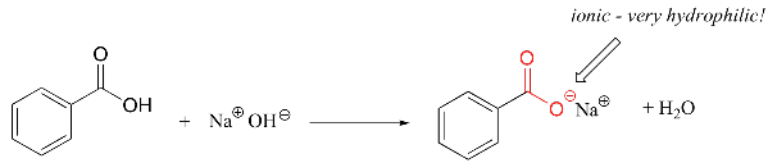


benzoic acid
insoluble in water

acetic acid
soluble in water

Acetic acid, however, is quite soluble. This is easy to explain using the small alcohol vs large alcohol argument: the hydrogen-bonding, hydrophilic effect of the carboxylic acid group is powerful enough to overcome the hydrophobic effect of a single methyl group on acetic acid, but not the larger hydrophobic effect of the 6-carbon benzene group on benzoic acid.

Now, try slowly adding some aqueous sodium hydroxide to the flask containing undissolved benzoic acid. As the solvent becomes more and more basic, the benzoic acid begins to dissolve, until it is completely in solution.



benzoic acid
insoluble in water

sodium benzoate
soluble in water

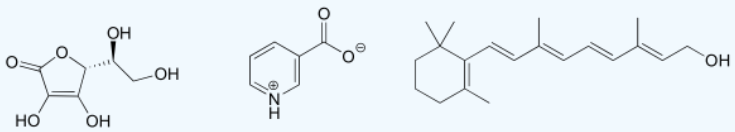
What is happening here is that the benzoic acid is being converted to its conjugate base, benzoate. The *neutral* carboxylic acid group was not hydrophilic enough to make up for the hydrophobic benzene ring, but the carboxylate group, with its *full negative charge*, is much more hydrophilic. Now, the balance is tipped in favor of water solubility, as the powerfully hydrophilic anion part of the molecule drags the hydrophobic part, kicking and screaming, (if a benzene ring can kick and scream) into solution. If you want to precipitate the benzoic acid back out of solution, you can simply add enough hydrochloric acid to neutralize the solution and reprotonate the carboxylate.

If you are taking a lab component of your organic chemistry course, you will probably do at least one experiment in which you will use this phenomenon to separate an organic acid like benzoic acid from a hydrocarbon compound like biphenyl.

Similar arguments can be made to rationalize the solubility of different organic compounds in nonpolar or slightly polar solvents. In general, the greater the content of charged and polar groups in a molecule, the less soluble it tends to be in solvents such as hexane. The ionic and very hydrophilic sodium chloride, for example, is not at all soluble in hexane solvent, while the hydrophobic biphenyl is very soluble in hexane.

Exercise

1. Vitamins can be classified as water-soluble or fat-soluble (consider fat to be a very non-polar, hydrophobic 'solvent'. Decide on a classification for each of the vitamins shown below.



Vitamin C
(ascorbic acid)

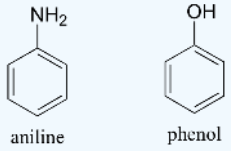
Vitamin B_3
(niacin)

Vitamin A
(retinol)

Solutions

Exercise

2. Both aniline and phenol are insoluble in pure water. Predict the solubility of these two compounds in 10% aqueous hydrochloric acid, and explain your reasoning. Hint – in this context, aniline is basic, phenol is not!

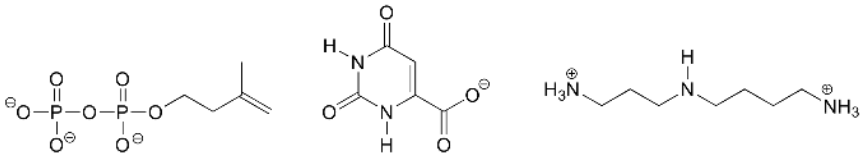


aniline phenol

Solutions

Illustrations of solubility concepts: metabolic intermediates, lipid bilayer membranes, soaps and detergents

Because water is the biological solvent, most biological organic molecules, in order to maintain water-solubility, contain one or more charged functional groups. These are most often phosphate, ammonium or carboxylate, all of which are charged when dissolved in an aqueous solution buffered to pH 7.



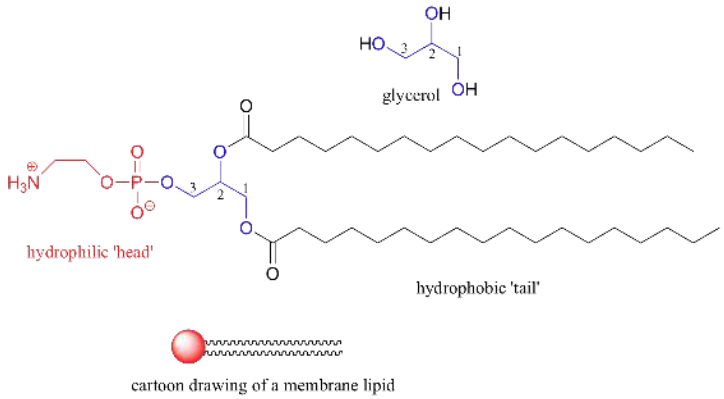
ispentenyl diphosphate
an early precuror to cholesterol

orotate
a precursor to the RNA base uridine

spermidine
binds tightly to DNA in rapidly dividing cells

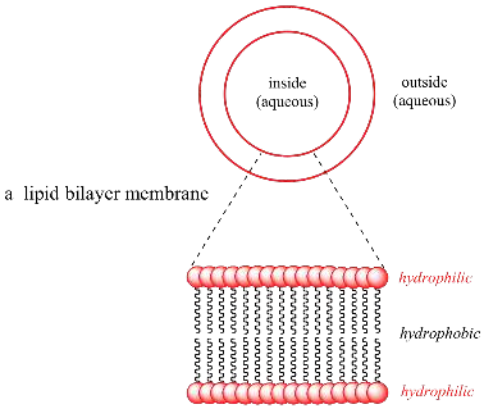
Sugars often lack charged groups, but as we discussed in our ‘thought experiment’ with glucose, they are quite water-soluble due to the presence of multiple hydroxyl groups.

Some biomolecules, in contrast, contain distinctly nonpolar, hydrophobic components. The ‘lipid bilayer’ membranes of cells and subcellular organelles serve to enclose volumes of water and myriad biomolecules in solution. The lipid (fat) molecules that make up membranes are **amphipathic**: they have a charged, hydrophilic ‘head’ and a hydrophobic hydrocarbon ‘tail’.



interactive 3D image of a membrane phospholipid *(BioTopics)*

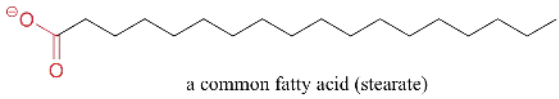
Notice that the entire molecule is built on a ‘backbone’ of glycerol, a simple 3-carbon molecule with three alcohol groups. In a biological membrane structure, lipid molecules are arranged in a spherical bilayer: hydrophobic tails point inward and bind together by London dispersion forces, while the hydrophilic head groups form the inner and outer surfaces in contact with water.



Interactive 3D Image of a lipid bilayer *(BioTopics)*

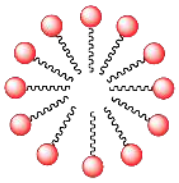
Because the interior of the bilayer is extremely hydrophobic, biomolecules (which as we know are generally charged species) are not able to diffuse through the membrane– they are simply not soluble in the hydrophobic interior. The transport of molecules across the membrane of a cell or organelle can therefore be accomplished in a controlled and specific manner by special transmembrane transport proteins, a fascinating topic that you will learn more about if you take a class in biochemistry.

A similar principle is the basis for the action of soaps and detergents. Soaps are composed of fatty acids, which are long (typically 18-carbon), hydrophobic hydrocarbon chains with a (charged) carboxylate group on one end,



a common fatty acid (stearate)

Fatty acids are derived from animal and vegetable fats and oils. In aqueous solution, the fatty acid molecules in soaps will spontaneously form **micelles**, a spherical structure that allows the hydrophobic tails to avoid contact with water and simultaneously form favorable London dispersion contacts.

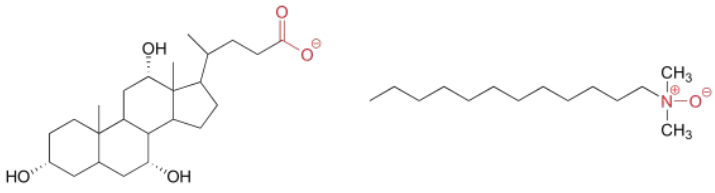


micelle

Interactive 3D images of a fatty acid soap molecule and a soap micelle (Edutopics)

Because the outside of the micelle is charged and hydrophilic, the structure as a whole is soluble in water. Micelles will form spontaneously around small particles of oil that normally would not dissolve in water (like that greasy spot on your shirt from the pepperoni slice that fell off your pizza), and will carry the particle away with it into solution. We will learn more about the chemistry of soap-making in a later chapter (section 12.4B).

Synthetic detergents are non-natural amphipathic molecules that work by the same principle as that described for soaps.



synthetic detergents

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2.13: Additional Practice Problems

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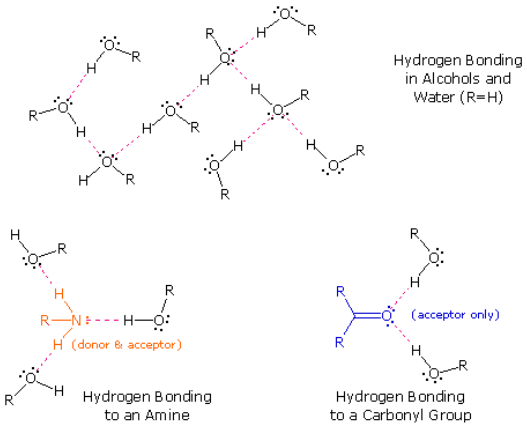
2.14: Organic Functional Groups: H-bond donors

Learning Objective

- distinguish between organic compounds that are H-bond donors versus H-bond acceptors

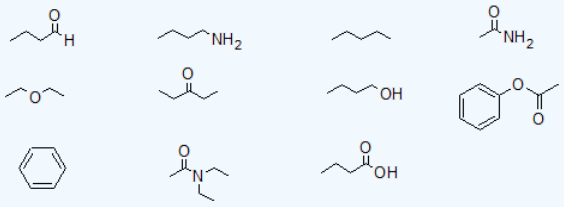
H-bond donors vs H-bond acceptors

Compounds with H-bonding as their dominant intermolecular force (IMF) are BOTH H-bond donors and H-bond acceptors. They are H-bond donors because they have a highly polar hydrogen atom bonded to a strongly electronegative atom, primarily nitrogen, oxygen, or fluorine (NOF). Because there is an equivalent partial negative charge on the atom bonded to hydrogen (mostly NOF), this atom can accept H-bonds from another atoms. Since H-bond donors are ALWAYS H-bond acceptors, we simplify communication to "H-bond donor". There are two H-bonding interactions for H-bond donors. The strongly electronegative elements (primarily nitrogen, oxygen, and fluorine) will always form a relatively large partial negative charge when bonded with carbon. These elements can accept H-bonds when they are part of the organic molecule. In this situation, there is only one H-bonding interaction. The diagram below illustrates the similarities and differences between H-bond donors and H-bond acceptors. Water and alcohols may serve as both donors and acceptors, whereas ethers, aldehydes, ketones and esters can function only as acceptors. Similarly, primary and secondary amines are both donors and acceptors, but tertiary amines function only as acceptors.



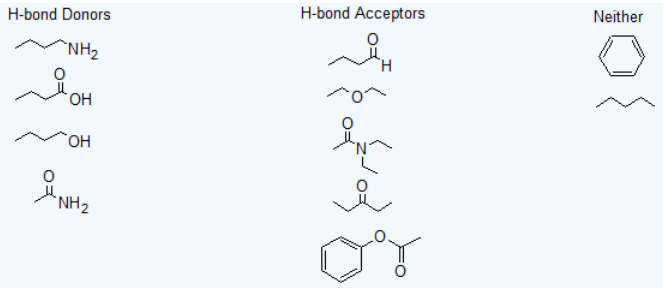
Exercise

1. Classify the compounds below as H-bond donors, H-bond acceptors, or neither.



Answer

1.

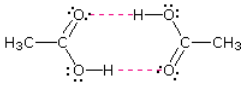


Comparing Physical Properties of H-bond Donors vs H-bond Acceptors

Once we are able to recognize compounds that can exhibit intermolecular hydrogen bonding, the relatively high boiling points they exhibit become understandable. The data in the following table serve to illustrate this point.

Compound	Formula	Mol. Wt.	Boiling Point	Melting Point
dimethyl ether	CH_3OCH_3	46	–24ºC	–138ºC
ethanol	CH_3CH_2OH	46	78ºC	–130ºC
propanol	$CH_3(CH_2)_2OH$	60	98ºC	–127ºC
diethyl ether	$(CH_3CH_2)_2O$	74	34ºC	–116ºC
propyl amine	$CH_3(CH_2)_2NH_2$	59	48ºC	–83ºC
methylaminoethane	$CH_3CH_2NHCH_3$	59	37ºC	
trimethylamine	$(CH_3)_3N$	59	3ºC	–117ºC
ethylene glycol	$HOCH_2CH_2OH$	62	197ºC	–13ºC
acetic acid	CH_3CO_2H	60	118ºC	17ºC
ethylene diamine	$H_2NCH_2CH_2NH_2$	60	118ºC	8.5ºC

Alcohols boil cosiderably higher than comparably sized ethers (first two entries), and isomeric 1º, 2º & 3º-amines, respectively, show decreasing boiling points, with the two hydrogen bonding isomers being substantially higher boiling than the 3º-amine (entries 5 to 7). Also, O–H---O hydrogen bonds are clearly stronger than N–H---N hydrogen bonds, as we see by comparing propanol with the amines.



As expected, the presence of two hydrogen bonding functions in a compound raises the boiling point even further. Acetic acid (the ninth entry) is an interesting case. A dimeric species, shown on the right, held together by two hydrogen bonds is a major component of the liquid state. If this is an accurate representation of the composition of this compound then we would expect its boiling point to be equivalent to that of a $C_4H_8O_4$ compound (formula weight = 120). A suitable approximation of such a compound is found in tetramethoxymethane, $(CH_3O)_4C$, which is actually a bit larger (formula weight = 136) and has a boiling point of 114ºC. Thus, the dimeric hydrogen bonded structure appears to be a good representation of acetic acid in the condensed state.

A related principle is worth noting at this point. Although the hydrogen bond is relatively weak (*ca.* 4 to 5 kcal per mole), when several such bonds exist the resulting structure can be quite robust. The hydrogen bonds between cellulose fibers confer great strength to wood and related materials. For additional information on this subject Click Here.

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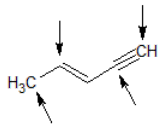
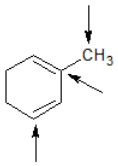
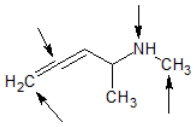
2.15: Additional Exercises

Hybridization

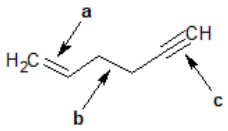
2-1 For each of the following compounds, identify the hybridization of each carbon or nitrogen atom with an arrow pointed at it.

(a) 

(b) 

(c) 

2-2 Rank the following bonds in order of decreasing bond length. Then rank the bonds in order from strongest to weakest.



2-3 How many sigma and pi bonds are in a molecule of ethane (C_2H_6)?

2-4 How many sigma and pi bonds are in a molecule of ethylene (C_2H_4)?

2-5 How many sigma and pi bonds are in a molecule of acetylene (C_2H_2)?

Hybridization, Electron Geometry, and Molecular Shape

2-6 What is the hybridization state and geometry of the carbon atom in methane (CH_4)?

a) *sp*, linear

b) sp^3, tetrahedral

c) sp^2, trigonal planar

d) None of the above

2-7 Identify the electron geometry of the following compounds.

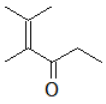
a) H_2O

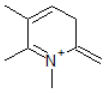
b) PF_5

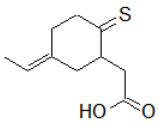
c) NH_4^+

d) The carbonyl carbon of acetone $(CH_3)_2CO$. (Note that double bonds between carbon and oxygen must be recognized.)

2-8 For the following compounds, identify which atoms have sp^2 hybridization.

(a) 

(b) 

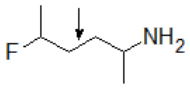
(c) 

2-9 Draw the orbitals showing the geometric shape of ammonia (NH_3). Identify its geometric shape.

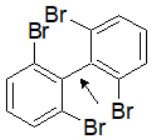
2-10 What is the geometric shape of the boron atom in BH_3? What is the bond angle of the hydrogen atoms?

Bond Rotation

2-11 Will the following compound experience free rotation around the middle bond? Explain why or why not.



2-12 Will the following compound experience free rotation around the middle bond? Explain why or why not.

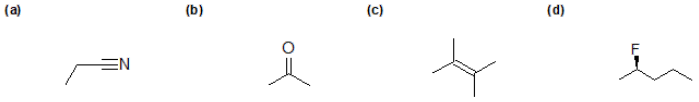


2-13 Can a molecule of ethylene experience free rotation around the C=C bond?

Polarity of Bonds and Molecules

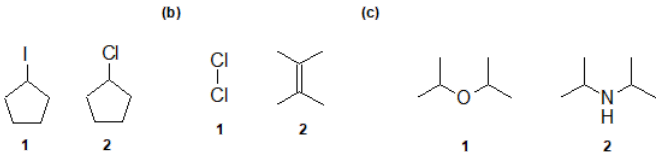
2-14 For the following compounds, draw an arrow to show the direction of the dipole moment (if any).

(a) (b) (c) (d)



2-15 In the following pairs of compounds, identify the compound with the larger dipole moment (if any).

(a) (b) (c)



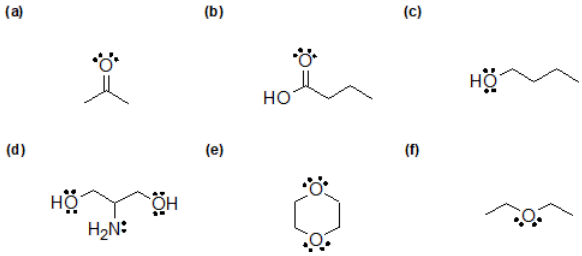
2-16 True or False: Generally, the larger the difference in electronegativity of connected atoms, the greater the dipole moment.

Intermolecular Forces (IMFs)

2-17 Identify which of the following compounds can form hydrogen bonds.

(a) (b) (c)

(d) (e) (f)



2-18 For the compounds in the previous problem (**2-17 above**) that can hydrogen bond, draw how they can form those bonds.

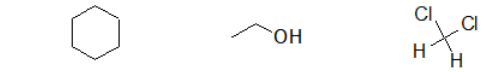
2-19 Identify what type of intermolecular force the following compounds experience.

(a) (b) (c) (d)

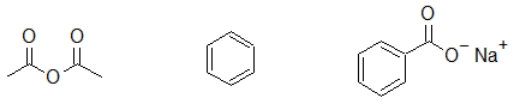
IMFs and Solubility

2-20 Identify whether the following compounds are miscible or soluble in water.

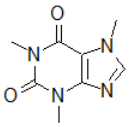
(a) (b) (c)



(d) (e) (f)



2-21 Identify which solvent, hexanes or dichloromethane (DCM), would be the better solvent to dissolve 3.0 grams of caffeine. Explain your answer.

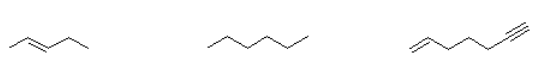


Caffeine

Hydrocarbons and an Introduction to Isomerism

2-22 Identify whether the following hydrocarbons are alkanes, alkenes, or alkynes.

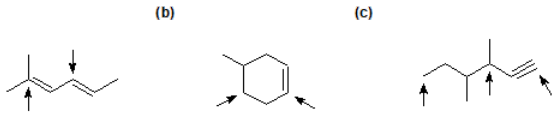
(a) (b) (c)



(d) (e) (f)

2-23 For the following compounds, identify the hybridization state of each labeled carbon.

(a) (b) (c)



2-24 Draw all possible isomers for the following compounds.

a) C_4H_{10}

b) C_6H_{14}

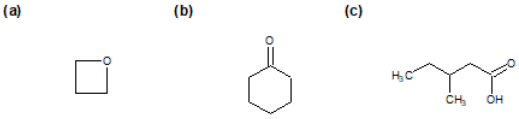
c) C_3H_6

2-25 Does $(CH_3)_2CHCCCH_3$ show cis/trans isomerism? Explain why or why not.

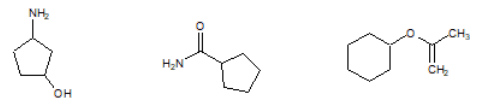
Organic Compounds with Oxygen

2-26 Identify the functional group(s) of each compound.

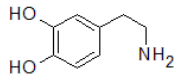
(a) (b) (c)



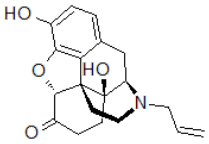
(d) (e) (f)



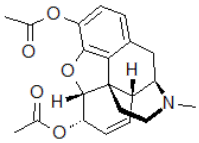
2-27 What functional groups are found in the following compounds?



Dopamine



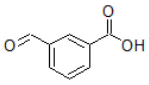
Naloxone



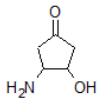
Heroin

2-28 What oxygen-containing functional groups are present in the following compounds. The nitrogen-containing group is a challenge question.

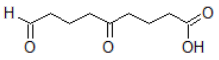
(a)



(b)

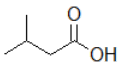


(c)



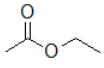
2-29 Identify whether the functional groups on the following compounds are classified correctly. If not, give the correct classification.

(a)



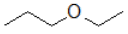
- ketone
-alcohol

(b)



- ether
- ketone

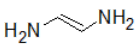
(c)



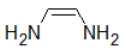
- ether

Organic Compounds with Nitrogen

2-30 First, identify which of the following compounds has a dipole moment. Then, predict which of the following compounds will have the higher boiling point and explain why.



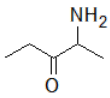
a



b

2-31 Identify whether the functional groups of the following compounds are classified correctly. If not, give the correct classification.

(a)

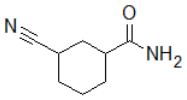


- amide

(b)

- cyanoamine

(c)



- ketone
- amine
- nitrile

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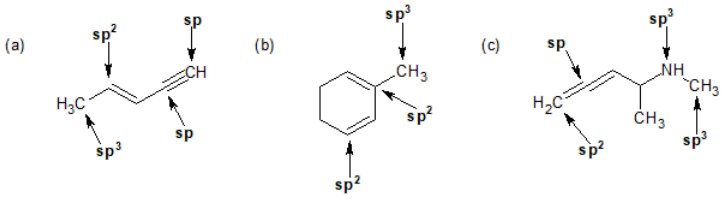
2.16: 2.15 Solutions to Additional Exercises

Hybridization

2-1



2-2

Longest to shortest bond length: b > a > c

Strongest to weakest bond: c > a > b

2-3

Sigma bonds: 7

Pi bonds: 0

2-4

Sigma bonds: 5

Pi bonds: 1

2-5

Sigma bonds: 3

Pi bonds: 2

Hybridization, Electron Geometry, and Molecular Shape

2-6 Correct answer is (b) sp^3, tetrahedral.

2-7

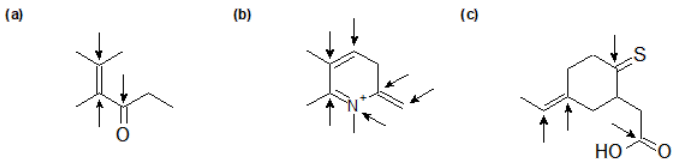
a) Tetrahedral

b) Trigonal bipyramidal

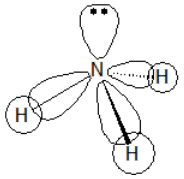
c) Tetrahedral

d) Trigonal planar

2-8



2-9



Trigonal Pyramidal

2-10 Boron has trigonal planar geometry. The hydrogen atoms are at a 120° angle from each other to be as far apart as possible.

Bond Rotation

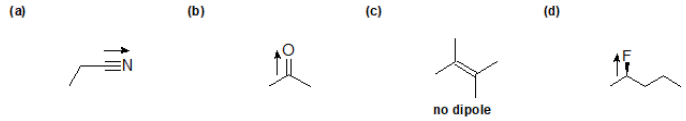
2-11 This molecule can rotate freely around the middle bond as there are no major steric hindrance interactions.

2-12 This molecule cannot rotate freely around the middle bond as the large bromine substituents attached at the ortho positions of the benzene rings experience significant steric hindrance with each other.

2-13 No; the pi-bond prevents free rotation about the C=C bond.

Polarity of Bonds and Molecules

2-14



2-15

a) 2

b) No dipole moment

c) 1

2-16 True

Intermolecular Forces (IMFs)

2-17

a) Cannot H-bond

b) Can H-bond

c) Can H-bond

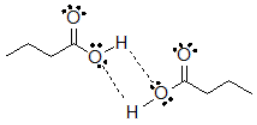
d) Can H-bond

e) Cannot H-bond

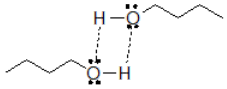
f) Cannot H-bond

2-18

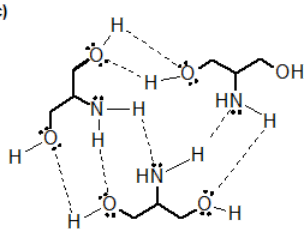
(a)



(b)



(c)



2-19

a) London Dispersion Forces

b) Dipole-Dipole Interactions

c) Ionic Forces

d) Hydrogen bonding

IMFs and Solubility

2-20

a) Not miscible

b) Miscible

c) Not miscible

d) Soluble

e) Not soluble

f) Soluble

2-21 Caffeine will dissolve in dichloromethane (DCM) significantly more than in hexanes as DCM is a more polar solvent and caffeine is a polar molecule (like dissolves like).

Hydrocarbons and an Introduction to Isomerism

2-22

a) Alkene

b) Alkane

c) Alkyne

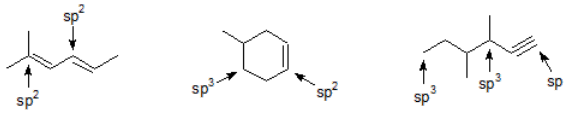
d) Alkane

e) Alkene

f) Alkene

2-23

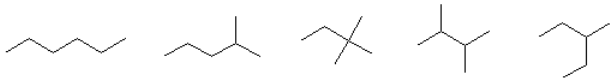
(a) (b) (c)



2-24

(a)

(b)



(c)

2-25 It does not have cis/trans configuration, as the triple bond in the compound $(CH_3)_2CHC{\equiv}CCH_3$ holds the four carbons in a straight line due to the *sp* hybridization of the middle two carbons (which have a linear geometric configuration).

Organic Compounds with Oxygen

2-26

a) Ether

b) Ketone

c) Carboxylic acid

d) Alcohol and Amine

e) Amide

f) Ether and Alkene

2-27

a) Alcohol and Amine (We will learn that the most correct classification for hydroxyl groups bonded to benzene rings is phenol)

b) Alcohol, Ether, Ketone, Amine and Alkene

c) Ester, Ether, Amine and Alkene

2-28

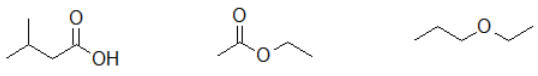
a) Aldehyde and carboxylic acid

b) Alcohol, Ketone, Amine

c) Alcohol, Ketone, Carboxylic acid

2-29

(a) (b) (c)

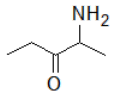


- carboxylic acid - ester - ether

2-30 Compound B has a slight dipole moment due to the cis configuration of the amine groups. Since it has a dipole moment, it experiences dipole-dipole interactions in addition to hydrogen bonding, thus increasing its boiling point.

2-31

(a)

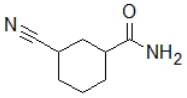


- ketone
- amine

(b)

- nitrile

(c)



- amide
- nitrile

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CHAPTER OVERVIEW

3: Structure and Stereochemistry of Alkanes

LEARNING OBJECTIVES

After reading this chapter and completing ALL the exercises, a student can be able to

- distinguish between the different hydrocarbon functional groups - refer to section 4.1
- explain & predict the physical properties of alkanes including relative bp and solubility in a mixture - refer to section 4.2
- interpret and draw the rotation about a carbon-carbon single bond using Newman projections and sawhorse structures - refer to section 4.3 - 4.5
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for butane, higher alkanes, cyclohexane, mono-substituted cyclohexanes, and disubstituted cyclohexanes - refer to sections 4.3, 4.3, 4.4, 4.5, and 4.7, 4.8, and 4.10 respectively
- explain the partial rotation of carbon-carbon single bonds in rings - refer to section 4.6
- explain ring strain and its relationship to cycloalkane stability - refer to section 4.6
- draw cyclohexane conformations (chair & boat) - refer to section 4.7
- draw mono-substituted cyclohexane conformers (chair only) - refer to section 4.8
- identify & draw the geometric (cis/trans) isomers of cycloalkanes - refer to section 4.9
- draw di-substituted cyclohexane conformers (chair only) - refer to section 4.10
- recognize and draw the three ways to join two rings - refer to section 4.11
- describe the uses and sources of alkanes - refer to section 4.12
- recognize and distinguish between the two major reactions of alkanes (combustion and halogenation) - refer to section 4.13

3.1: Hydrocarbon Functional Groups
3.2: Physical Properties of Alkanes
3.3: Structure and Conformations of Alkanes
3.4: Conformations of Butane
3.5: Conformations of Higher Alkanes
3.6: Cycloalkanes and Ring Strain
3.7: Cyclohexane Conformations
3.8: Conformations of Monosubstituted Cyclohexanes
3.9: Cis-trans Isomerism in Cycloalkanes
3.10: Conformations of Disubstituted Cyclohexanes
3.11: Joined Rings
3.12: Uses and Sources of Alkanes
3.13: Reactions of Alkanes - a Brief Overview
3.14: Additional Exercises
3.15: Solutions to Additional Exercises

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3.1: Hydrocarbon Functional Groups

Learning Objective

- distinguish between the different hydrocarbon functional groups

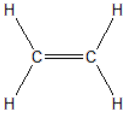
Saturated vs. Unsaturated Molecules

Hydrocarbons are organic compounds that contain **only** carbon and hydrogen. The broadest distinction between hydrocarbons is whether they are saturated and unsaturated. Saturated hydrocarbons only contain carbon-carbon single bonds with the maximum number of hydrogens relative to the number of carbon atoms. It can be said that the carbon atoms are "saturated" with hydrogen atoms in the same way a saturated solution has dissolved the maximum amount of solute. Hydrocarbons that contain pi bonds as carbon-carbon double or triple bonds are classified as unsaturated hydrocarbons. Unsaturation indicates that some of the carbon-hydrogen bonds were lost to from pi bonds between carbon atoms. There are less than the maximum number os hydrogens relative to the number of carbon atoms.

1. Saturated hydrocarbons (alkanes) are the simplest of the hydrocarbon species. They are composed entirely of single bonds and are saturated with hydrogen. Saturated hydrocarbons are the basis of petroleum fuels and are found as either linear or branched species.The simplest alkanes have their C atoms bonded in a straight chain; these are called *normal* alkanes. They are named according to the number of C atoms in the chain. The smallest alkane is methane:

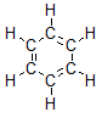
2. Unsaturated hydrocarbons have one or more double or triple bonds between carbon atoms. Those with double bond are called alkenes and those with one double bond have the formula C_nH_{2n} (assuming non-cyclic structures). Those containing triple bonds are called alkynes, with general formula C_nH_{2n-2}.

The smallest alkene—ethene—has two C atoms and is also known by its common name ethylene:



The smallest alkyne is ethyne, which is also known as acetylene:

3. For now, we will focus on benzene as the representative aromatic hydrocarbon. Aromatic compounds were first noted for their strong aromas and low chemical reactivity compared to other saturated hydrocarbons. Aromatic compounds will be discussed in greater detail in the second semester to organic chemistry.



Hydrocarbon Functional Groups

The four distinct hydrocarbon functional groups are: alkanes, alkenes, alkynes and arenes. Aromatic compounds derive their names from the fact that many of these compounds in the early days of discovery were grouped because they were oils with fragrant odors.

Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes have the general formula C_nH_{2n+2}. Alkanes can be subdivided into the following three groups: the **linear straight-chain alkanes**, **branched alkanes**, and **cycloalkanes**. Alkanes are also *saturated hydrocarbons*. Alkanes are the simplest and least reactive hydrocarbon species containing only carbons and hydrogens. The distinguishing feature of an alkane, making it distinct

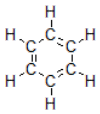
from other compounds that also exclusively contain carbon and hydrogen, is its lack of unsaturation. That is to say, it contains no double or triple bonds, which are highly reactive in organic chemistry. Though not totally devoid of reactivity, their lack of reactivity under most laboratory conditions makes them a relatively uninteresting, though very important component of organic chemistry. As you will learn about later, the energy confined within the carbon-carbon bond and the carbon-hydrogen bond is quite high and their rapid oxidation produces a large amount of heat, typically in the form of fire.

The general formula for saturated hydrocarbons is C_nH_{2n+2}(assuming non-cyclic structures) as shown in hexane (C_6H_{14}) below.

Cycloalkanes are hydrocarbons containing one or more carbon rings to which hydrogen atoms are attached. The general formula for a cyclic hydrocarbon containing one ring is C_nH_{2n} as shown in cyclohexane (C_6H_{12}) below.

Akenes contain at least one carbon-carbon double bond and alkynes contain at least one carbon-carbon triple bond. Alkenes have the general formula C_nH_{2n}. Alkynes have the general formula C_nH_{2n-2}. The ratio of carbon to hydrogen increased because hydrogen atoms are replaced with pi bonds as shown in trans-2-butene (C_4H_8) and 2-butyne (C_4H_6) below. Since both double and triple bonds include pi bonds, Alkenes and alkynes share similar chemical reactivity.

Aromatic hydrocarbons, also known as arenes, are hydrocarbons that have at least one aromatic ring. Aromatic compounds contain the benzene unit. Benzene itself is composed of six C atoms in a ring, with alternating single and double C–C bonds:



Calculating Degrees of Unsaturation (DU)

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 (DU) is useful information. Knowing the degrees of unsaturation tells us the combined number of pi bonds and rings within a compound which makes it easier to figure out the molecular structure.

Degree of Unsaturation (DU) can be calculated with the equation below and the molecular formula

DU= (2C+2+N-X-H)/2

where: C is the number of carbons; N is the number of nitrogens; X is the number of halogens (F, Cl, Br, I); and H is the number of hydrogens from the molecular formula.

As stated before, a saturated molecule contains only single bonds and no rings. Another way of interpreting this is that a saturated molecule has the maximum number of hydrogen atoms possible to be an acyclic alkane. Thus, the number of hydrogens can be represented by 2C+2, which is the general molecular representation of an alkane. 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]*. The compound needs 4 more hydrogens in order to be fully saturated *(expected number of hydrogens-observed number of hydrogens=8-4=4)*. Degrees of unsaturation is equal to 2, or half the number of hydrogens the molecule needs to be classified as saturated. Hence, the DoB formula divides by 2. The formula subtracts the number of X's because a halogen (X) replaces a hydrogen in a compound. For instance, in chloroethane, C_2H_5Cl, there is one less hydrogen compared to ethane, C_2H_6.

For a compound to be saturated, there is one more hydrogen in a molecule when nitrogen is present. Therefore, we add the number of nitrogens (N). This can be seen with C_3H_9N compared to C_3H_8. Oxygen and sulfur are not included in the formula because saturation is unaffected by these elements. As seen in alcohols, the same number of hydrogens in ethanol, C_2H_5OH, matches the number of hydrogens in ethane, C_2H_6.

The following chart illustrates the possible combinations of the number of double bond(s), triple bond(s), and/or ring(s) for a given degree of unsaturation. Each row corresponds to a different combination.

- 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).

DU	**Possible combinations of rings/ bonds**		
	# of rings	# of double bonds	# of triple bonds
1	1	0	0
	0	1	0
2	2	0	0
	0	2	0
	0	0	1
	1	1	0
3	3	0	0
	2	1	0
	1	2	0
	0	1	1
	0	3	0
	1	0	1

Remember, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or rings. For instance, a degree of unsaturation of 3 can contain 3 rings, 2 rings+1 double bond, 1 ring+2 double bonds, 1 ring+1 triple bond, 1 double bond+1 triple bond, *or* 3 double bonds.

Example

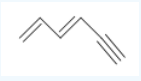
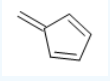
What is the Degree of Unsaturation for benzene?

Solution - "Thinking it through"

The molecular formula for benzene is C_6H_6. Thus,

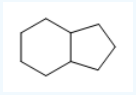
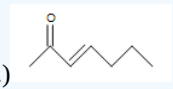
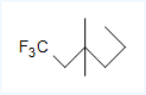
DU= 4, where C=6, N=0,X=0, and H=6. 1 DU can equal 1 ring or 1 double bond. This corresponds to benzene containing 1 ring and 3 double bonds.

Even though there are other possible structures with a DU = 4, like the ones shown below. We will learn the benzene rings have unusual stability and occur frequently in the world of organic chemistry. When the DU for a compound is $\geq$ 4, we can assume the presence of at least one benzene ring.

Exercise

1. Are the following molecules saturated or unsaturated:

1.  (b.)  (c.)  (d.) $C_{10}H_6N_4$

2. Using the molecules from 1., give the degrees of unsaturation for each.
3. Calculate the degrees of unsaturation for the following molecular formulas:
    1. (a.) C_9H_{20} (b.) C_7H_8 (c.) C_5H_7Cl (d.) $C_9H_9NO_4$
4. Using the molecular formulas from 3, are the molecules unsaturated or saturated.
5. Using the molecular formulas from 3, if the molecules are unsaturated, how many rings/double bonds/triple bonds are predicted?

Answer

1.

(a.) **unsaturated** (E*ven though rings only contain single bonds, rings are considered unsaturated.)*

(b.) **unsaturated**

(c.) **saturated**

(d.) **unsaturated**

2. *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**

(b.) **2** *(one double bond and the double bond from the carbonyl)*

(c.) **0**

(d.) **10**

3. *Use the formula to solve*

(a.) **0**

(b.) **4**

(c.) **2**

(d.) **6**

4.

(a.) **saturated**

(b.) **unsaturated**

(c.) **unsaturated**

(d.) **unsaturated**

5.

(a.) **0** (Remember-a saturated molecule only contains single bonds)

(b.) *The molecule can contain any of these combinations* **(i) 4 double bonds (ii) 4 rings (iii) 2 double bonds+2 rings (iv) 1 double bond+3 rings (v) 3 double bonds+1 ring (vi) 1 triple bond+2 rings (vii) 2 triple bonds (viii) 1 triple bond+1 double bond+1 ring (ix) 1 triple bond+2 double bonds**

(c.) (**i) 1 triple bond (ii) 1 ring+1 double bond (iii) 2 rings (iv) 2 double bonds**

(d.) **(i) 3 triple bonds (ii) 2 triple bonds+2 double bonds (iii) 2 triple bonds+1 double bond+1 ring (iv)...** *(As you can see, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or ring. Thus, the formula may give numerous possible structures for a given molecular formula.)*

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)

Contributors and Attributions

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3.2: Physical Properties of Alkanes

Learning Objective

- explain & predict the physical properties of alkanes including relative bp and solubility in a mixture

Overview

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. The differences in the physical states occurs because there is a direct relationship between the size and shape of molecules and the strength of the intermolecular forces (IMFs).

Because alkanes have relatively predictable physical properties and undergo relatively few chemical reactions other than combustion, they serve as a basis of comparison for the properties of many other organic compound families. Let's consider their physical properties first.

Boiling Points

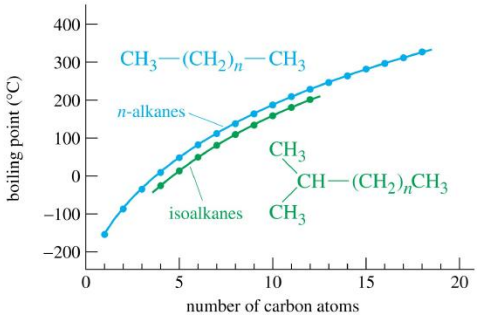
Table **3.2.1** describes some of the properties of some of the first 10 straight-chain alkanes. Because alkane molecules are nonpolar, they are insoluble in water, which is a polar solvent, but are soluble in nonpolar and slightly polar solvents. Consequently, alkanes themselves are commonly used as solvents for organic substances of low polarity, such as fats, oils, and waxes. Nearly all alkanes have densities less than 1.0 g/mL and are therefore less dense than water (the density of H_2O is 1.00 g/mL at 20°C). These properties explain why oil and grease do not mix with water but rather float on its surface.

Table* 3.2.1: Physical Properties of Some Alkanes*

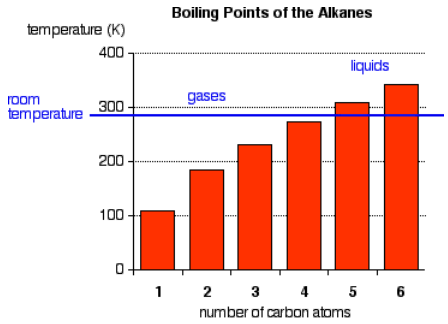
Molecular Name	Formula	Melting Point (°C)	Boiling Point (°C)	Density (20°C)*	Physical State (at 20°C)
methane	CH_4	–182	–164	0.668 g/L	gas
ethane	C_2H_6	–183	–89	1.265 g/L	gas
propane	C_3H_8	–190	–42	1.867 g/L	gas
butane	C_4H_{10}	–138	–1	2.493 g/L	gas
pentane	C_5H_{12}	–130	36	0.626 g/mL	liquid
hexane	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.



This next diagrams summarizes the physical states of the first six alkanes. 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. By the time you get 17 carbons into an alkane, there are unbelievable numbers of isomers!



Cycloalkanes have boiling points that are approximately 20 K higher than the corresponding straight chain alkane.

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.

Where you have 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.

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 tidier and less "wriggly"!

Solubility

Alkanes (both alkanes and cycloalkanes) 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.

The energy only description of solvation is an oversimplification because entropic effects are also important when things dissolve.

The lack of water solubility can lead to environmental concerns when oils are spilled into natural bodies of water as shown below.

Oil Spills. Crude oil coats the water's surface in the Gulf of Mexico after the Deepwater Horizon oil rig sank following an explosion. The leak was a mile below the surface, making it difficult to estimate the size of the spill. One liter of oil can create a slick 2.5 hectares (6.3 acres) in size. This and similar spills provide a reminder that hydrocarbons and water don't mix. Source: Photo courtesy of NASA Goddard / MODIS Rapid Response Team, http://www.nasa.gov/topics/earth/features/oilspill/oil-20100519a.html.

Solubility in organic solvents

In most organic solvents, the primary forces of attraction between the solvent molecules are Van der Waals - either dispersion forces or dipole-dipole attractions. 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.

Looking Closer: Gas Densities and Fire Hazards

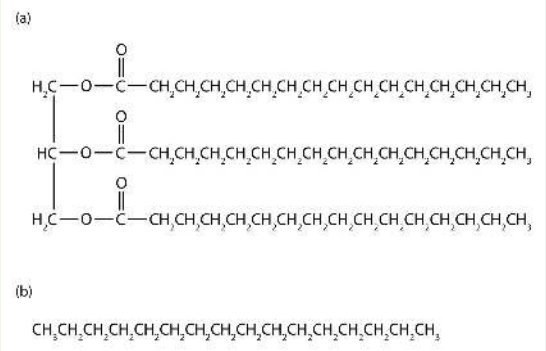
Table **3.2.1** indicates that the first four members of the alkane series are gases at ordinary temperatures. Natural gas is composed chiefly of methane, which has a density of about 0.67 g/L. The density of air is about 1.29 g/L. Because natural gas is less dense than air, it rises. When a natural-gas leak is detected and shut off in a room, the gas can be removed by opening an upper window. On the other hand, bottled gas can be either propane (density 1.88 g/L) or butanes (a mixture of butane and isobutane; density about 2.5 g/L). Both are much heavier than air (density 1.2 g/L). If bottled gas escapes into a building, it collects near the floor. This presents a much more serious fire hazard than a natural-gas leak because it is more difficult to rid the room of the heavier gas.

Also shown in Table **3.2.1** are the boiling points of the straight-chain alkanes increase with increasing molar mass. This general rule holds true for the straight-chain homologs of all organic compound families. Larger molecules have greater surface areas and consequently interact more strongly; more energy is therefore required to separate them. For a given molar mass, the boiling points of alkanes are relatively low because these nonpolar molecules have only weak dispersion forces to hold them together in the liquid state.

Looking Closer: An Alkane Basis for Properties of Other Compounds

An understanding of the physical properties of the alkanes is important in that 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 fatlike 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.



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.

Exercise

1. Without referring to a table, predict which has a higher boiling point—hexane or octane. Explain.

2. If 25 mL of hexane were added to 100 mL of water in a beaker, which of the following would you expect to happen? Explain.

    1. Hexane would dissolve in water.
    2. Hexane would not dissolve in water and would float on top.
    3. Hexane would not dissolve in water and would sink to the bottom of the container.

3. Without referring to a table or other reference, predict which member of each pair has the higher boiling point.

    1. pentane or butane
    2. heptane or nonane

4. For which member of each pair is hexane a good solvent?

    1. pentane or water
    2. sodium chloride or soybean oil

Answer

    1. octane because of its greater molar mass

2. b; Hexane is insoluble in water and is less dense than water so it floats on top.

3. a) pentane

b) nonane

4. a) pentane

b) soybean oil

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3.3: Structure and Conformations of Alkanes

Learning Objective

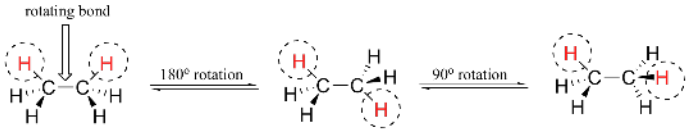
- interpret and draw the rotation about a carbon-carbon single bond using Newman projections and sawhorse structures
- correlate energies of conformations with rotational energy diagrams

Single Bond Rotation and Conformational Isomerism

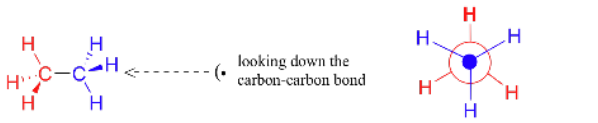
Conformational isomerism involves rotation about sigma bonds, and does not involve any differences in the connectivity or geometry of bonding. Two or more structures that are categorized as conformational isomers, or **conformers**, are really just two of the exact same molecule that differ only in terms of the angle about one or more sigma bonds. The carbon-carbon single bonds of alkanes rotate freely. Conformers are the same molecule shown with different sigma bond rotations. Newman projections are one way to communicate bond rotation.

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. When there are multiple carbons,then we specify the bond of interest using the carbon numbers from the IUPAC name. We depict the ‘front’ atom as a dot, and the ‘back’ atom as a larger circle.

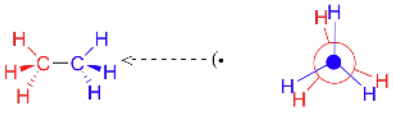


'staggered' conformation (Newman projection)

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.

The lowest energy conformation of ethane, shown in the figure above, is called the ‘staggered’ or 'anti' conformation, in which all of the C-H bonds on the front carbon are positioned at dihedral angles of 60°relative to the C-H bonds on the back carbon. In this conformation, the distance between the bonds (and the electrons in them) is maximized.

If we now rotate the front CH_3 group 60°clockwise, the molecule is in the highest energy ‘eclipsed' conformation, where the hydrogens on the front carbon are as close as possible to the hydrogens on the back carbon.



'eclipsed' conformation

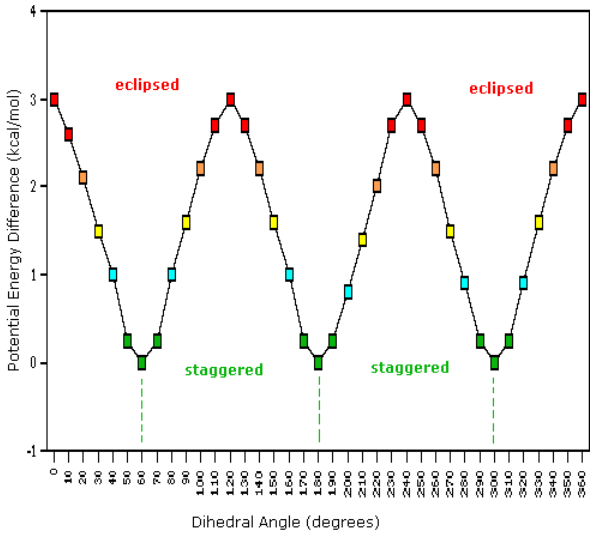
This is the highest energy conformation because of unfavorable interactions between the electrons in the front and back C-H bonds. The energy of the eclipsed conformation is approximately 3 kcal/mol higher than that of the staggered conformation.

Another 60°rotation returns the molecule to a second eclipsed 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.

The carbon-carbon bond is not *completely* free to rotate – there is indeed a small, 3 kcal/mol barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not high enough to prevent constant rotation except at extremely cold temperatures. 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 state.

Free Rotations Do Not Exist in Ethane

The carbon-carbon bond is not *completely* free to rotate – there is indeed a small, 3 kcal/mol barrier to rotation that must be overcome for the bond to rotate from one staggered conformation to another. This rotational barrier is not high enough to prevent constant rotation except at extremely cold temperatures. 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 state. The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds, as shown below.



The potential energy associated with the various conformations of ethane varies with the dihedral angle of the bonds.

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

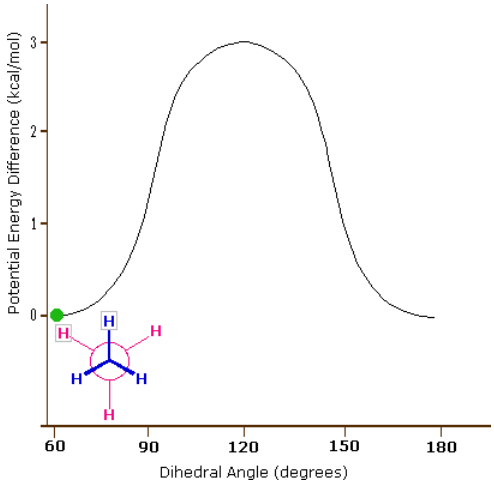


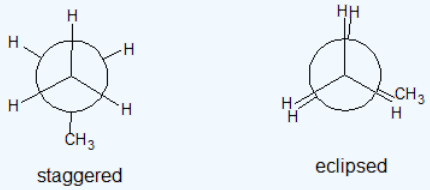
Figure 3.6.X: Animation of potential energy vs. dihedral angle in ethane

Exercise

1. Draw the Newman projections for the staggered and eclipsed conformers of propane along the C1-C2 axis.

Answer

1.



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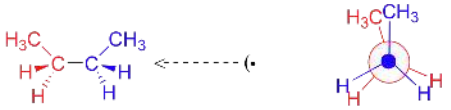
3.4: Conformations of Butane

Learning Objective

- interpret and draw the rotation about a carbon-carbon single bond using Newman projections and sawhorse structures
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for butane

Butane Conformations

Now let's consider butane, with its four-carbon chain. There are now three rotating carbon-carbon 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, with the two C-C bonds at a 0° dihedral angle.



eclipsed (A)

If we rotate the front, (blue) carbon by 60° clockwise, the butane molecule is now in a staggered conformation.

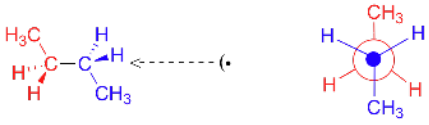
gauche

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.

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)

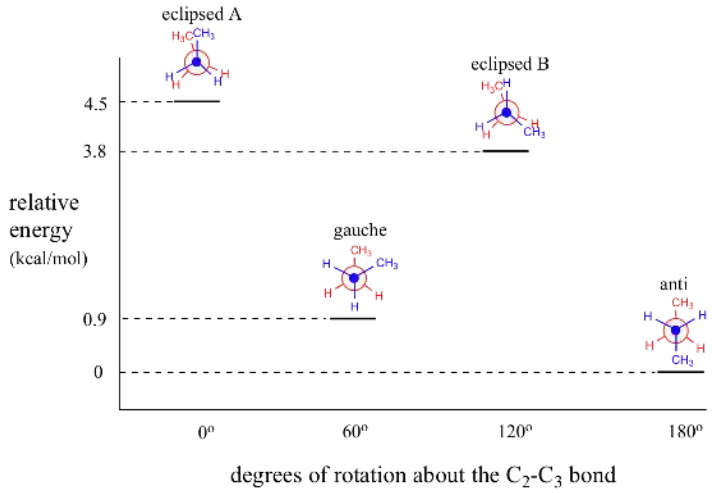
One more 60 rotation produces another staggered conformation called the **anti** conformation, where the two methyl groups are positioned opposite each other (a dihedral angle of 180°).



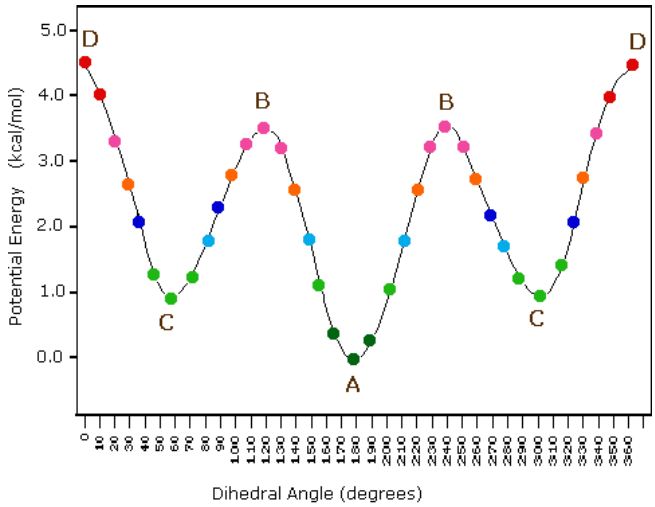
anti

As with ethane, the staggered conformations of butane are energy 'valleys', and the eclipsed conformations are energy 'peaks'. However, in the case of butane there are two different valleys, and two different peaks. The gauche conformation is a higher energy valley than the anti conformation due to **steric strain**, which is the repulsive interaction caused by the two bulky methyl groups being forced too close together. Clearly, steric strain is lower in the anti conformation. In the same way, steric strain causes the eclipsed A conformation - where the two methyl groups are as close together as they can possibly be - to be higher in energy than the two eclipsed B conformations.

The diagram below summarizes the relative energies for the various eclipsed, staggered, and gauche conformations.

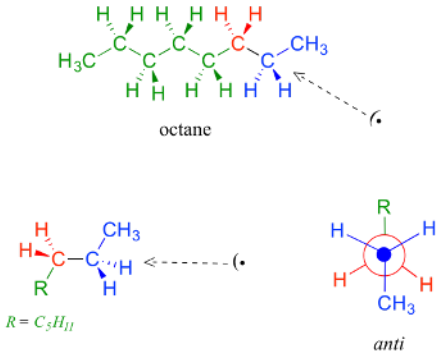


The following diagram illustrates the change in potential energy that occurs with rotation about the C_2–C_3 bond at smaller rotational increments.



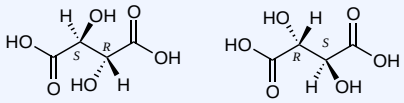
Potential curve vs dihedral angle of the C_2-C_3 bond of butane.

Because the anti conformation (staggered) is lowest in energy (and also simply for ease of drawing), it is conventional to draw open-chain alkanes in a 'zigzag' form, which implies anti conformation at all carbon-carbon bonds. The figure below shows, as an example, a Newman projection looking down the C_2-C_3 bond of octane.

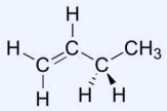


Exercise

1: Using free rotation around C-C single bonds, show that (R,S) and (S,R)-tartaric acid are identical molecules.



2: Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below (C_2 should be your *front* carbon).



Solutions to exercises

Online lectures from Kahn Academy

Newman projections part I

Newman projections part II

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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3.5: Conformations of Higher Alkanes

Learning Objective

- interpret and draw the rotation about a carbon-carbon single bond using Newman projections and sawhorse structures
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for higher alkanes

Pentane and Higher Alkanes

Pentane and higher alkanes have conformational preferences similar to ethane and butane. Each dihedral angle tries to adopt a staggered conformation and each internal C-C bond attempts to take on an anti conformation to minimize the potential energy of the molecule. The most stable conformation of any unbranched alkane follows these rules to take on zigzag shapes:

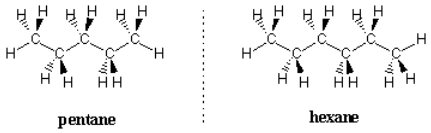


Figure %: The zigzag shapes of unbranched alkanes in their most stable conformations.

Let's analyze the staggered conformations of pentane in more detail, considering conformations about the $C_2 –C_3 $ and $C_3 –C_4 $ bonds. shows a few possible permutations. The most stable conformation is anti at both bonds, whereas less stable conformations contain gauche interactions. One gauche-gauche conformer is particularly unfavorable because methyl groups are aligned with parallel bonds in close proximity. This conformation is called syn. This type of steric hindrance across five atoms is called a syn-pentane interaction. Syn-pentane interactions have an energetic cost of about 3.6 kcal/mol relative to the anti-anti conformation and are therefore disfavored.

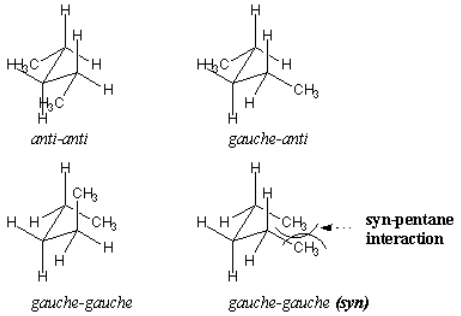
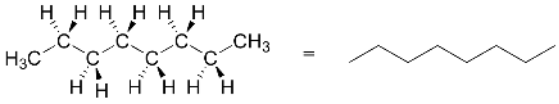
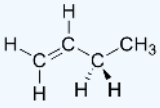


Figure %: Staggered conformations of pentane.



Exercises

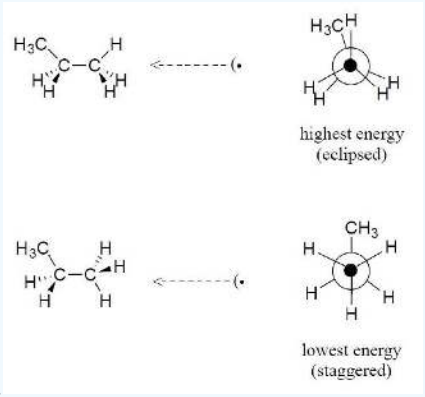
1. Draw Newman projections of the eclipsed and staggered conformations of propane.
2. Draw a Newman projection, looking down the C_2-C_3 bond, of 1-butene in the conformation shown below.



3. Draw the energy diagram for the rotation of the bond highlighted in pentane.

Answer

1.



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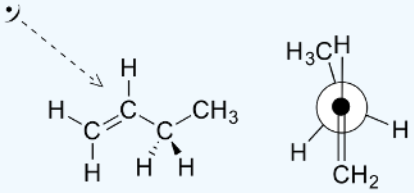
2.



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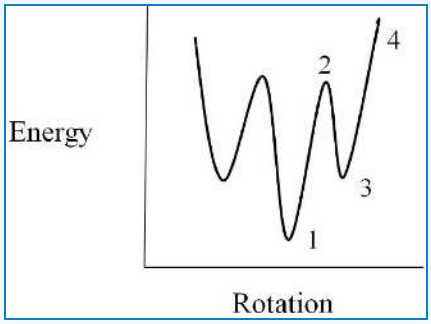
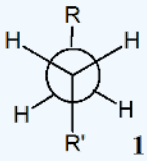
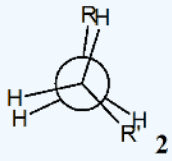



1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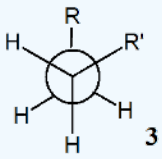
R=Methyl
R'=Ethyl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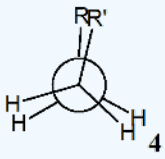
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3.6: Cycloalkanes and Ring Strain

Learning Objective

- explain the partial rotation of carbon-carbon single bonds in rings
- explain ring strain and its relationship to cycloalkane stability

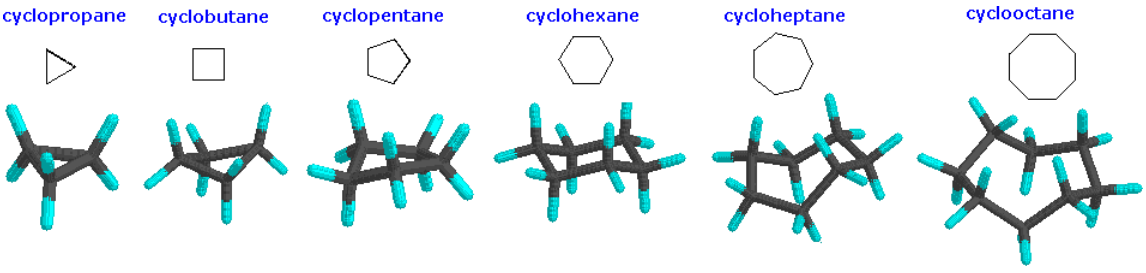
Cycloalkanes (aka Rings)

Cycloalkanes have one or more rings of carbon atoms. The simplest examples of this class consist of a single, unsubstituted carbon ring, and these form a homologous series similar to the unbranched alkanes. The IUPAC names of the first five members of this series are given in the following table. The last column gives the general formula for a cycloalkane of any size. If a simple unbranched alkane is converted to a cycloalkane two hydrogen atoms, one from each end of the chain, must be lost. Hence the general formula for a cycloalkane composed of **n** carbons is $\mathbf{C_nH_{2n}}$. Although a cycloalkane has two fewer hydrogens than the equivalent alkane, each carbon is bonded to four other atoms so such compounds are still considered to be **saturated** with hydrogen.

Table: Examples of Simple Cycloalkanes

Name	Cyclopropane	Cyclobutane	Cyclopentane	Cyclohexane	Cycloheptane	Cycloalkane
Molecular Formula	C_3H_6	C_4H_8	C_5H_{10}	C_6H_{12}	C_7H_{14}	C_nH_{2n}
Structural Formula						$(CH_2)_n$
Line Formula						

Although the customary line drawings of simple cycloalkanes are geometrical polygons, the actual shape of these compounds in most cases is very different. Cyclic systems are a little different from open-chain systems. In an open chain, any bond can be rotated 360 degrees, going through many different conformations. Complete rotation isn't possible in a cyclic system, because the parts that you would be trying to twist away from each other would still be connected together. 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.



The Baeyer Theory and the Experimental Evidence of Ring Strain

Many of the properties of cyclopropane and its derivatives are similar to the properties of alkenes. In 1890, the famous German organic chemist, A. Baeyer, suggested that cyclopropane and cyclobutane derivatives are different from cyclopentane and cyclohexane, because their C—C—C angles cannot have the tetrahedral value of 109.5°. At the same time, Baeyer hypothesized that the difficulties encountered in synthesizing cycloalkane rings from C7 upward was the result of the angle strain that would be expected if the large rings were regular planar polygons (see Table 12-3). Baeyer also believed that cyclohexane had a planar

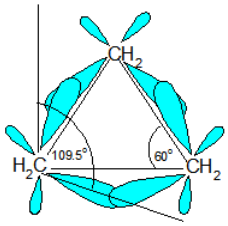
structure like that shown in Figure 12-2, which would mean that the bond angles would have to deviate 10.5° from the tetrahedral value. However, in 1895, the then unknown chemist H. Sachse suggested that cyclohexane exists in the strain-free chair and boat forms discussed in Section 12-3. This suggestion was not accepted at the time because it led to the prediction of several possible isomers for compounds such as chlorocyclohexane (cf. Exercise 12-4). The idea that such isomers might act as a single substance, as the result of rapid equilibration, seemed like a needless complication, and it was not until 1918 that E. Mohr proposed a definitive way to distinguish between the Baeyer and Sachse cyclohexanes. As will be discussed in Section 12-9, the result, now known as the Sachse-Mohr theory, was complete confirmation of the idea of nonplanar large rings.

Table: Strain in Cycloalkane Rings and Heats of Combustion of Cycloalkanes

Compound	n	Angle Strain at each CH2	Heat of Combustion ΔHo (kcal/mol)	Heat of Combustion ΔHo per CH2/N (kcal/mol)	Total Strain (kcal/mol)
ethene	2	109.5	337.2	168.6	22.4
cyclopropane	3	49.5	499.9	166.6	27.7
cyclobutane	4	19.5	655.9	164.0	26.3
cyclopentane	5	1.5	793.4	158.7	6.5
cyclohexane	6	10.5	944.8	157.5	0.4
cycloheptane	7	19.1	1108.1	158.4	6.3
cyclooctane	8	25.5	1268.9	158.6	9.7
cyclononane	9	30.5	1429.5	158.8	12.9
cyclodecane	10	34.5	1586.1	158.6	12.1
cyclopentadecane	15	46.5	2362.5	157.5	1.5
open chain alkane				157.4	-

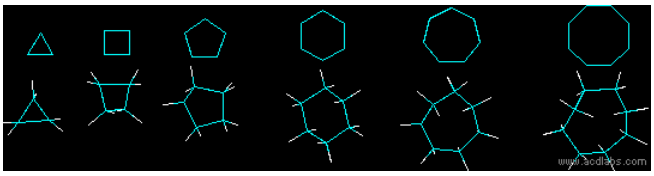
Ring Strain in Cycloalkanes

Ring Strain occurs because the carbons in cycloalkanes are sp^3 hybridized, which means that they do not have the expected ideal bond angle of 109.5^o ; this causes an increase in the potential energy because of the desire for the carbons to be at an ideal 109.5^o. An example of ring strain can be seen in the diagram of cyclopropane below in which the bond angle is 60° between the carbons.



The reason for ring strain can be seen through the tetrahedral carbon model. 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^o. This bond angle causes cyclopropane and cyclobutane to have a high ring strain. However, molecules, such as cyclohexane and cyclopentane, would have a much lower ring strain because the bond angle between the carbons is much closer to 109.5^o.

Below are some examples of cycloalkanes. Ring strain can be seen more prevalently in the cyclopropane and cyclobutane models



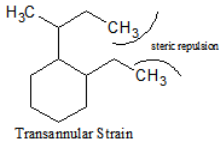
Below is a chart of cycloalkanes and their respective heats of combustion (ΔH_{comb}). The ΔH_{comb} value increases as the number of carbons in the cycloalkane increases (higher membered ring), and the $\Delta H_{comb}/CH_2$ ratio decreases. The increase in ΔH_{comb} can be attributed to the greater amount of London Dispersion forces. However, the decrease in $\Delta H_{comb}/CH_2$can be attributed to a decrease in the ring strain.

Cycloalkane	$\triangle H_{comb}$ (KJ/Mol)	$\Delta H_{comb}/CH_2$(KJ/mol)
△	-499.8	-166.6
□	-655.9	-164.0
⬠	-793.5	-158.7
⬡	-944.5	-157.4

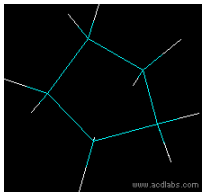
Certain cycloalkanes, such as cyclohexane, deal with ring strain by forming conformers. A conformer is a stereoisomer in which molecules of the same connectivity and formula exist as different isomers, in this case, to reduce ring strain. The ring strain is reduced in conformers due to the rotations around the sigma bonds.

Other Types of Strain

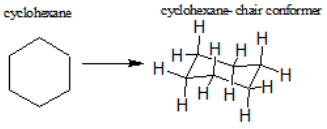
There are many different types of strain that occur with cycloalkanes. In addition to ring strain, there is also transannular strain, eclipsing, or torsional strain and bond angle strain.Transannular strain exists when there is steric repulsion between atoms. Eclipsing (torsional) strain exists when a cycloalkane is unable to adopt a staggered conformation around a C-C bond, and bond angle strain is the energy needed to distort the tetrahedral carbons enough to close the ring. The presence of angle strain in a molecule indicates that there are bond angles in that particular molecule that deviate from the ideal bond angles required (i.e., that molecule has conformers).



Transannular Strain



This is an example of torsional strain through cylcopentane. The torsional strain is caused by the hudrogen bonds in the ring (shown in yellow)



this conformer is more stable

Cyclopropane

A three membered ring has no rotational freedom whatsoever, so the three carbon atoms in cyclopropane are all constrained to lie in the same plane 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.

cyclopropane

Furthermore, if you look at a model you will find that the neighboring C-H bonds (C-C bonds, too) are all held in eclipsed conformations.

Cyclopropane is always at maximum torsional strain. This strain can be illustrated in a line drawing of cyclopropane as shown from the side. In this oblique view, the dark lines mean that those sides of the ring are closer to you.

However, the ring isn't big enough to introduce any steric strain, which does not become a factor until we reach six membered rings. Until that point, rings are not flexible enough for two atoms to reach around and bump into each other.

The really big problem with cyclopropane is that the C-C-C bond angles are all too small.

- All the carbon atoms in cyclopropane appear to be tetrahedral.
- These bond angles ought to be 109 degrees.
- The angles in an equilateral triangle are actually 60 degrees, about half as large as the optimum angle.
- This factor introduces a huge amount of strain in the molecule, called ring strain.

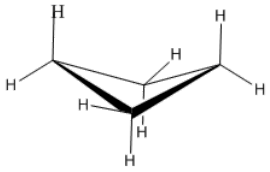
Cyclobutane

Cyclobutane is a four membered ring. In two dimensions, it is a square, with 90 degree angles at each corner. 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 10 kcal/mol) if it remained planar. Consequently, the five-membered ring adopts non-planar puckered conformations whenever possible.

cyclobutane

However, in three dimensions, cyclobutane is flexible enough to buckle into a "butterfly" shape, relieving torsional strain a little bit. When it does that, the bond angles get a little worse, going from 90 degrees to 88 degrees.

In a line drawing, this butterfly shape is usually shown from the side, with the near edges drawn using darker lines.



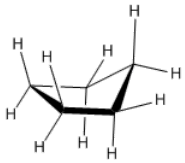
- With bond angles of 88 rather than 109 degrees, cyclobutane has a lot of ring strain, but less than in cyclopropane.
- Torsional strain is still present, but the neighbouring bonds are not exactly eclipsed in the butterfly.
- Cyclobutane is still not large enough that the molecule can reach around to cause crowding. Steric strain is very low.
- Cyclobutanes are a little more stable than cyclopropanes and are also a little more common in nature.

Cyclopentane

Cyclopentanes are even more stable than cyclobutanes, and they are the second-most common paraffinic ring in nature, after cyclohexanes. In two dimensions, a cyclopentane appears to be a regular pentagon.

cyclopentane

In three dimensions, there is enough freedom of rotation to allow a slight twist out of this planar shape. In a line drawing, this three-dimensional shape is drawn from an oblique view, just like cyclobutane.



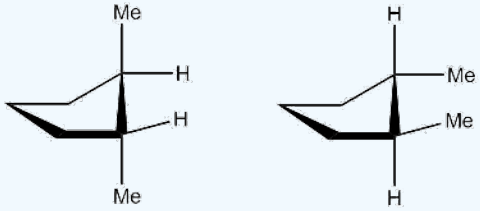
- The ideal angle in a regular pentagon is about 107 degrees, very close to a tetrahedral bond angle.
- Cyclopentane distorts only very slightly into an "envelope" shape in which one corner of the pentagon is lifted up above the plane of the other four, and as a result, ring strain is entirely removed.
- The envelope removes torsional strain along the sides and flap of the envelope. However, the neighbouring carbons are eclipsed along the "bottom" of the envelope, away from the flap. There is still some torsional strain in cyclopentane.
- Again, there is no steric strain in this system.

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).

Exercise 3.6.1

1. 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?

2. In the two conformations of *cis*-cyclopentane one is more stable than the other. Explain why this is.



Answer

1. There are 8 eclipsing interactions (two per C-C bond). The extra strain on this molecule would be 32 kJ/mol (4 kJ/mol x 8).

2. The first conformation is more stable. Even though the methyl groups are *cis* in the model on the left, they are eclipsing due the conformation, therefore increasing the strain within the molecule.

Contributors and Attributions

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- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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3.7: Cyclohexane Conformations

Learning Objective

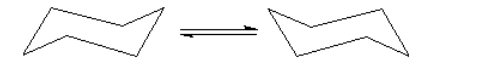
- draw cyclohexane conformations (chair & boat)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for cyclohexane

Introduction

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).

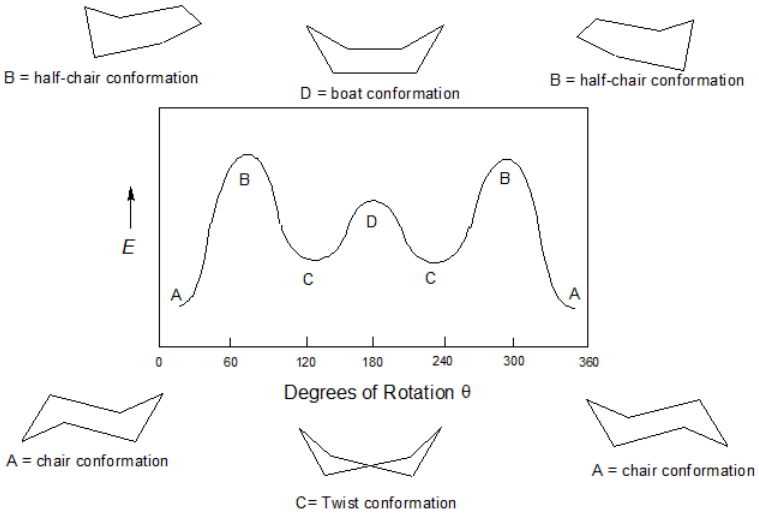
Cyclohexane Conformations (aka Chair Flips)

Cyclohexane is rapidly rotating between the two most stable conformations known as the chair conformations in what is called the "Chair Flip" shown below.



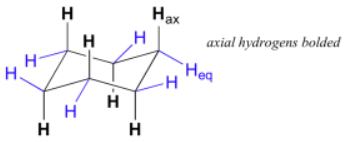
The "Chair Flip" describes the rapid equilibrium of cyclohexane rings between the two chair conformations.

Several other notable cyclohexane conformations occur during the transition from one chair conformer to the other - the boat, the twist, and the half-chair. The relative energies of the conformations is a direct reflection of their relative stabilities. These structural and energetic relationships are summarized in the conformational energy diagram for cyclohexane below.

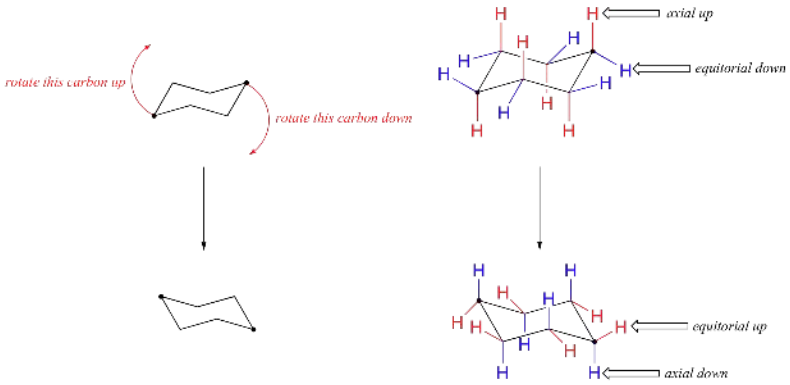


The Chair Conformation - a closer look

Since the chair conformation has the lowest potential energy, it is the most relevant to the conformation of cyclohexane. On careful examination of a chair conformation of cyclohexane, we find 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 in bold. Since there are two equivalent chair conformations of cyclohexane in rapid equilibrium, all twelve hydrogens have 50% equatorial and 50% axial character. 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 hydrogens to become axial, and vice-versa.



How to draw stereo bonds ("up" and "down" bonds)

There are various ways to show these orientations. The solid (dark) "up wedge" I used is certainly common. Some people use an analogous "down wedge", which is light, to indicate a down bond; unfortunately, there is no agreement as to which way the wedge should point, and you are left relying on the lightness of the wedge to know it is "down". The "down bond" avoids this wedge ambiguity, and just uses some kind of light line. The down bond I used (e.g., in Figure 5B) is a dashed line; IUPAC encourages a series of parallel lines, something like ⁞⁞⁞⁞ What I did is a variation of what is recommended by IUPAC:

- In **ISIS/Draw**, the "up wedge" and "down bond" that I used, along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the tool button for ordinary C-C bonds.
- In **Symyx Draw**, the "up wedge" and "down bond", along with other variations, are available from a tool button that may be labeled with any of them, depending on most recent use. It is located directly below the "Chain" tool button.
- **ChemSketch** provides up and down wedges, but not the simple up and down bonds discussed above. The wedges are available from the second toolbar across the top. For an expanded discussion of using these wedges, see the section of my ChemSketch Guide on Stereochemistry: Wedge bonds.

As always, the information provided on these pages in intended to help you get started. Each program has more options for drawing bonds than discussed here. When you feel the need, look around!

How to Draw chairs

Most of the structures shown on this page were drawn with the free program **ISIS/Draw**. I have posted a guide to help you get started with ISIS/Draw. ISIS/Draw provides a simple cyclohexane (6-ring) hexagon template on the toolbar across the top. It provides templates for various 6-ring chair structures from the Templates menu; choose Rings. There are templates for simple chairs, without substituents (e.g., Fig 1B), and for chairs showing all the substituents (e.g., Fig 2B). In either case, you can add, delete, or change things as you wish. Various kinds of stereo bonds (wedges and bars) are available by clicking the left-side tool button that is just below the regular C-C single bond button. It may have a wedge shown on it, but this will vary depending on how it has been used. To choose a type of stereo bond, click on the button and hold the mouse click; a new menu will appear to the right of the button.

The free drawing program **Symyx Draw**, the successor to ISIS/Draw, provides similar templates and tools. A basic chair structure is provided on the default template bar that is shown. More options are available by choosing the Rings template. See my page Symyx Draw for a general guide for getting started with this program.

The free drawing program **ChemSketch** provides similar templates and tools. To find the special templates for chairs, go to the **Templates** menu, choose **Template Window**, and then choose "Rings" from the drop-down menu near upper left. See my page ChemSketch for a general guide for getting started with this program.

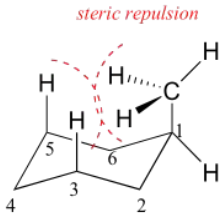
If you want to draw chair structures by hand (and if you are going on in organic chemistry, you should)... Be careful. The precise zigs and zags, and the angles of substituents are all important. Your textbook may offer you some hints for how to draw chairs. A short item in the Journal of Chemical Education offers a nice trick, showing how the chair can be thought of as consisting of an M and a W. The article is V Dragojlovic, A method for drawing the cyclohexane ring and its substituents. J Chem Educ 78:923, 7/01. (I thank M Farooq Wahab, Chemistry, Univ Karachi, for suggesting that this article be noted here.)

Aside from drawing the basic chair, the key points in adding substituents are:

- Axial groups alternate up and down, and are shown "vertical".
- Equatorial groups are approximately horizontal, but actually somewhat distorted from that, so that the angle from the axial group is a bit more than a right angle -- reflecting the common 109 degree bond angle.
- As cautioned before, it is usually easier to draw and see what is happening at the four corners of the chair than at the two middle positions. Try to use the corners as much as possible.

Because axial bonds are parallel to each other, substituents larger than hydrogen generally suffer greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents assume equatorial orientation***.

When the methyl group in the structure above occupies an axial position it suffers steric crowding by the two axial hydrogens located on the same side of the ring.



The conformation in which the methyl group is equatorial is more stable, and thus the equilibrium lies in this direction

Exercise

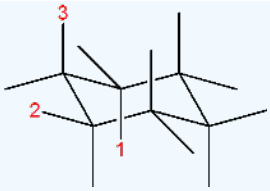
Questions

1. Consider the conformations of cyclohexane, chair, boat, twist boat. Order them in increasing strain in the molecule.

2. Draw two conformations of cyclohexyl amine ($C_6H_{11}NH_2$). Indicate axial and equatorial positions.

3. Draw the two isomers of 1,4-dihydroxylcyclohexane, identify which are equatorial and axial.

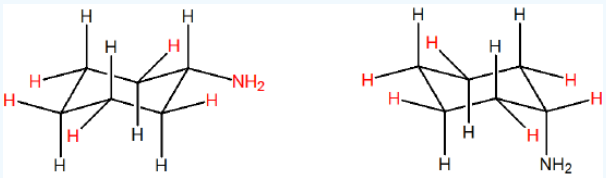
4. In the following molecule, label which are equatorial and which are axial, then draw the chair flip (showing labels 1,2,3).



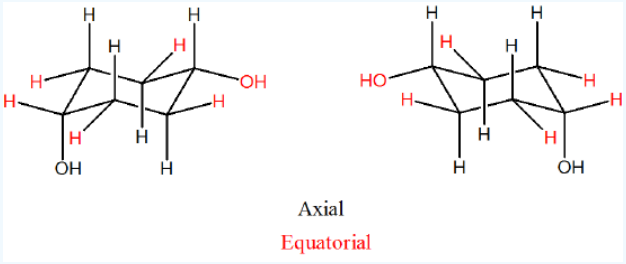
Answer

1. Chair < Twist Boat < Boat (most strain)

2.

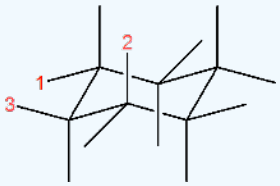


3.



4. Original conformation: 1 = axial, 2 = equatorial, 3 = axial

Flipped chair now looks like this.



Contributors and Attributions

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Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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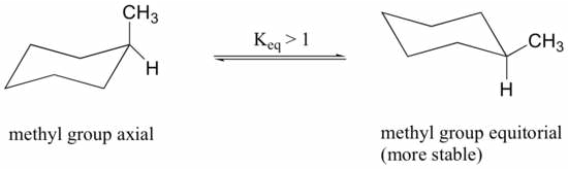
3.8: Conformations of Monosubstituted Cyclohexanes

Learning Objective

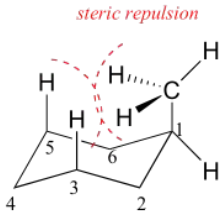
- draw mono-substituted cyclohexane conformers (chair only)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for butane, higher alkanes, cyclohexane, mono-substituted cyclohexanes, and disubstituted cyclohexanes

Introduction

Because axial bonds are parallel to each other, substituents larger than hydrogen generally suffer greater steric crowding when they are oriented axial rather than equatorial. Consequently, ***substituted cyclohexanes will preferentially adopt conformations in which the larger substituents assume equatorial orientation***.



When the methyl group in the structure above occupies an axial position it suffers steric crowding by the two axial hydrogens located on the same side of the ring. The conformation in which the methyl group is equatorial is more stable, and thus the equilibrium lies in this direction.



In examining possible structures for monosubstituted cyclohexanes, it is useful to follow two principles:

i. Chair conformations are generally more stable than other possibilities.
ii. Substituents on chair conformers prefer to occupy equatorial positions due to the increased steric hindrance of axial locations.

Experimental Measurements of Steric Hindrance

The relative steric hindrance experienced by different substituent groups oriented in an axial versus equatorial location on cyclohexane may be determined by the conformational equilibrium of the compound. The corresponding equilibrium constant is related to the energy difference between the conformers and collecting such data allows us to evaluate the relative tendency of substituents to exist in an equatorial or axial location.

Looking at the energy values the table, it is clear that the apparent "size" of a substituent (in terms of its preference for equatorial over axial orientation) is influenced by its width and bond length to cyclohexane, as evidenced by the fact that an axial vinyl group is less hindered than ethyl, and iodine slightly less than chlorine.

A Selection of AG° Values for the Change from Axial to Equatorial Orientation of Substituents for Monosubstituted Cyclohexanes

Substituent	$-\Delta G^o$ kcal/mol	Substituent	$-\Delta G^o$ kcal/mol
CH_3-	1.7	O_2N-	1.1
CH_2H_5-	1.8	$N\equiv C-$	0.2
$(CH_3)_2CH-$	2.2	CH_3O-	0.5
$(CH_3)_3C-$	≥ 5.0	$(CH_3)_3C$-	0.7
F-	0.3	F-	1.3
Cl-	0.5	C_6H_5-	3.0
Br-	0.5		
I-	0.5		

Exercise

1. In the molecule, cyclohexyl ethyne there is little steric strain, why?

Answer

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.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

>Robert Bruner (http://bbruner.org)

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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3.9: Cis-trans Isomerism in Cycloalkanes

Learning Objective

- identify & draw the geometric (cis/trans) isomers of cycloalkanes

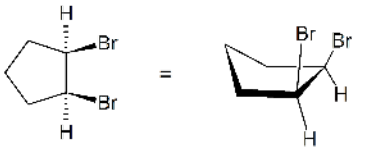
Geometric Isomerism of Cycloalkanes

The carbon ring of cycloalkanes forms a pseudo-plane that can be used to assign the relative orientation of atoms or substituents bonded to the ring (stereochemistry). One side of the ring is called "up" while the other side is called "down". By agreement, chemists use heavy, wedge-shaped bonds to indicate a substituent located above the average plane of the ring (up), and a hatched line for bonds to atoms or groups located below the ring (down).

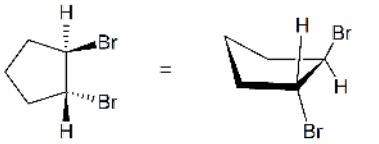
Disubstituted cycloalkane stereoisomers may be designated by nomenclature prefixes such as *cis* and *trans*. Cis and trans isomers are also called "geometric isomers".

For the cis isomer, both substituents are aobe or below the carbon ring. For the trans isomer, one substituent is above the ring while the other substituent is below the ring.

The cis and trans isomers for 1,2-dibromocyclopentane are shown as an example below.



cis-1,2-dibromocyclopentane

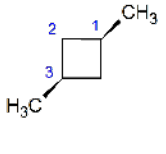


trans-1,2-dibromocyclopentane

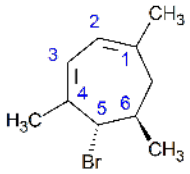
While the carbon-carbon single bonds of the rings can rotate partially, there is NO way to inter-convert between the cis and trans isomers. Cis and trans isomers are unique compounds with their own unique melting points, boiling points, densities, etc.

Further explanation:

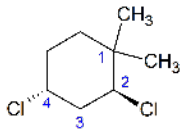
In general, if any two sp^3 carbons in a ring have two different substituent groups (not counting other ring atoms) stereoisomerism is possible. This is similar to the substitution pattern that gives rise to stereoisomers in alkenes; indeed, one might view a double bond as a two-membered ring. Four other examples of this kind of stereoisomerism in cyclic compounds are shown below.



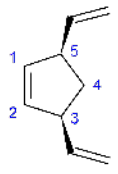
cis-1,3-dimethylcyclobutane



trans-5-bromo-1,4,6-trimethyl-1,3-cycloheptadiene



trans-2,4-dichloro-1,1-dimethylcyclohexane



cis-3,5-divinylcyclopentene

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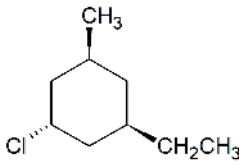
If more than two ring carbons have different substituents (not counting other ring atoms) the stereochemical notation distinguishing the various isomers becomes more complex. However, we can always state the relationship of any two substituents using cis or trans. For example, in the trisubstitutued cyclohexane below, we can say that the methyl group is *cis* to the ethyl group, and *trans* to the chlorine. We can also say that the ethyl group is *trans* to the chlorine. We cannot, however, designate the entire molecule as a *cis* or trans *isomer*.



Exercise

1. Draw the following molecules:

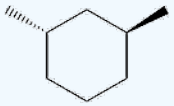
trans-1,3-dimethylcyclohexane

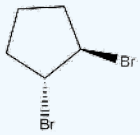
trans-1,2-dibromocyclopentane

cis-1,3-dichlorocyclobutane

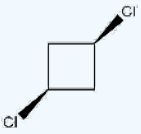
Answer

1.


1



2



3

Contributors and Attributions

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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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3.10: Conformations of Disubstituted Cyclohexanes

Learning Objective

- draw di-substituted cyclohexane conformers (chair only)
- correlate energies of conformations with rotational energy diagrams and predict the most stable conformations for disubstituted cyclohexanes

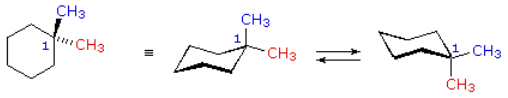
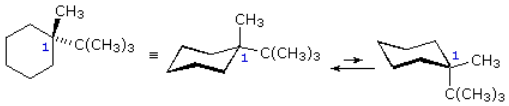
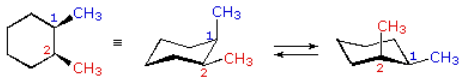
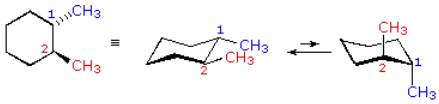
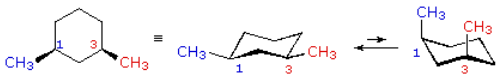
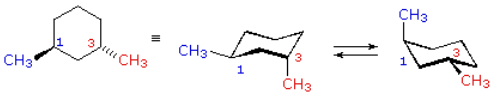
Conformational Structures of Disubstituted Cyclohexanes

In a sample of cyclohexane, the two identical chair conformers are present in equal concentration, and the hydrogens are all equivalent (50% equatorial & 50% axial) due to rapid interconversion of the conformers. When the cyclohexane ring bears a substituent, the two chair conformers are not the same. In one conformer the substituent is axial, in the other it is equatorial. Due to steric hindrance in the axial location, substituent groups prefer to be equatorial and that chair conformer predominates in the equilibrium.

When cycloalkanes have two substituents on different ring carbon atoms, then a pair of configurational stereoisomers exist. Now we must examine the way in which favorable ring conformations influence the properties of the configurational isomers. Remember, configurational stereoisomers are stable, unique chemical compounds, whereas, conformational isomers are different rotations of the same compound. In examining possible structures for disubstituted cyclohexane, it is useful to follow two principles:

1. Substituents on chair conformers prefer to occupy equatorial positions due to the increased steric hindrance of axial locations.

The following equations and formulas illustrate how the presence of two or more substituent on a cyclohexane ring perturbs the interconversion of the two chair conformers in ways that can be predicted. When there is a potential energy difference between the conformers, then the lower energy conformation is favored as indicated by the equilibrium reaction arrows.

1,1-dimethylcyclohexane	
1-t-butyl-1-methylcyclohexane	
cis-1,2-dimethylcyclohexane	
trans-1,2-dimethylcyclohexane	
cis-1,3-dimethylcyclohexane	
	

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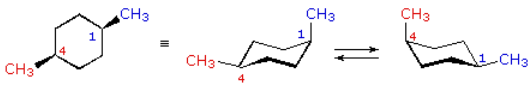
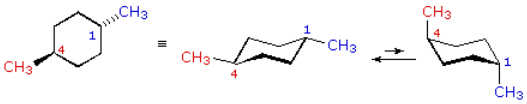
trans-1,3-dimethylcyclohexane	
cis-1,4-dimethylcyclohexane	
trans-1,4-dimethylcyclohexane	

In the case of 1,1-disubstituted cyclohexanes, one of the substituents must necessarily be axial and the other equatorial, regardless of which chair conformer is considered. Since the substituents are the same in 1,1-dimethylcyclohexane, the two conformers are identical and present in equal concentration. In 1-t-butyl-1-methylcyclohexane the t-butyl group is much larger than the methyl, and that chair conformer in which the larger group is equatorial will be favored in the equilibrium(> 99%). Consequently, the methyl group in this compound is almost exclusively axial in its orientation.

In the cases of 1,2-, 1,3- and 1,4-disubstituted compounds the analysis is a bit more complex. It is always possible to have both groups equatorial, but whether this requires a cis-relationship or a trans-relationship depends on the relative location of the substituents. As we count around the ring from carbon #1 to #6, the uppermost bond on each carbon changes its orientation from equatorial (or axial) to axial (or equatorial) and back. It is important to remember that the **bonds on a given side of a chair ring-conformation always alternate in this fashion**. Therefore, it should be clear that for cis-1,2-disubstitution, one of the substituents must be equatorial and the other axial; in the trans-isomer both may be equatorial. Because of the alternating nature of equatorial and axial bonds, the opposite relationship is true for 1,3-disubstitution (cis is all equatorial, trans is equatorial/axial). Finally, 1,4-disubstitution reverts to the 1,2-pattern.

The conformations of some substituted cyclohexanes may be examined as interactive models by Clicking Here.

It can be helpful to add the hydrogen atoms at the axial positions to help recognize the equatorial position.

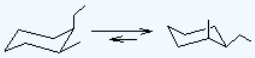
Exercise

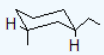
1. Draw the two chair conformations for cis-1-ethyl-2-methylcyclohexane using bond-line structures and indicate the more energetically favored conformation.

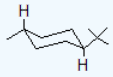
2. Draw the most stable conformation for trans-1-ethyl-3-methylcyclohexane using bond-line structures.

3. Draw the most stable conformation for trans-1-t-butyl-4-methylcyclohexane using bond-line structures.

Answer

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

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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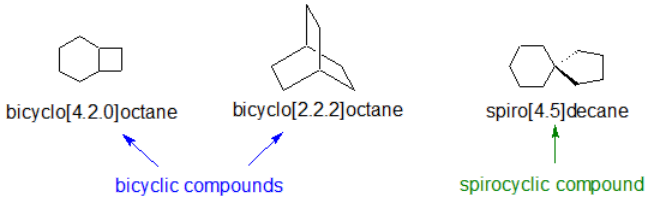
3.11: Joined Rings

Learning Objective

- recognize, classify, and draw the three ways to join two rings

Bicyclic Ring Systems

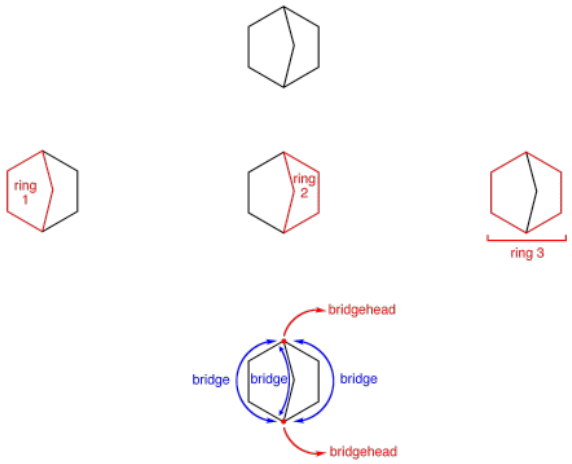
There are three ways to join two rings. If two rings share two or more atoms, then the structure is called a bicyclic compound. If the two rings share a single atom, then the structure is called a spirocyclic compound. Examples of each way to join rings is shown below.



Bicyclic Compounds

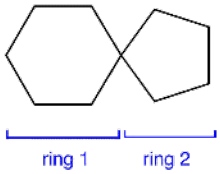
Fused rings share two adjacent carbon atoms. Decalin is a fused bicyclic compound. Its IUPAC name is bibyclo[4.4.0]decane to communicate the bonding arrangement.

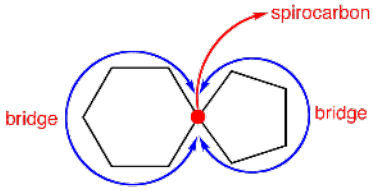
Bridged rings share two non-adjacent carbon atoms and one or more carbon atoms between them. Bicyclo[2.2.1]heptane shows the difference between the bridgehead carbons and the bridge carbons.



Spirocyclic Compounds

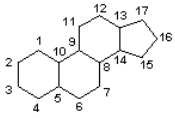
A spirobicycloalkane is a molecule in which only one carbon atom is shared by the two rings in the molecule. The carbon atom shared by the two rings is called the spirocarbon. A chain of bonds originating and ending at the spirocarbon is called a bridge. The compound below is named spiro[4.5]decane to communicate the number of carbons in each bridge with the spirocarbon.





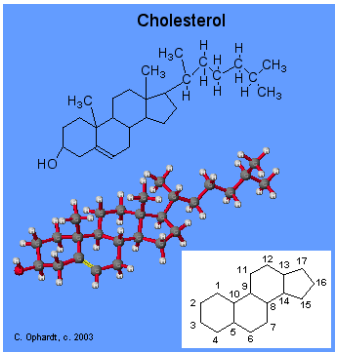
Steroids

Steroids include such well known compounds as cholesterol, sex hormones, birth control pills, cortisone, and anabolic steroids.



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.

Much research is currently underway to determine if a correlation exists between cholesterol levels in the blood and diet. Not only does cholesterol come from the diet, but cholesterol is synthesized in the body from carbohydrates and proteins as well as fat. Therefore, the elimination of cholesterol rich foods from the diet does not necessarily lower blood cholesterol levels. Some studies have found that if certain unsaturated fats and oils are substituted for saturated fats, the blood cholesterol level decreases. The research is incomplete on this problem.



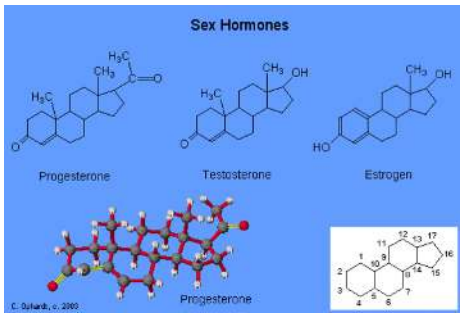
Structures of Sex Hormones

Sex hormones are also 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 ans is synthesized from cholesterol in the testes. It also promotes secondary male sexual characteristics such as deep voice, facial and body hair.

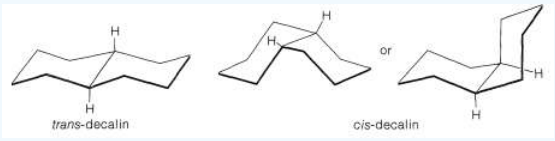
Estrogen, along with progesterone regulates changes occurring in the uterus and ovaries known as the menstrual cycle. For more details see Birth Control. Estrogen is synthesized from testosterone by making the first ring aromatic which results in mole double

bonds, the loss of a methyl group and formation of an alcohol group.



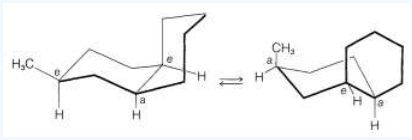
Exercise

1. Someone stated that *trans*-decalin is more stable than *cis*-decalin. Explain why this is incorrect.



Answer

1. *Cis*-decalin has fewer steric interactions than *trans*-decalinbecause each ring can assume the chair form in both conformations. Working with models can be helpful.



Contributors and Attributions

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John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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3.12: Uses and Sources of Alkanes

Learning Objective

- describe the uses and sources of alkanes

Occurrence

The most important sources for alkanes are oil and natural gas. Oil is a mixture of liquid alkanes and other hydrocarbons. Higher alkanes (which are solid) occur as residues from oil distillation ("tar"). One of the largest natural deposits of solid alkanes is in an asphalt lake known as the Pitch Lake in Trinidad and Tobago. Natural gas contains primarily methane (70-90%) with some ethane, propane and butane; some gas sources deliver up to 8% CO_2. Traces of methane (about 0.00017% or 1.7 ppm) occur in the Earth's atmosphere, the content in the oceans is negligible due to the low solubility of methane in water.(1)

Use of Alkanes

Alkanes are important raw materials of the chemical industry and the principal constituent of gasoline and lubricating oils. Natural gas mainly contains methane and ethane and is used for heating and cooking purposes and for power utilities (gas turbines). For transportation purposes, natural gas may be liquefied by applying pressure and cooling it (LNG = liqid natural gas). The Sultanate of Oman, for example, exports most of its natural gas as LNG - see the LNG plant at Qalhat which has been designed to liquefy 6.6 million tons natural gas per year. Crude oil is separated into its components by fractional distillation at oil refineries. The different "fractions" of crude oil have different boiling points and consist mostly of alkanes of similar chain lengths (the higher the boiling point the more carbon atoms the components of a particular fraction contain - see the list of alkanes for details about the boiling points).

The following table provides a short survey of the different fractions of crude oil:

$C_3..C_4$	Propane and butane can be liquefied at fairly low pressures, and are used, for example, in the propane gas burner, or as propellants in aerosol sprays. Butane in used in cigarette lighters (where the pressure at room temperature is about 2 bar).
$C_5..C_8$	The alkanes from pentane to octane are highly volatile liquids and good solvents for nonpolar substances. They are used as fuels in internal combustion engines.
$C_9..C_{16}$	Alkanes from nonane to hexadecane are liquids of higher viscosity, being used in diesel and aviation fuel (kerosene). The higher melting points of these alkanes can cause problems at low temperatures and in polar regions, where the fuel becomes too viscous.
$C_{17}..C_{35}$	Alkanes with 17 to 35 carbon atoms form the major components of lubricating oil. They also act as anti-corrosive agents, as their hydrophobic nature protects the metal surface from contact with water. Solid alkanes also find use as paraffin wax in candles(2).
$>C_{35}$	Alkanes with a chain length above 35 carbon atoms are found in bitumen (as it is used in road surfacing). These higher alkanes have little chemical and commercial value and are usually split into lower alkanes by cracking.

Notes:

(1)	Methane can co-crystallize with water at high pressures and low temperatures, forming a solid methane hydrate. The energy content of the known submarine methane hydrate fields exceeds that of all known natural gas and oil deposits put together.
(2)	Paraffin wax should not be mixed up with true animal or plant wax, which consist of esters of various carboxylic acids and alcohols.

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3.13: Reactions of Alkanes - a Brief Overview

Learning Objective

- recognize and distinguish between the two major reactions of alkanes - combustion and halogenation

Combustion

Complete combustion (given sufficient oxygen) of any hydrocarbon produces *carbon dioxide* and *water*. It is quite important that you can write properly balanced equations for these reactions, because they often come up as a part of thermochemistry calculations. Some are easier than others. For example, with alkanes, the ones with an even number of carbon atoms are marginally harder than those with an odd number!

Example: Propane Combustion

For example, with propane (C_3H_8), you can balance the carbons and hydrogens as you write the equation down. Your first draft would be:

$$C_3H_8 + O_2 \rightarrow 3CO_2 + 4H_2O \tag{3.13.1}$$

Counting the oxygens leads directly to the final version:

$$C_3H_8 + 5O_2 \rightarrow 3CO_2 + 4H_2O \tag{3.13.2}$$

Example: Butane Combustion

With butane (C_4H_{10}), you can again balance the carbons and hydrogens as you write the equation down.

$$C_4H_{10} + O_2 \rightarrow 4CO_2 + 5H_2O \tag{3.13.3}$$

Counting the oxygens leads to a slight problem - with 13 on the right-hand side. The simple trick is to allow yourself to have "six-and-a-half" O_2 molecules on the left.

$$C_4H_{10} + 6\frac{1}{2}\,O_2 \rightarrow 4CO_2 + 5H_2O \tag{3.13.4}$$

If that offends you, double everything:

$$2C_4H_{10} + 13O_2 \rightarrow 8CO_2 + 10H_2O \tag{3.13.5}$$

The hydrocarbons become harder to ignite as the molecules get bigger. This is because the bigger molecules don't vaporize so easily - the reaction is much better if the oxygen and the hydrocarbon are well mixed as gases. If the liquid is not very volatile, only those molecules on the surface can react with the oxygen. Bigger molecules have greater Van der Waals attractions which makes it more difficult for them to break away from their neighbors and turn to a gas.

Provided the combustion is complete, all the hydrocarbons will burn with a blue flame. However, combustion tends to be less complete as the number of carbon atoms in the molecules rises. That means that the bigger the hydrocarbon, the more likely you are to get a yellow, smoky flame. Incomplete combustion (where there is not enough oxygen present) can lead to the formation of carbon or carbon monoxide. As a simple way of thinking about it, the hydrogen in the hydrocarbon gets the first chance at the oxygen, and the carbon gets whatever is left over! The presence of glowing carbon particles in a flame turns it yellow, and black carbon is often visible in the smoke. Carbon monoxide is produced as a colorless poisonous gas.

Note: Why carbon monoxide is poisonous

Oxygen is carried around the blood by hemoglobin, which unfortunately binds to exactly the same site on the hemoglobin that oxygen does. The difference is that carbon monoxide binds irreversibly (or very strongly) - making that particular molecule of

> hemoglobin useless for carrying oxygen. If you breath in enough carbon monoxide you will die from a sort of internal suffocation.

Halogenation of Alkanes

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. The chlorination of methane, shown below, provides a simple example of this reaction.

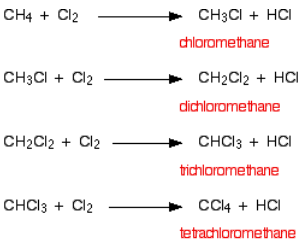
$CH_4 + Cl_2 + \text{energy} \rightarrow CH_3Cl + HCl$

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.

$CH_4 + Cl_2 + \text{energy} \rightarrow CH_3Cl + CH_2Cl_2 + CHCl_3 + CCl_4 + HCl$

In the presence of a flame, the reactions are rather like the fluorine one - producing a mixture of carbon and the hydrogen halide. The violence of the reaction drops considerably as you go from fluorine to chlorine to bromine. The interesting reactions happen in the presence of ultra-violet light (sunlight will do). These are photochemical reactions that happen at room temperature. We'll look at the reactions with chlorine, although the reactions with bromine are similar, but evolve more slowly.

Substitution reactions happen in which hydrogen atoms in the methane are replaced one at a time by chlorine atoms. You end up with a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.

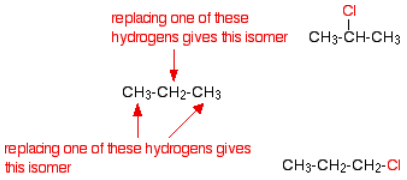


The original mixture of a colorless and a green gas would produce steamy fumes of hydrogen chloride and a mist of organic liquids. All of the organic products are liquid at room temperature with the exception of the chloromethane which is a gas.

If you were using bromine, you could either mix methane with bromine vapor, or bubble the methane through liquid bromine - in either case, exposed to UV light. The original mixture of gases would, of course, be red-brown rather than green. One would not choose to use these reactions as a means of preparing these organic compounds in the lab because the mixture of products would be too tedious to separate. The mechanisms for the reactions are explained on separate pages.

Larger alkanes and chlorine

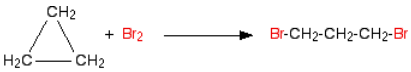
You would again get a mixture of substitution products, but it is worth just looking briefly at what happens if only one of the hydrogen atoms gets substituted (monosubstitution) - just to show that things aren't always as straightforward as they seem! For example, with propane, you could get one of two isomers:



If chance was the only factor, you would expect to get three times as much of the isomer with the chlorine on the end. There are 6 hydrogens that could get replaced on the end carbon atoms compared with only 2 in the middle. In fact, you get about the same amount of each of the two isomers. If you use bromine instead of chlorine, the great majority of the product is where the bromine is attached to the center carbon atom.

Cycloalkanes

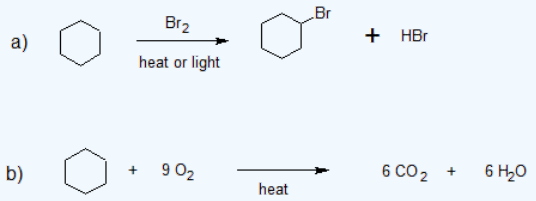
The reactions of the cycloalkanes are generally just the same as the alkanes, with the exception of the very small ones - particularly cyclopropane. In the presence of UV light, cyclopropane will undergo substitution reactions with chlorine or bromine just like a non-cyclic alkane. However, it also has the ability to react in the dark. In the absence of UV light, cyclopropane can undergo addition reactions in which the ring is broken. For example, with bromine, cyclopropane gives 1,3-dibromopropane.



This can still happen in the presence of light - but you will get substitution reactions as well. The ring is broken because cyclopropane suffers badly from ring strain. The bond angles in the ring are 60° rather than the normal value of about 109.5° when the carbon makes four single bonds. The overlap between the atomic orbitals in forming the carbon-carbon bonds is less good than it is normally, and there is considerable repulsion between the bonding pairs. The system becomes more stable if the ring is broken.

Exercise

1. Classify the following reactions as combustion or halogenation.



Answer

1. a) halogentation

   b) combustion

Contributors and Attributions

- Jim Clark (Chemguide.co.uk)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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3.14: Additional Exercises

Structural and Geometric Isomerism

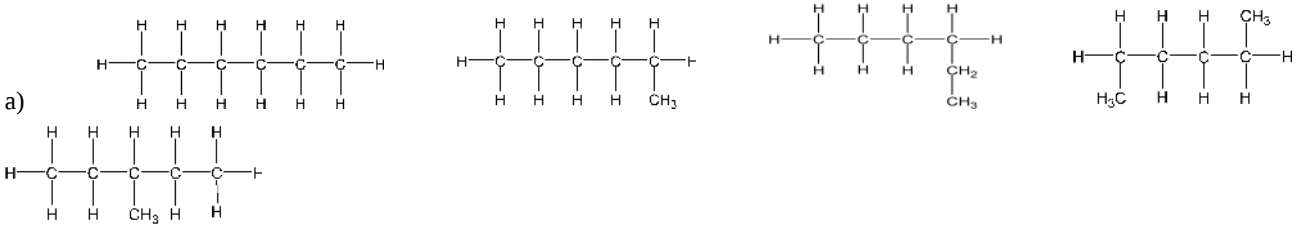
4-1

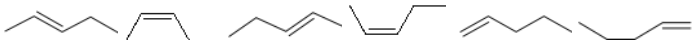
a) There are five alkane isomers of hexane C_6H_{14}. Draw and name all of them.

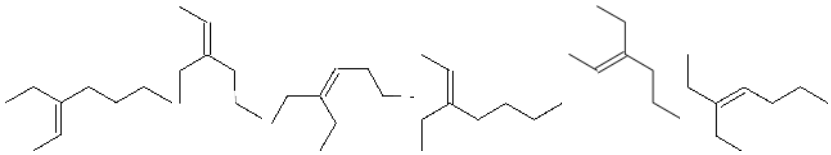
b) The heat of combustion of hexane is 4163.2 kJ/mol. Heat of combustion of neohexane is 4159.5 kJ/mol. Predict the relative stability of these two compounds?

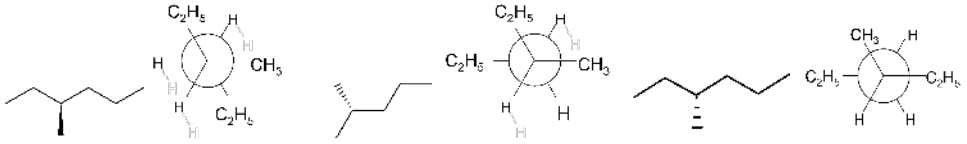
c) Draw and name all cycloalkane isomers of C_5H_{10}, including all possible geometric (cis-trans) stereoisomers.

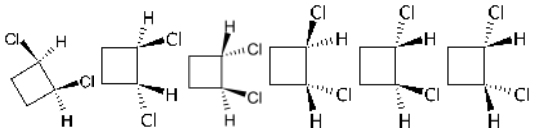
4-2 Which of the following structures represent the same compound? Name the structures given in part (a), (d), (e), (f), (g)

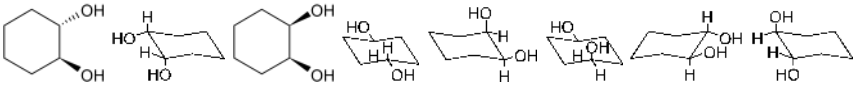
a) 

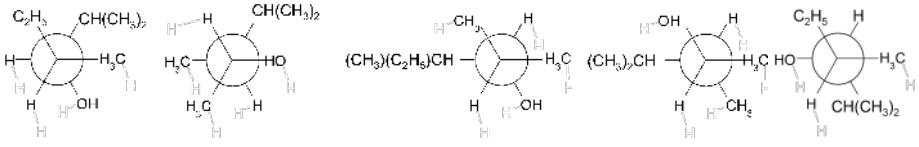
b) 

c) 

d) 

e) 

f) 

g) 

4-3 Each of the following descriptions applies to more than one alkane. In each case, draw and name two structures that match the description.

(a) a sec-butylheptane

(b) a trans-dimethylcyclobutane

(c) a cis-di-tert-butylcyclohexane

(d) an isopropyloctane

(e) a (1,2-dimethylpropyl)cycloalkane

(f) a bicycloheptane

4-4 Write structures for a homologous series of alcohols (R-OH) having from one to five carbons.

4-5 In each pair of compound, which compound has the higher boiling point? Explain your reasoning.

(a) Nonane or 3-ethylhexane

(b) Pentane or 2-methylbutane

(c) Octane or 2,2,4-trimethylpentane

4-6 There are four isomeric four-carbon alkyl groups. Draw them, give their systematic names and label the degree of substitution (primary, secondary, or tertiary) of the head carbon atom which is bonded to the main chain.

4-7 Draw Newman projection of the most stable conformation of the following compounds as viewed from the indicated bond.

(a) 3-methylhexane viewed at C3-C4 bond

(b) 2,2-dimethylbutane viewed at C2-C3 bond

4-8

(a) Draw two chair conformations of trans-1,2-dimethylcyclohexane and label all position as (a) for axial or (e) for equatorial.

(b) Determine the higher-energy and the lower-energy conformations

(c) Calculate the energy difference in these two conformations

4-9 Draw the two chair conformations of each compound and label the substituents as axial or equatorial. In each case, determine which conformation is more stable.

(a) cis-1-ethyl-4-methylcyclohexane

(b) trans-1-ethyl-4-methylcyclohexane

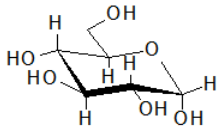
(c) cis-1-bromo-3-methylcyclohexane

(d) trans-1-bromo-3-methylcyclohexane

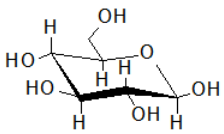
(e) cis-1-methyl-2-isopropylcychlohexane

(f) trans-1-methyl-2-isopropylchyclohexane

4-10 Glucose with molecular formula $C_6H_{12}O_6$ is by far the most abundant sugar in nature. Glucose can take form as an open chain or as can be closed into a ring form. Below are chair conformations of α and β D-glucose. Using what you know about the conformational energy of substituted cyclohexane, predict which of the two isomers predominates in equilibrium. Explain your reasoning.

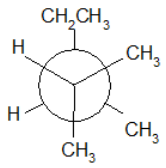


α-D-Glucopyranose

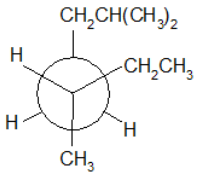


β-D-Glucopyranose

4-11 Provide a line drawing corresponding to each of the following Newman projections and name them using IUPAC rules.



(a)



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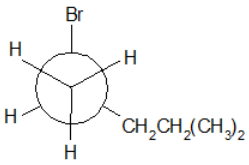
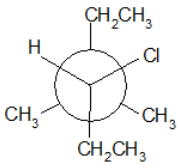


(c)



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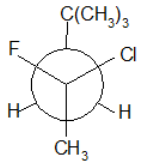

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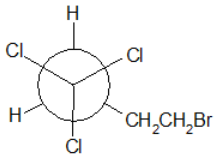

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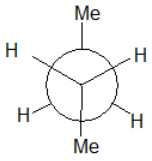
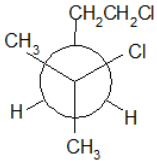


(g)



(h)

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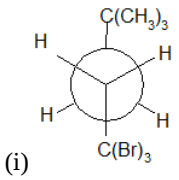
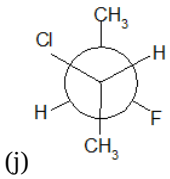


(i)

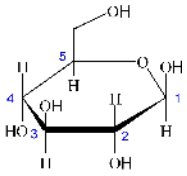


(j)

4-12 Draw Newman projections along the C3-C4 bond to show the most stable and the least stable conformation of 2,3,5-trimethylhexane.

4-13 In β-D-glucose, the hydroxyl group in C1 position is *cis* to the CH_2OH group in C5 position, as shown in the figure below.

There are two chair conformations of β-D-glucose. Draw them and identify which conformation is more stable.



β-D-Glucose

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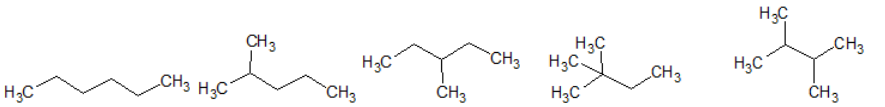
3.15: Solutions to Additional Exercises

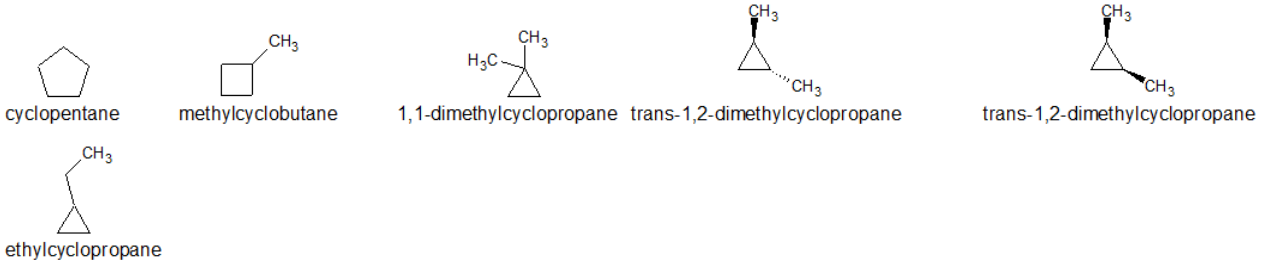
Structural and Geometric Isomerism

4-1 a)



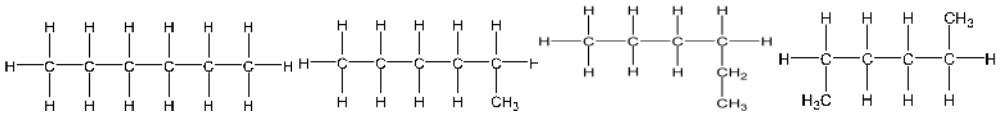
b) The isomer that releases the least energy is the most stable, so neohexane is more stable than hexane.

c)

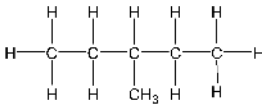


4-2

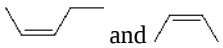
a) The following structures all represent hexane.



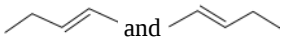
The following structure represents 3-methylpentane:



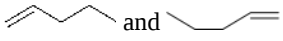
b) Both structures represent cis-2-pentene:



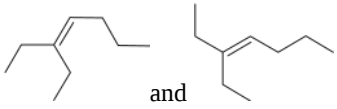
Both structures represent trans-2-pentene:



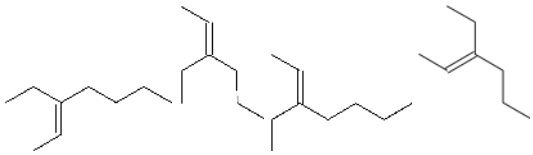
Both structures represent 1-pentene:



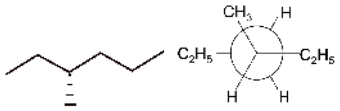
c) Both structures represent 3-ethyl-3-heptene:



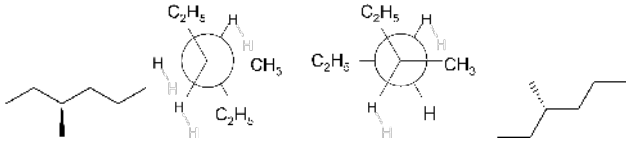
These three structures all represent 3-ethyl-2-heptene:



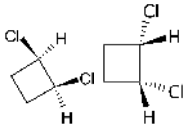
d) Both structures represent (3R)-3-methylhenxane:



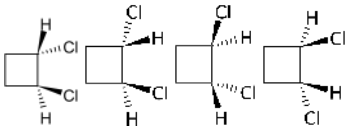
All four structures represent (3S)-3-methylhenxane:



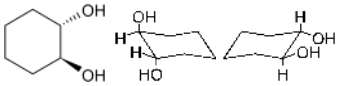
e) Both structures represent trans-1,2-dichlorocyclobutane:



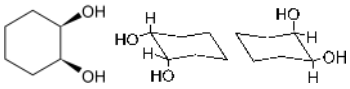
All four structures represent cis-1,2-dichlorocyclobutane:



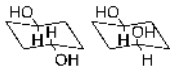
f) All three structures represent trans-1,2-cyclohexanediol:



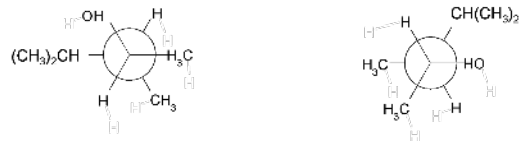
All three structures represent cis-1,2-cyclohexanediol:



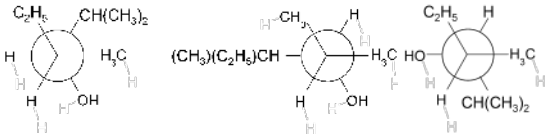
Both structures represent trans-1,4-cyclohexanediol Cis-1,4-cyclohexanediol:



g) Both structures represent 3,4-dimethylpentan-2-ol:

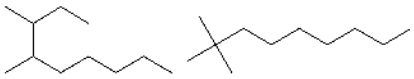


All three structures represent 2,4-dimethylhexan-3-ol:



4-3

(a) a dimethylnonane



3,4-dimethylnonane 2,2-dimethylnonane

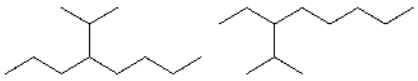
(b) a trans-dimethylcyclobutane

trans-1,2-dimethylcyclobutane trans-1,3-dimethylcyclobutane

(c) a cis-di-tert-butylcyclohexane

cis-1,2-di-*tert*-butylcyclohexane cis-1,3-di-*tert*-butylcyclohexane

(d) an isopropyloctane



4-isopropyloctane 3-ethyl-2-methyloctane

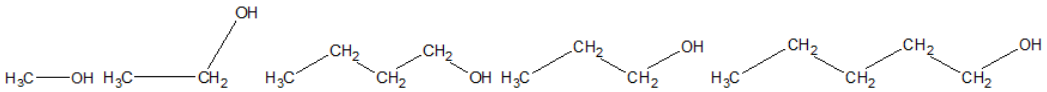
(e) a (1,2-dimethylpropyl)cycloalkane

(1,2-dimethylpropyl)cyclohexane (1,2-dimethylpropyl)cycloheptane

(f) a bicycloheptane

Bicyclo[2.2.1]heptane Bicyclo[3.1.1]heptane

4-4



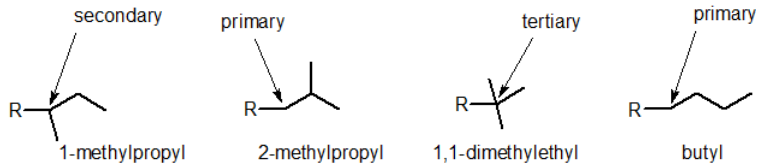
4-5

(a) Nonane has the higher boiling point because it has the higher molecular weight. Recall that higher molecular weight compounds have more surface area, and therefore they have stronger London dispersion forces. As a result, higher molecular weight compounds have the higher boiling temperatures.

(b) Pentane has the higher boiling point. Pentane has a straight chain while 2-methylbutane is branched. Compared to a straight-chain isomer, a branched hydrocarbon has a lower boiling temperature because of its smaller surface area.

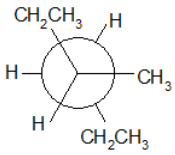
(c) Octane has the higher boiling point because 2,2,4-trimethylpentane is highly branched while octane is a straight-chain hydrocarbon.

4-6

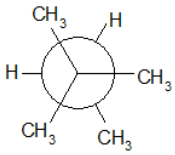


4-7

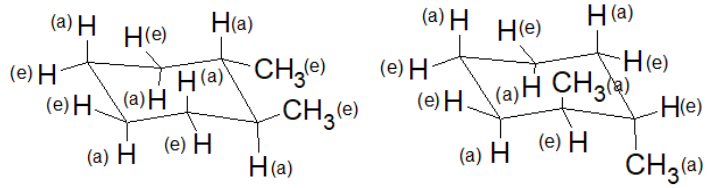
(a)



(b)



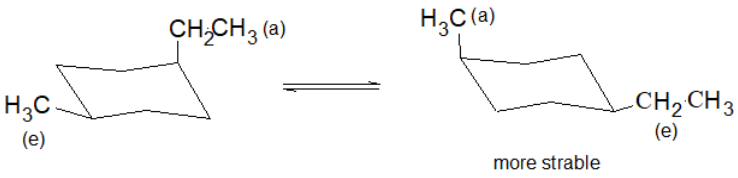
4-8



(c) The first conformer has one gauche interaction between the $–CH_3$ groups, so the strain energy of this conformer is 0.9 kcal/mol. The second conformer has four 1,3-diaxial interaction between H and $–CH_3$ groups, so its strain energy is 4 x 0.9 = 3.6 kcal/mol. Therefore, the energy difference in these two conformations is 3.6 – 0.9 =2.7 kcal/mol.

4-9

(a)



(b)

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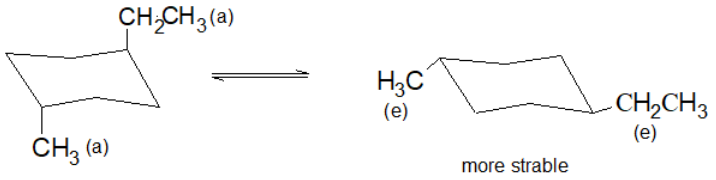
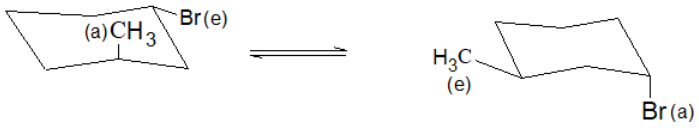


more strable

(c)

more strable

(d)

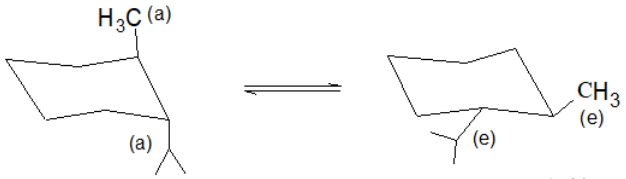


more strable

(e)

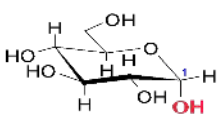
more strable

(f)

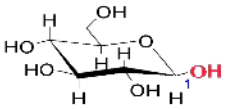


more strable

4-10



α-D-Glucopyranose

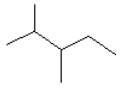


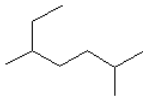
β-D-Glucopyranose

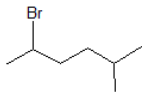
In α-D-glucopyranose, the hydroxyl group at C1 occupies an axial position. In β-D-glucopyranose, the hydroxyl group at C1 of occupies an equatorial position, which is the more stable structure. So the β forms predominates in equilibrium.

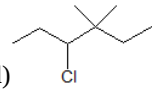
4.11

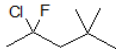
(a)

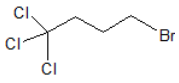


(b) 

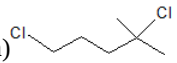
(c) 

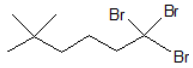
(d) 

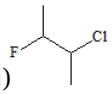
(e) 

(f) 

(g)

(h) 

(i) 

(j) 

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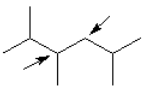
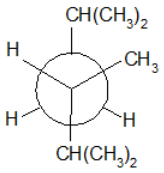
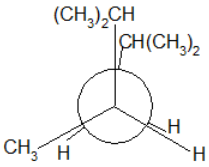


2,3,5-trimethylhexane

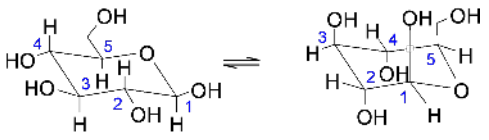


most stable



least stable

4.13



more stable

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CHAPTER OVERVIEW

4: Stereochemistry at Tetrahedral Centers

Learning Objectives

After reading this chapter and completing the exercises and homework, a student can be able to:

- recognize and classify molecules as chiral or achiral and identify planes of symmetry - refer to section 6.1
- draw, interpret, and convert between perspective formulae and Fischer projections for chiral compounds - refer to section 6.2
- name chiral compounds using (R) & (S) nomenclature - refer to section 6.3
- recognize and classify diastereomers and meso compounds - refer to section 6.4 and 6.5 respectively
- explain how physical properties differ for different types of stereoisomers - refer to section ?????
- distinguish and discern the structural and chemical relationships between isomeric compounds - refer to section 6.6
- define and explain the lack of optical activity of racemic mixtures - refer to section 6.7
- determine the percent composition of an enantiomeric mixture from polarimetry data and the for specific rotation formula - refer to section 6.7
- explain how to resolve (separate) a pair of enantiomers - refer to section 6.8
- interpret the stereoisomerism of compounds with three or more chiral centers - refer to section 6.9
- compare and contrast absolute configuration with relative configuration - refer to section 6.10
- interpret the stereoisomerism of compounds with nitrogen, phosphorus, or sulfur as chiral centers - refer to section 6.11
- recognize and explain biochemical applications of chirality - refer to section 6.12
- describe Jean Baptiste Biot and Louis Pasteur's contributions to the understanding of optical isomers - refer to section 6.13

4.1: Chirality
4.2: Fischer Projections to communicate Chirality
4.3: Absolute Configuration and the (R) and (S) System
4.4: Diastereomers - more than one chiral center
4.5: Meso Compounds
4.6: Isomerism Summary Diagram
4.7: Optical Activity and Racemic Mixtures
4.8: 6.8 Resolution (Separation) of Enantiomers
4.9: Stereochemistry of Molecules with Three or More Asymmetric Carbons
4.10: Absolute and Relative Configuration - the distinction
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CHAPTER OVERVIEW

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4: Stereochemistry at Tetrahedral Centers

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4.1: Chirality

Learning Objective

- recognize and classify molecules as chiral or achiral and identify planes of symmetry

Stereoisomers are isomers that differ in spatial arrangement of atoms, rather than order of atomic connectivity. One of their most interesting type of isomer is the mirror-image stereoisomers, a non-superimposable set of two molecules that are mirror image of one another. The existence of these molecules are determined by concept known as chirality.

Introduction

Organic compounds, molecules created around a chain of carbon atom (more commonly known as carbon backbone), play an essential role in the chemistry of life. These molecules derive their importance from the energy they carry, mainly in a form of potential energy between atomic molecules. Since such potential force can be widely affected due to changes in atomic placement, it is important to understand the concept of an isomer, a molecule sharing same atomic make up as another but differing in structural arrangements. This article will be devoted to a specific isomers called stereoisomers and its property of chirality (Figure 1).

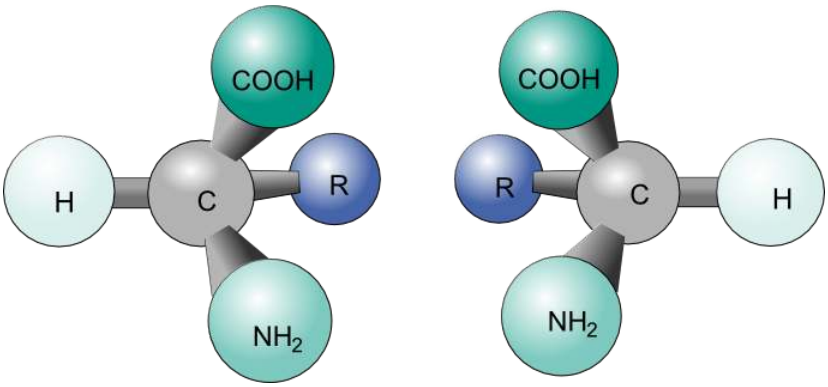


Figure 1: Two enantiomers of a tetrahedral complex.

The concepts of steroisomerism and chirality command great deal of importance in modern organic chemistry, as these ideas helps to understand the physical and theoretical reasons behind the formation and structures of numerous organic molecules, the main reason behind the energy embedded in these essential chemicals. In contrast to more well-known constitutional isomerism, which develops isotopic compounds simply by different atomic connectivity, stereoisomerism generally maintains equal atomic connections and orders of building blocks as well as having same numbers of atoms and types of elements.

What, then, makes stereoisomers so unique? To answer this question, the learner must be able to think and imagine in not just two-dimensional images, but also three-dimensional space. This is due to the fact that stereoisomers are isomers because their atoms are different from others in terms of spatial arrangement.

Spatial Arrangement

First and foremost, one must understand the concept of spatial arrangement in order to understand stereoisomerism and chirality. Spatial arrangement of atoms concern how different atomic particles and molecules are situated about in the space around the organic compound, namely its carbon chain. In this sense, spatial arrangement of an organic molecule are different another if an atom is shifted in any three-dimensional direction by even one degree. This opens up a very broad possibility of different molecules, each with their unique placement of atoms in three-dimensional space .

Stereoisomers

Stereoisomers are, as mentioned above, contain different types of isomers within itself, each with distinct characteristics that further separate each other as different chemical entities having different properties. Type called entaniomer are the previously-

mentioned mirror-image stereoisomers, and will be explained in detail in this article. Another type, diastereomer, has different properties and will be introduced afterwards.

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

Enantiomers

This type of stereoisomer is the essential mirror-image, non-superimposable type of stereoisomer introduced in the beginning of the article. Figure 3 provides a perfect example; note that the gray plane in the middle demotes the mirror plane.

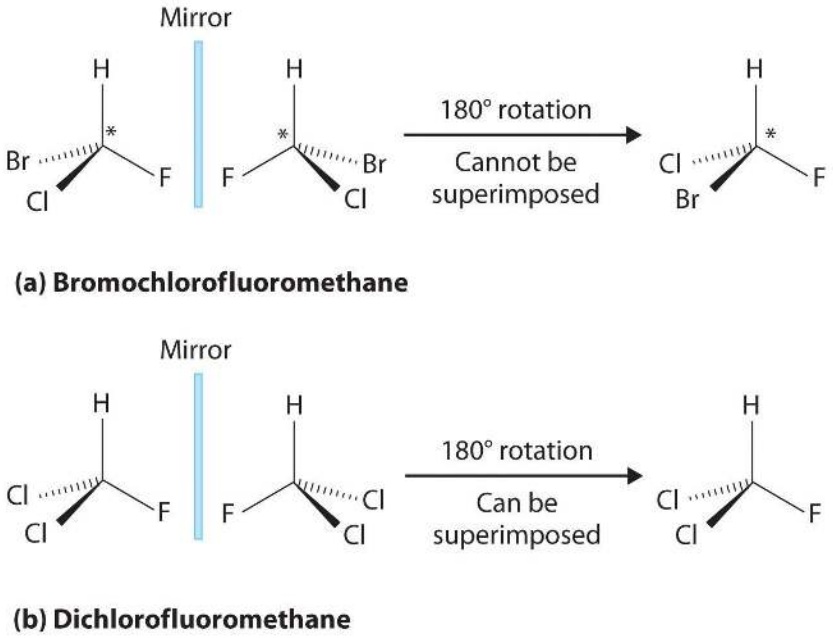


Figure 2: Comparison of Chiral and Achiral Molecules. (a) Bromochlorofluoromethane is a chiral molecule whose stereocenter is designated with an asterisk. Rotation of its mirror image does not generate the original structure. To superimpose the mirror images, bonds must be broken and reformed. (b) In contrast, dichlorofluoromethane and its mirror image can be rotated so they are superimposable.

Note that even if one were to flip over the left molecule over to the right, the atomic spatial arrangement will not be equal. This is equivalent to the left hand - right hand relationship, and is aptly referred to as 'handedness' in molecules. This can be somewhat counter-intuitive, so this article recommends the reader try the 'hand' example. Place both palm facing up, and hands next to each other. Now flip either side over to the other. One hand should be showing the back of the hand, while the other one is showing the palm. They are not same and non-superimposable.

This is where the concept of chirality comes in as one of the most essential and defining idea of stereoisomerism.

Chirality

Chirality essentially means 'mirror-image, non-superimposable molecules', and to say that a molecule is chiral is to say that its mirror image (it must have one) is not the same as it self. Whether a molecule is chiral or achiral depends upon a certain set of overlapping conditions. Figure 4 shows an example of two molecules, chiral and achiral, respectively. Notice the distinct characteristic of the achiral molecule: it possesses two atoms of same element. In theory and reality, if one were to create a plane that runs through the other two atoms, they will be able to create what is known as bisecting plane: The images on either side of the plan is the same as the other (Figure 4).

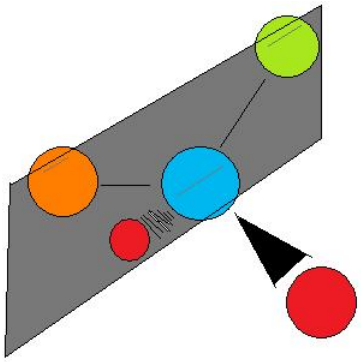


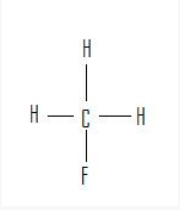
Figure 4.

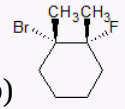
In this case, the molecule is considered 'achiral'. In other words, to distinguish chiral molecule from an achiral molecule, one must search for the existence of the bisecting plane in a molecule. All chiral molecules are deprive of bisecting plane, whether simple or complex.

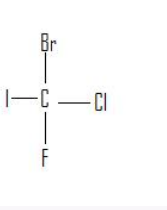
As a universal rule, no molecule with different surrounding atoms are achiral. Chirality is a simple but essential idea to support the concept of stereoisomerism, being used to explain one type of its kind. The chemical properties of the chiral molecule differs from its mirror image, and in this lies the significance of chilarity in relation to modern organic chemistry.

Exercise 1

Identify the following as either a constitutional isomer or stereoisomer. If stereoisomer, determine if it is an enantiomer or diastereomer. Explain the reason behind the answer. Also mark chirality for each molecule.

a) 

b) 

c) 

Solutions

a) achiral

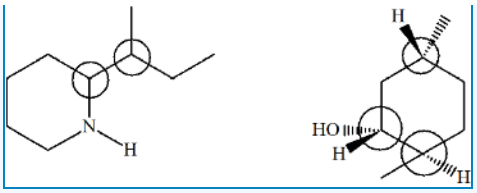
b) chiral

c) chiral

Exercise 2

Identify the chiral centers in each of the following:

Solutions



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2. Hick, Janice M. The Physical Chemistry of Chirality. New York, N.Y.: An American Chemical Society Publication. 2001.
3. Vollhardt, K. Peter C. and Schore, Neil E. Organic Chemistry: Structure and Function. Fifth Edition. New York, N.Y.: W. H. Freeman Company, 2007.

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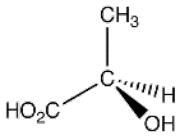
4.2: Fischer Projections to communicate Chirality

Learning Objective

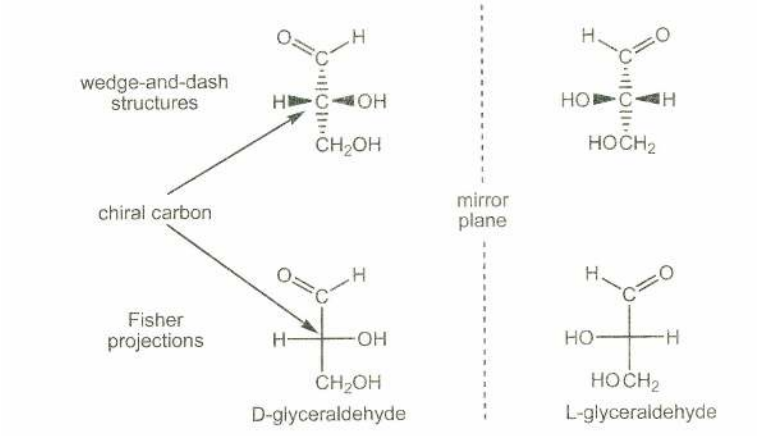
- draw, interpret, and convert between perspective formulae and Fischer projections for chiral compounds

Perspective Formulas and Fischer Projections

So far, we have communicated the stereochemical orentation of compounds using the wedges and dashes of perspective formulas. For example, the perspective formula for (*R*)-Lactic acid is shown below.



A Fischer projection is a convention used to depict stereochemistry in two dimensions. The horizontal bonds are seen as wedges and the vertical bonds are seen as dashed lines as shown below in the example below for glyceraldehyde.



Converting between Perspective and Fischer Formulas

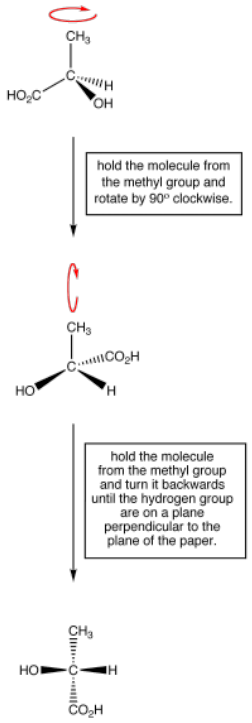
It can be useful to convert between perspective formulas and Fischer projections. Below is one approach using (R)-lactic acid as an example..

Step 1: Hold the molecule so that

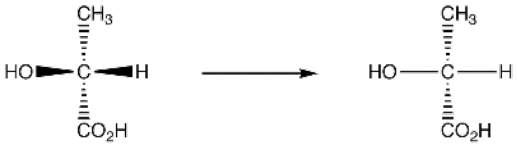
a) the chiral center is on the plane of the paper,

b) two bonds are coming out of the plane of the paper and are on a horizontal plane,

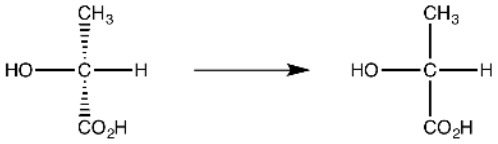
c) the two remaining bonds are going into the plane of the paper and are on a vertical plane



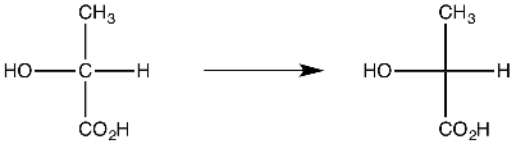
Step 2: Push the two bonds coming out of the plane of the paper onto the plane of the paper.



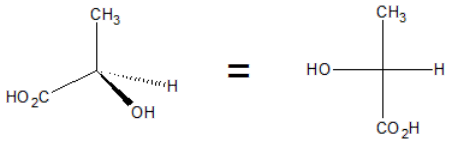
Step 3: Pull the two bonds going into the plane of the paper onto the plane of the paper.



Step 4: Omit the chiral atom symbol for convenience. This is the Fischer Projection of (*R*)-Lactic acid.



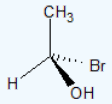
The stereochemical formula for (R)-lactic acid can be drawn using either method. To build this skill, we begin by drawing the structures and converting them step wise. Models can also be helpful. Eventually, we will be able to mentally conversion between these two structures.

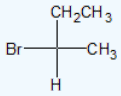


(R)-lactic acid (R)-lactic acid

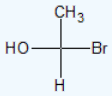
Exercise 1

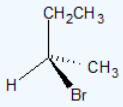
1. Convert each compound into the alternate sterochemical structure (Perspective ⟷ Fischer).

a) 

b) 

Answer

a) 

b) 

Other representations are possible. If you are not sure, use a molecular model kit to make a model for each structure and then compare the models.

See also D,L-convention.

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4.3: Absolute Configuration and the (R) and (S) System

Learning Objective

- name chiral compounds using (R) & (S) nomenclature

USE YOUR MODELING KIT: Models assist in visualizing the structure. When using a model, make sure the lowest priority is pointing away from you. Then determine the direction from the highest priority substituent to the lowest: clockwise (R) or counterclockwise (S).

IF YOU DO NOT HAVE A MODELING KIT: remember that the dashes mean the bond is going into the screen and the wedges means that bond is coming out of the screen. If the lowest priority bond is not pointing to the back, mentally rotate it so that it is. However, it is very useful when learning organic chemistry to use models.

If you have a modeling kit use it as you read through this section and work the practice problems.

Introduction and the Cahn-Ingold-Prelog rules of Priority

To name the enantiomers of a compound unambiguously, their names must include the "handedness" of the molecule. The letters "R" and "S" are determined by applying the Cahn-Ingold-Prelog (CIP) rules. The optical activity (+/-) can also be communicated in the name, but must be empirically derived. There are also biochemical conventions for carbohydrates (sugars) and amino acids (the building blocks of proteins).

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 CIP system, there are two ways of experimentally determining the absolute configuration of an enantiomer:

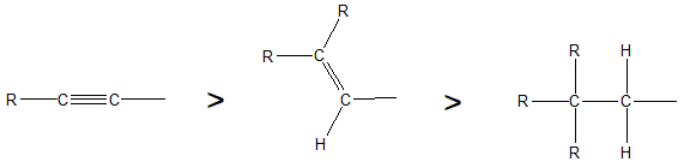
1. X-ray diffraction analysis. Note that there is no correlation between the sign of rotation and the structure of a particular enantiomer.
2. Chemical correlation with a molecule whose structure has already been determined via X-ray diffraction.

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.

The **Cahn-Ingold-Prelog** rules of priority are based on the atomic numbers of the atoms of interest. For chirality, the atoms of interest are the atoms bonded to the chiral carbon.

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].
3. When there is a tie in (2) above, establish relative priority by proceeding to the next atom(s) along the chain until the first difference is observed.

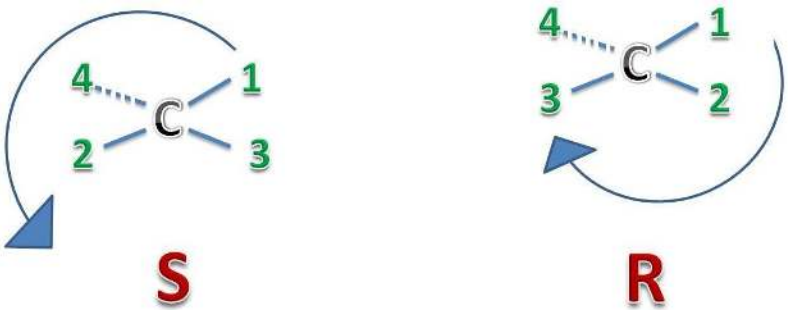
Multiple bonds are treated as if each bond of the multiple bond is bonded to a unique atom. For example, the ethenyl group (CH_2=CH) has higher priority than the ethyl group (CH_3CH_2). The ethenyl carbon priority is "two" bonds to carbon atoms and one bond to a hydrogen atom compared with the ethyl carbon that has only one bond to a carbon atom and two bonds to two hydrogen atoms. Similarly, the carbon-carbon triple bond of acetylene would give it higher CIP priority than the ethenyl group as summarized below.



Relative Priority according to the Cahn-Ingold-Prelog Rules

Stereocenters are labeled R or S

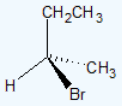
The "right hand" and "left hand" nomenclature is used to name the enantiomers of a chiral compound. The stereocenters are labeled as R or S.



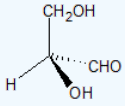
Consider the diagram above on the left: a curved arrow is drawn counter-clockwise (c-cw) from the highest priority substituent (*1*) to the lowest priority substituent *(4)* in the ***S-configuration*** ("Sinister" → Latin= "left"). The counterclockwise direction can be recognized by the movement left when leaving the 12 o' clock position. Now consider the diagram above on the right where a curved arrow is drawn clockwise (cw) from the highest priority substituent (*1*) to the lowest priority substituent *(4)* in the R configuration ("Rectus" → Latin= "right"). The ***R*** *or* ***S*** is then added as a prefix, in parenthesis, to the name of the enantiomer of interest. A locator number is required if there is more than one chiral center. Otherwise, the person reading the name is expected to recognize the chiral center.

Example 1

The two chiral compounds below are drawn to emphasize the chiral carbon with the full chemical name below each structure.



(2*R*)-2-bromobutane



(2*S*)-2,3-dihydroxypropanal

Absolute Configurations of Perspective Formulas

Chemists need a convenient way to distinguish one stereoisomer from another. The **Cahn-Ingold-Prelog system** is a set of rules that allows us to unambiguously define the stereochemical configuration of any stereocenter, using the designations '***R*** ' (from the Latin *rectus*, meaning right-handed) or ' ***S*** ' (from the Latin *sinister*, meaning left-handed).

The rules for this system of stereochemical nomenclature are, on the surface, fairly simple.

Rules for assigning an R/S designation to a chiral center

1: Assign priorities to the four substituents, with #1 being the highest priority and #4 the lowest. Priorities are based on the atomic number.

2: Trace a circle from #1 to #2 to #3.

3: Determine the orientation of the #4 priority group. If it is oriented into the plane of the page (away from you), go to step 4a. If it is oriented out of the plane of the page (toward you) go to step 4b.

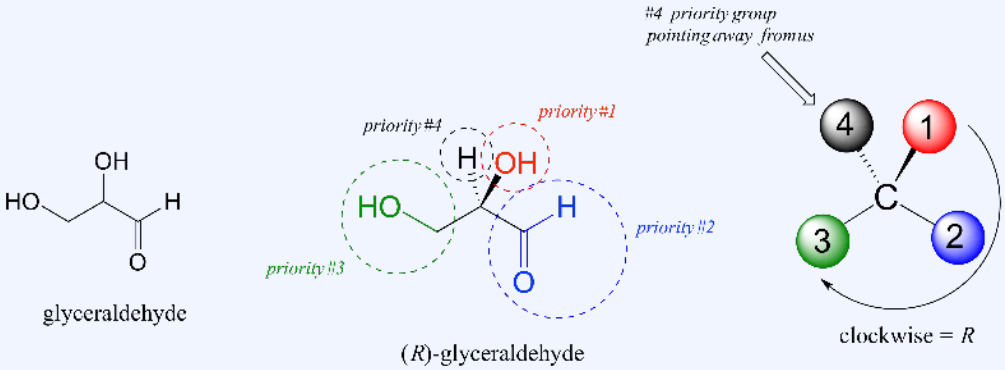
4a: *(#4 group pointing away from you)*: a clockwise circle in part 2 corresponds to the *R* configuration, while a counterclockwise circle corresponds to the *S* configuration.

4b: *(#4 group pointing toward you)*: a clockwise circle in part 2 corresponds to the *S* configuration, while a counterclockwise circle corresponds to the *R* configuration.

We'll use the 3-carbon sugar glyceraldehyde as our first example. The first thing that we must do is to assign a **priority** to each of the four substituents bound to the chiral center. We first look at the atoms that are directly bonded to the chiral center:

these are H, O (in the hydroxyl), C (in the aldehyde), and C (in the CH_2OH group).

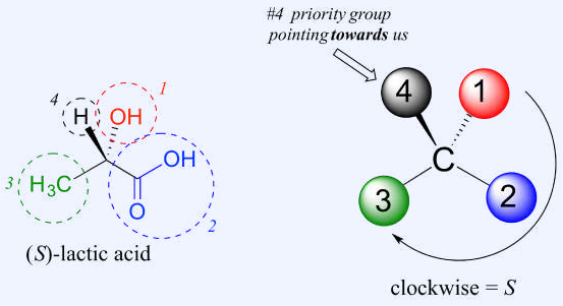
Assigning R/S configuration to glyceraldehyde:



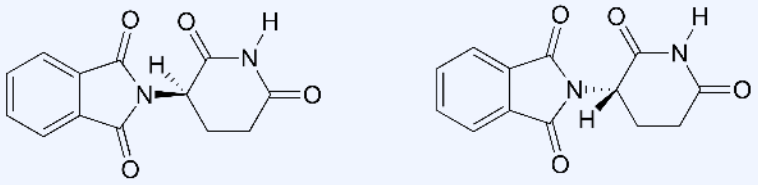
Two priorities are easy: hydrogen, with an atomic number of 1, is the lowest (#4) priority, and the hydroxyl oxygen, with atomic number 8, is priority #1. Carbon has an atomic number of 6. Which of the two 'C' groups is priority #2, the aldehyde or the CH_2OH? To determine this, we move one more bond away from the chiral center: for the aldehyde we have a *double* bond to an oxygen, while on the CH_2OH group we have a *single* bond to an oxygen. If the atom is the same, double bonds have a higher priority than single bonds. Therefore, the aldehyde group is assigned #2 priority and the CH_2OH group the #3 priority.

With our priorities assigned, we look next at the #4 priority group (the hydrogen) and see that it is pointed back away from us, into the plane of the page - thus step 4a from the procedure above applies. Then, we trace a circle defined by the #1, #2, and #3 priority groups, in increasing order. The circle is clockwise, which by step 4a tells us that this carbon has the '*R*' configuration, and that this molecule is (*R*)-glyceraldehyde. Its enantiomer, by definition, must be (*S*)-glyceraldehyde.

Next, let's look at one of the enantiomers of lactic acid and determine the configuration of the chiral center. Clearly, H is the #4 substituent and OH is #1. Owing to its three bonds to oxygen, the carbon on the acid group takes priority #2, and the methyl group takes #3. The #4 group, hydrogen, happens to be drawn pointing *toward* us (out of the plane of the page) in this figure, so we use step 4b: The circle traced from #1 to #2 to #3 is clockwise, which means that the chiral center has the *S* configuration.

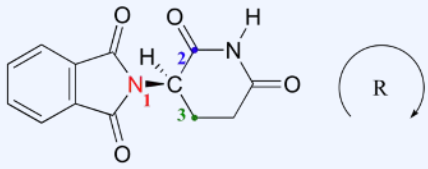


The drug thalidomide is an interesting - but tragic - case study in the importance of stereochemistry in drug design. First manufactured by a German drug company and prescribed widely in Europe and Australia in the late 1950's as a sedative and remedy for morning sickness in pregnant women, thalidomide was soon implicated as the cause of devastating birth defects in babies born to women who had taken it. Thalidomide contains a chiral center, and thus exists in two enantiomeric forms. It was marketed as a **racemic mixture**: in other words, a 50:50 mixture of both enantiomers.



two enantiomers of thalidomide

Let's try to determine the stereochemical configuration of the enantiomer on the left. Of the four bonds to the chiral center, the #4 priority is hydrogen. The nitrogen group is #1, the carbonyl side of the ring is #2, and the $–CH_2$ side of the ring is #3.



(R)-thalidomide

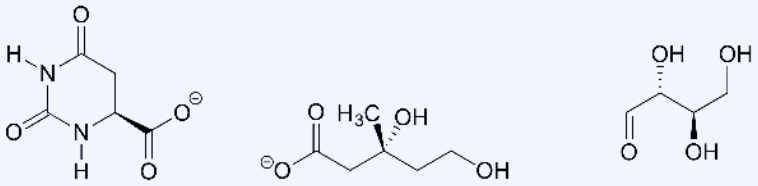
The hydrogen is shown pointing away from us, and the prioritized substituents trace a clockwise circle: this is the *R* enantiomer of thalidomide. The other enantiomer, of course, must have the S configuration.

Although scientists are still unsure today how thalidomide works, experimental evidence suggests that it was actually the *R* enantiomer that had the desired medical effects, while the *S* enantiomer caused the birth defects. Even with this knowledge, however, pure (*R*)-thalidomide is not safe, because enzymes in the body rapidly convert between the two enantiomers - we will see how that happens in chapter 12.

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.

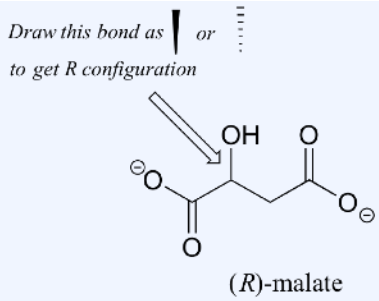
Very recently a close derivative of thalidomide has become legal to prescribe again in the United States, with strict safety measures enforced, for the treatment of a form of blood cancer called multiple myeloma. In Brazil, thalidomide is used in the treatment of leprosy - but despite safety measures, children are still being born with thalidomide-related defects.

Exercise 1.: Determine the stereochemical configurations of the chiral centers in the biomolecules shown below.



dihydroorotate mevalonate (D)-erythrose

Exercise 2.: Should the (*R*) enantiomer of malate have a solid or dashed wedge for the C-O bond in the figure below?



(*R*)-malate

Exercise 3.: Using solid or dashed wedges to show stereochemistry, draw the (*R*) enantiomer of ibuprofen and the (*S*) enantiomer of 2-methylerythritol-4-phosphate (structures are shown earlier in this chapter without stereochemistry).

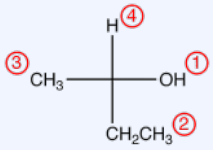
Solutions to exercises

Absolute Configurations of Fischer Projections

To determine the absolute configuration of a chiral center in a Fisher projection, use the following two-step procedure.

Step 1

Assign priority numbers to the four ligands (groups) bonded to the chiral center using the CIP priority system.



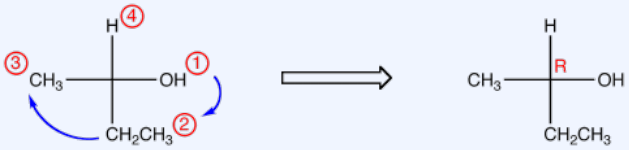
Step 2 - vertical option

If the lowest priority ligand is on a Vertical bond, then it is pointing away from the viewer.

Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Very correct answer.

direction of ① → ② → ③	absolute configuration
clockwise	R
counterclockwise	S

In the compound below, the movement is clockwise indicating an R-configuration. The complete IUPAC name for this compound is (R)-butan-2-ol.



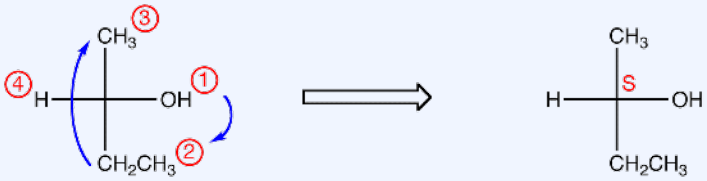
Step 2 - horizontal option

If the lowest-priority ligand is on a Horizontal bond, then it is pointing toward the viewer.

Trace the three highest-priority ligands starting at the highest-priority ligand (① → ② → ③) in the direction that will give a Horribly wrong answer. Note in the table below that the configurations are reversed from the first example.

direction of ① → ② → ③	absolute configuration
clockwise	S
counterclockwise	R

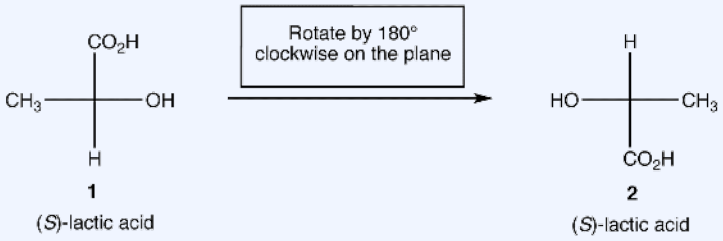
In the compound below, the movement is clockwise (R) which is Horribly wrong, so the actual configuration is S. The complete IUPAC name for this compound is (S)-butan-2-ol.

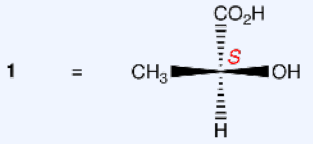


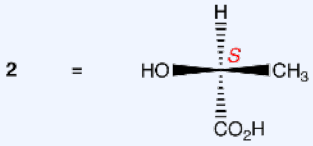
Manipulating Fischer Projections with NO Change to Configuration

A Fischer projection restricts a three-dimensional molecule into two dimensions. Consequently, there are limitations as to the operations that can be performed on a Fischer projection without changing the absolute configuration at chiral centers. The operations that do not change the absolute configuration at a chiral center in a Fischer projections can be summarized as two rules.

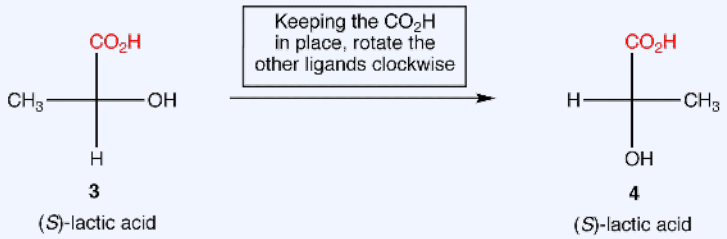
Rule 1: Rotation of the Fischer projection by 180° in either direction without lifting it off the plane of the paper does not change the absolute configuration at the chiral center.

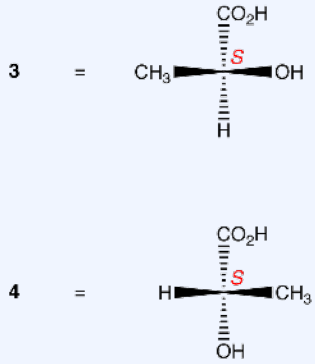






Rule 2: Rotation of three ligands on the chiral center in either direction, keeping the remaining ligand in place, does not change the absolute configuration at the chiral center.

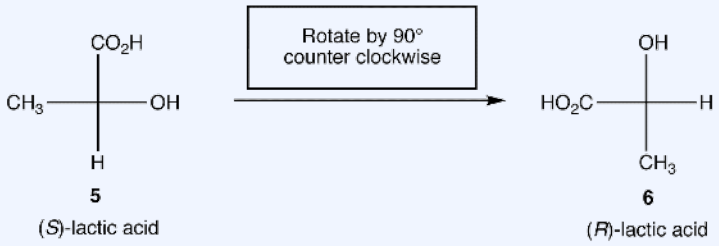


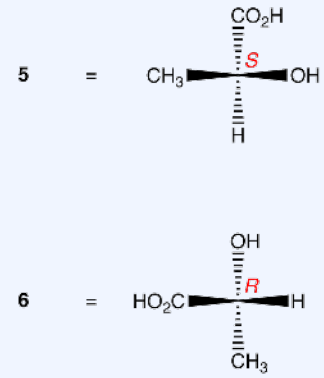


Manipulating Fischer Projections with Change to Configuration

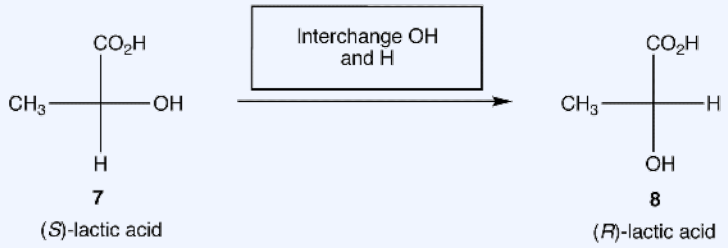
The operations that do change the absolute configuration at a chiral center in a Fischer projection can be summarized as two rules.

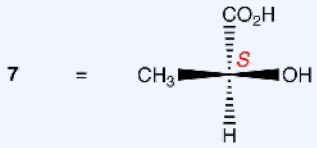
Rule 1: Rotation of the Fischer projection by 90º in either direction changes the absolute configuration at the chiral center.

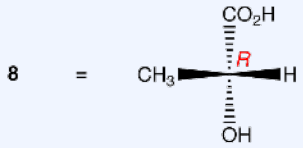




Rule 2: Interchanging any two ligands on the chiral center changes the absolute configuration at the chiral center.



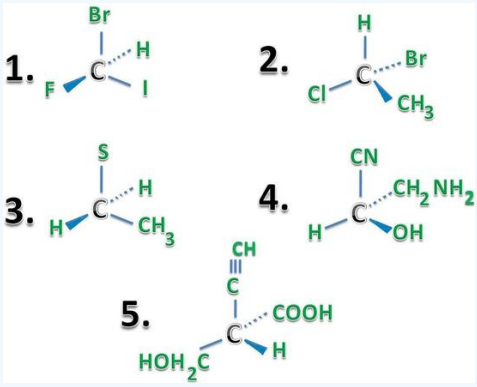




The above rules assume that the Fischer projection under consideration contains only one chiral center. However, with care, they can be applied to Fischer projections containing any number of chiral centers.

Exercise 1

Classify the following compounds as R or S?

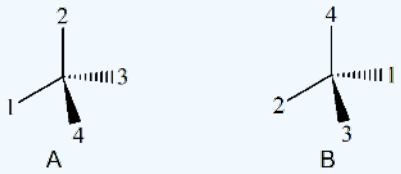


Solution

1. **S:** I > Br > F > H. The lowest priority substituent, H, is already going towards the back. It turns left going from I to Br to F, so it's a S.
2. **R:** Br > Cl > CH_3 > H. You have to switch the H and Br in order to place the H, the lowest priority, in the back. Then, going from Br to Cl, CH_3 is turning to the right, giving you a R.
3. **Neither R or S**: This molecule is achiral. Only chiral molecules can be named R or S.
4. **R:** OH > CN > CH_2NH_2 > H. The H, the lowest priority, has to be switched to the back. Then, going from OH to CN to CH_2NH_2, you are turning right, giving you a R.
5. **(5) S:** $-COOH$ > $-CH_2OH$ > $C{\equiv}CH$ > H. Then, going from $-COOH$ to $-CH_2OH$ to $-C{\equiv}CH$ you are turning left, giving you a S configuration.

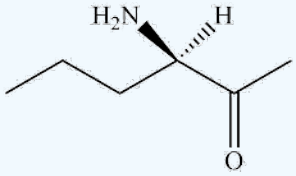
Exercises

6. Orient the following so that the least priority (4) atom is paced behind, then assign stereochemistry (*R* or *S*).



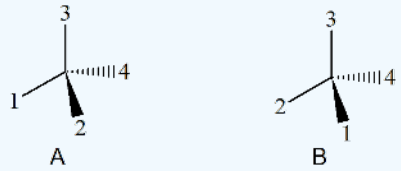
7. Draw (*R*)-2-bromobutan-2-ol.

8. Assign *R/S* to the following molecule.



Solutions

6.



A = *S*; B = *R*

7.

8. The stereo center is *R*.

Other Resources

Kahn Academy video tutorial on the R-S naming system

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.

Contributors and Attributions

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4.4: Diastereomers - more than one chiral center

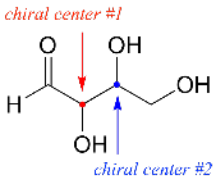
Learning Objective

- recognize and classify diastereomers

Diastereomers are stereoisomers with two or more chiral centers that are not enantiomers. Diastereomers have different physical properties (melting points, boiling points, and densities). Depending on the reaction mechanism, diastereomers can produce different stereochemical products.

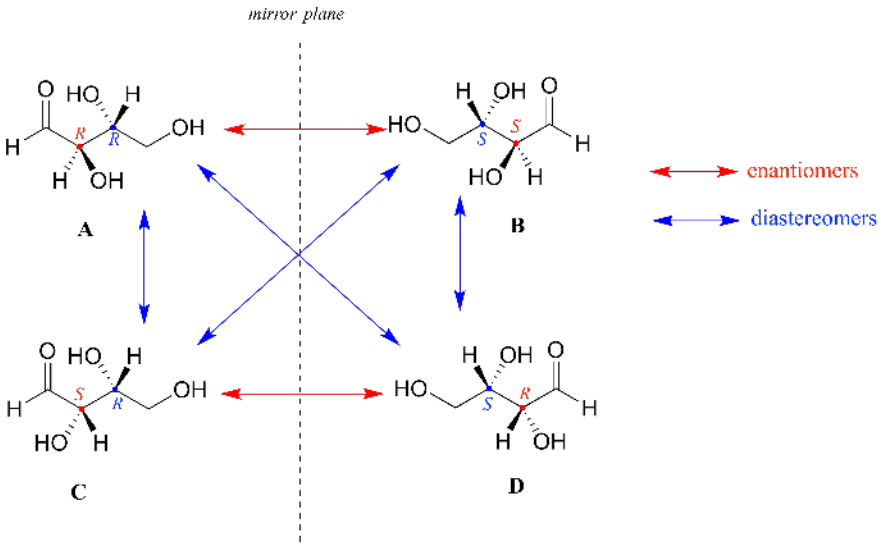
Introduction

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.



To avoid confusion, we will simply refer to the different stereoisomers by capital letters.

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:

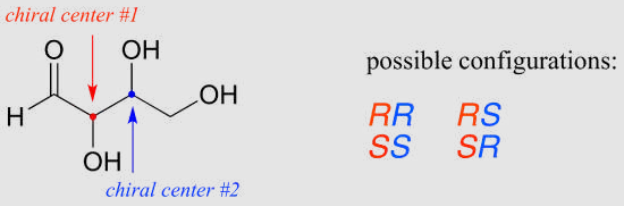
Stereoisomer shortcuts

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.

(*Note: 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.

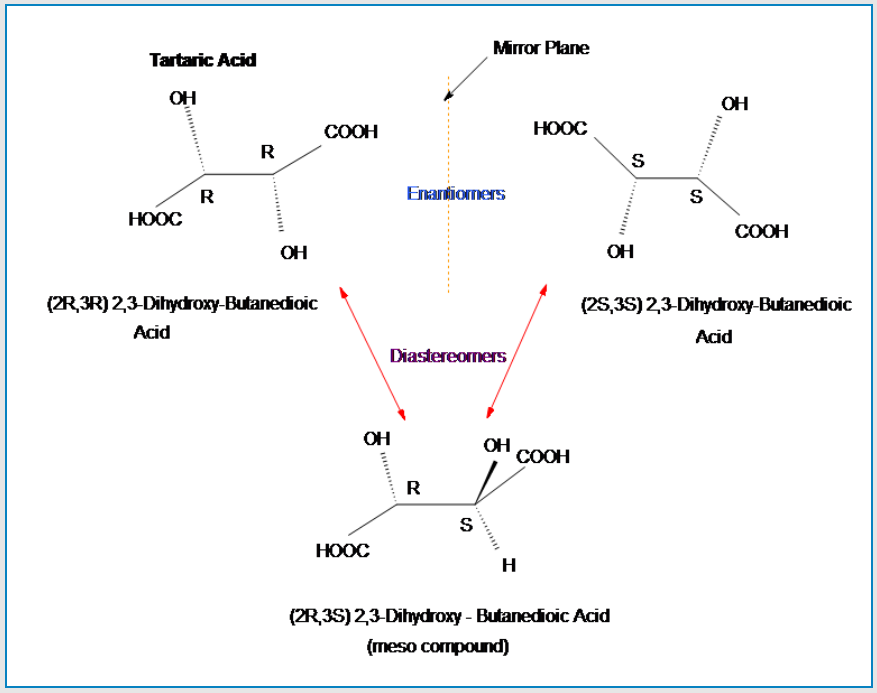


We know, using the shortcut above, that the enantiomer of RR must be SS - both chiral centers are different. We also know that RS and SR are diastereomers of RR, because in each case one - but not both - chiral centers are different.

Diastereomers vs. Enantiomers in Wine Chemistry

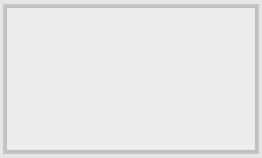
Tartaric acid, $C_4H_6O_6$, is an organic compound that can be found in grape, bananas, and in wine. The structures of tartaric acid itself is really interesting. Naturally, it is in the form of (R,R) stereocenters. Artificially, it can be in the meso form (R,S), which is achiral. R,R tartaric acid is enantiomer to is mirror image which is S,S tartaric acid and diasteromers to meso-tartaric acid (Figure 5.6.2).

(R,R) and (S,S) tartaric acid have similar physical properties and reactivity. However, meso-tartaric acid have different physical properties and reactivity. For example, melting point of (R,R) & (S,S) tartaric is about 170 degree Celsius, and melting point of meso-tartaric acid is about 145 degree Celsius.



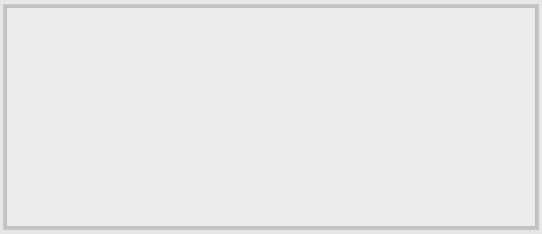
Diastereomers vs. Enantiomers in Sugar Chemistry

D-erythrose is a common four-carbon sugar.



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.

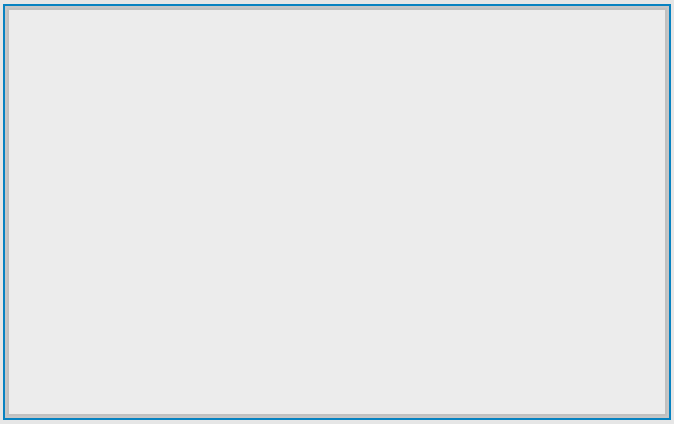
As you can see, *D*-erythrose is a chiral molecule: C_2 and C_3 are stereocenters, both of which have the *R* configuration. In addition, you should make a model to convince yourself that it is impossible to find a plane of symmetry through the molecule, regardless of the conformation. Does D-erythrose 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.

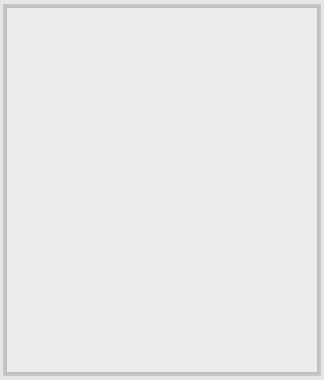
> **Note**
>
> In a pair of enantiomers, **all** of the chiral centers are of the opposite configuration.

What happens if we draw a stereoisomer of erythrose in which the configuration is *S* at C_2 and *R* at C_3? This stereoisomer, which is a sugar called D-threose, is *not* a mirror image of erythrose. D-threose is a **diastereomer** of both D-erythrose and L-erythrose.



The definition of diastereomers is simple: if two molecules are stereoisomers (same molecular formula, same connectivity, different arrangement of atoms in space) but are *not* enantiomers, then they are diastereomers by default. *In practical terms, this means that at least one - but not all - of the chiral centers are opposite in a pair of diastereomers.* By definition, two molecules that are diastereomers are *not* mirror images of each other.

L-threose, the enantiomer of D-threose, has the *R* configuration at C_2 and the *S* configuration at C_3. L-threose is a diastereomer of both erythrose enantiomers.

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. 

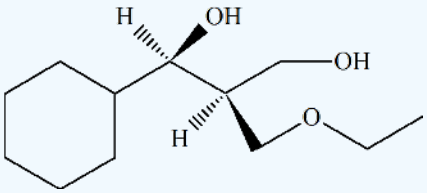
In total, there are 2^{10} = 1024 stereoisomers in the erythronolide B family: 1022 of these are diastereomers of the structure above, one is the enantiomer of the structure above, and the last ***is*** the structure above.

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.

Exercises

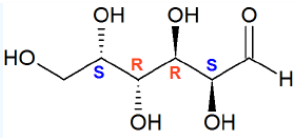
1. Draw the structures of L-galactose (the enantiomer of D-galactose) and two more diastereomers of D-glucose (one should be an epimer).

2. Determine the stereochemistry of the following molecule:

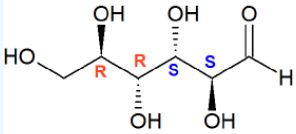


Answer

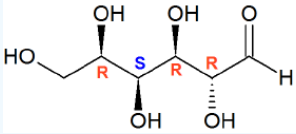
1.



L-galactose

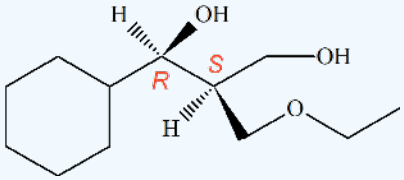


L-mannose
(epimer of D-glucose)



L-gulose
(diastereomer of D-glucose)

2.



Contributors and Attributions

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4.5: Meso Compounds

Learning Objective

- recognize and classify meso compounds

A meso compound is an achiral compound that has chiral centers. It is superimposed on its mirror image and is optically inactive although it contains two or more stereocenters.

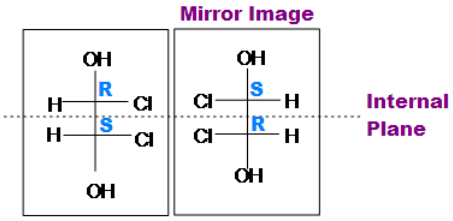
Introduction

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 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, result in optically inactive. Cyclic compounds may also be meso.

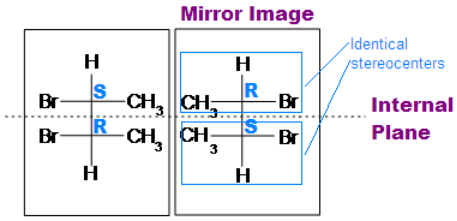
Identification

If A is a meso compound, it should have two or more stereocenters, an internal plane, and the stereochemistry should be R and S.

1. Look for an internal plane, or internal mirror, that lies in between the compound.
2. The stereochemistry (e.g. R or S) is very crucial in determining whether it is a meso compound or not. As mentioned above, a meso compound is optically inactive, so their stereochemistry should cancel out. For instance, R cancels S out in a meso compound with two stereocenters.

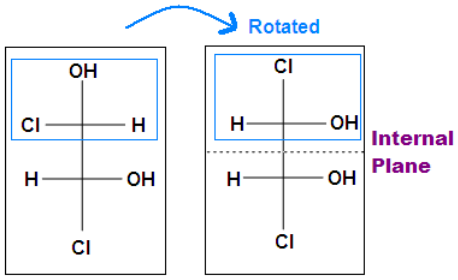


trans-1,2-dichloro-1,2-ethanediol

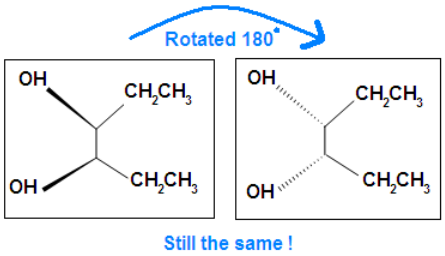


(meso)-2,3-dibromobutane

Tips: An interesting thing about single bonds or sp3-orbitals is that we can rotate the substituted groups that attached to a stereocenter around to recognize the internal plane. As the molecule is rotated, its stereochemistry does not change. For example:

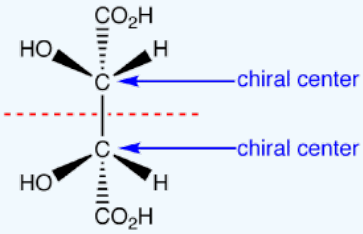


Another case is when we rotate the whole molecule by 180 degree. Both molecules below are still meso.



Remember the internal plane here is depicted on two dimensions. However, in reality, it is three dimensions, so be aware of it when we identify the internal mirror.

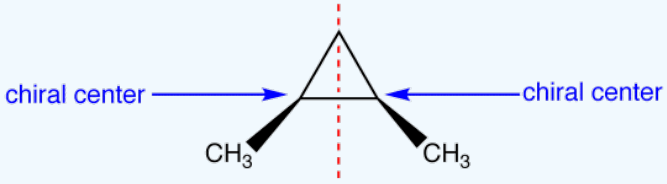
Example 4.5.1:



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 4.5.2:

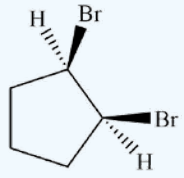


2

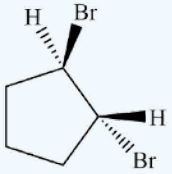
This molecules has a plane of symmetry (the vertical plane going through the red broken line perpendicular to the plane of the ring) and, therefore, is achiral, but has has two chiral centers. Thus, its is a meso compound.

Exercise 4.5.1

Which of the following are meso-compounds:



A



B

a.

b. C – 2,3-dibromobutane

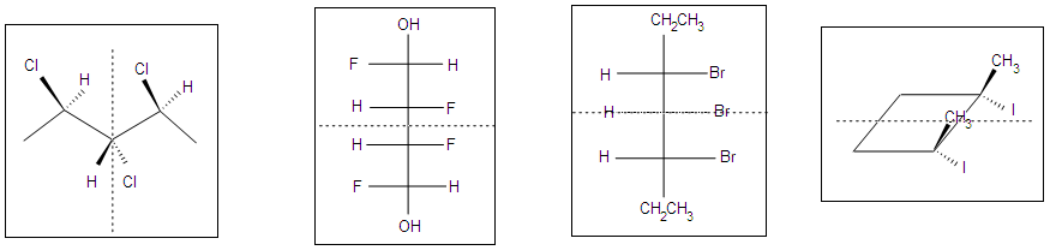
c. D – 2,3-dibromopentane

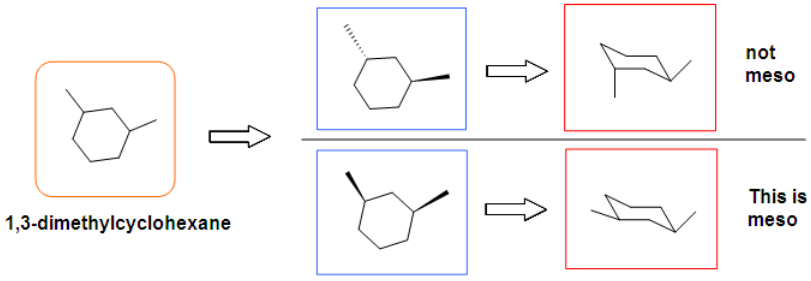
Answer

Compounds A and C are meso.

Other Examples of meso compounds

Meso compounds can exist in many different forms such as pentane, butane, heptane, and even cyclobutane. They do not necessarily have to be two stereocenters, but can have more.



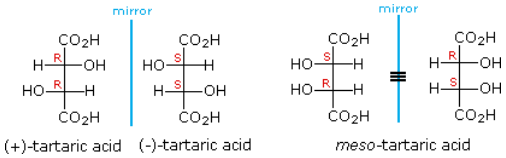


The chiral centers in the preceding examples have all been different. In the case of 2,3-dihydroxybutanedioic acid, known as tartaric acid, the two chiral centers have the same four substituents and are equivalent. As a result, two of the four possible stereoisomers of this compound are identical due to a plane of symmetry, so there are only three stereoisomeric tartaric acids. Two of these stereoisomers are enantiomers and the third is an achiral diastereomer, called a meso compound. Meso compounds are achiral (optically inactive) diastereomers of chiral stereoisomers. Investigations of isomeric tartaric acid salts, carried out by Louis

Pasteur in the mid 19th century, were instrumental in elucidating some of the subtleties of stereochemistry. Some physical properties of the isomers of tartaric acid are given in the following table.

(+)-tartaric acid:	[α]D = +13º	m.p. 172 ºC
(–)-tartaric acid:	[α]D = –13º	m.p. 172 ºC
meso-tartaric acid:	[α]D = 0º	m.p. 140 ºC

Fischer projection formulas provide a helpful view of the configurational relationships within the structures of these isomers. In the following illustration a mirror line is drawn between formulas that have a mirror-image relationship. In demonstrating the identity of the two meso-compound formulas, remember that a Fischer projection formula may be rotated 180º in the plane.



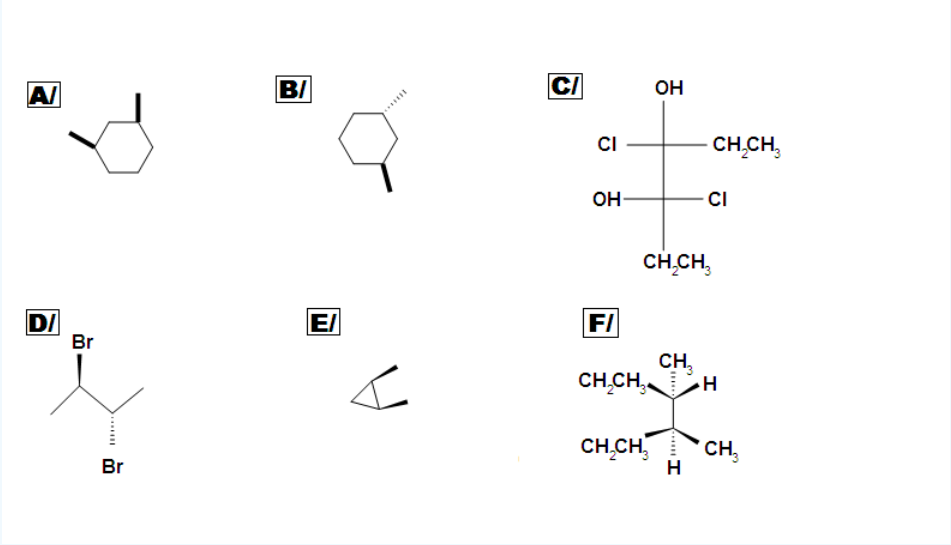
Optical Activity Analysis

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 (+).

Achiral Diastereomers (meso-Compounds)

Exercise 4.5.1

Beside meso, there are also other types of molecules: enantiomer, diastereomer, and identical. Determine if the following molecules are meso.



Answer

A C, D, E are meso compounds.

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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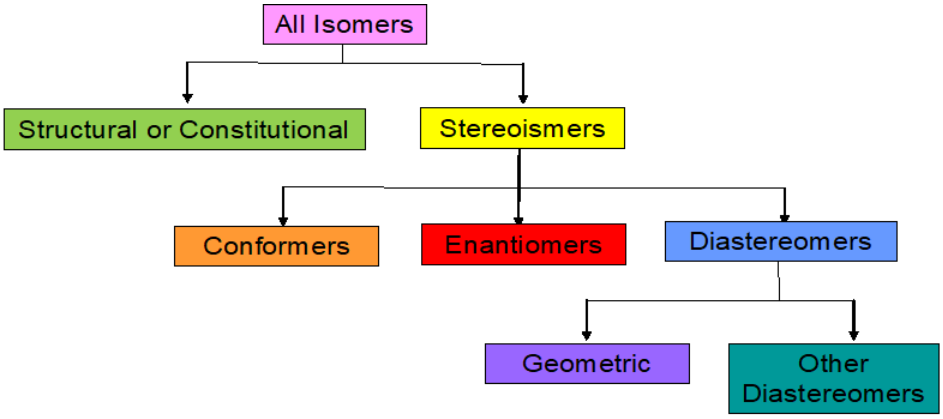
4.6: Isomerism Summary Diagram

Learning Objective

- distinguish and discern the structural and chemical relationships between isomeric compounds

The various types of isomers have been introduced and explored over several chapters. It can be helpful to review, compare, and contrast all of the forms of isomerism to build our skills of discernment. A brief review of each type of isomerism follows the summary diagram. See the respective chapter for a complete explanation.



Conformational Isomers

The rotation of C–C single bonds both carbon chains creates conformers (the same compound shown in different rotations). 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). While complete rotation of C-C single bonds is not possible in rings. The freedom of bond movement does allow the rings to assume different conformations, such as the chair and boat for 6-membered rings.

Structural (Constitutional) Isomers

Unlike conformational isomers, structural isomers differ in connectivity, as illustrated below 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 creating a unique compounds with differences in their physical and chemical properties.

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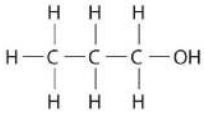
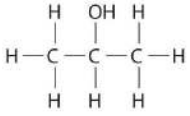
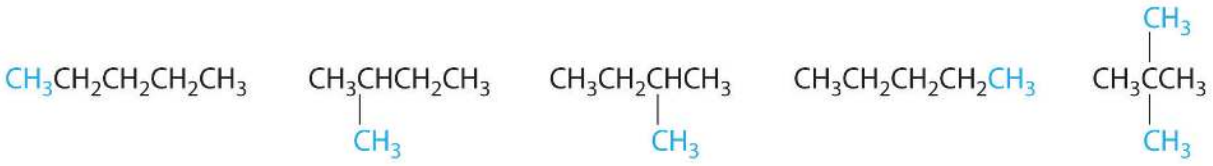


1-Propanol (*n*-propanol)



2-Propanol (isopropanol)

Consider, for example, the following five structures represented by the formula C_5H_{12}. 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.

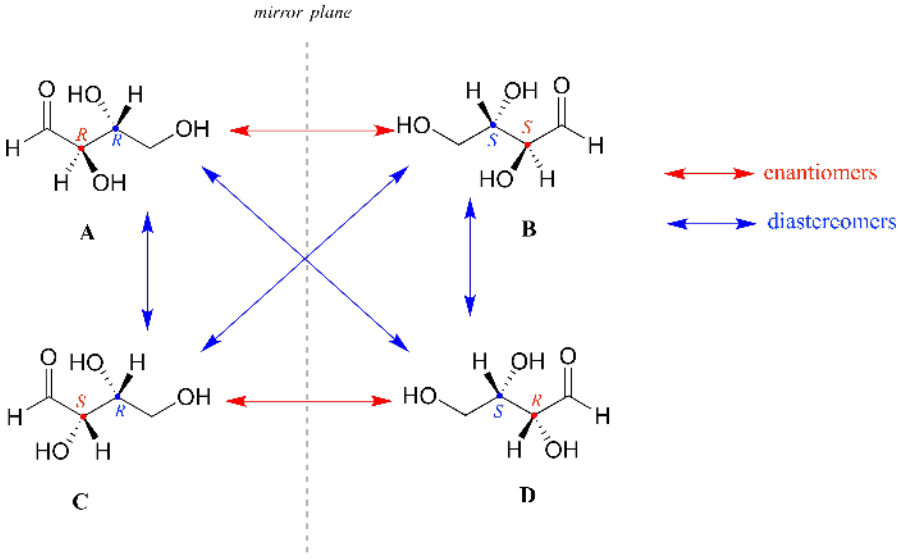


(a) (b) (c) (d) (e)

Structures (a) and (d) above represent the same compound, n-pentane. Structures (b) and (c) represent the same compound, 2-methylbutane. No bonds need to be broken and reformed to convert between (a) and (d) or between (b) and (c). The molecules are simply rotated 180° about a vertical axis. Structure (e) is named 2,2-dimethylpropane. There are only three structural isomers possible with the chemical formula C_5H_{12}: n-pentane, 2-methylbutane, and 2,2-dimethylpropane. Structural isomers have distinct physical and chemical properties.

Stereoisomers

Enantiomers are pairs of compounds that are non-superimposable images. When there are two or more chiral centers in a compounds, the diatereomers can exist. Diastereomers are stereoisomers that are NOT enantiomers. Enatiomers share all physical properties except for their interaction with plane polarized light. Diastereomers have different physical properties (melting points and boiling points and densities).



Exercise

1. What kind of isomers are the following pairs? Note: It can be difficult to answer this question directly from the names. It can be helpful to draw the structures.

a. (R)-5-chlorohexene and 6-chlorohexene
b. (2R,3R)-dibromohexane and (2R,3S)-dibromohexane

Answer

1.

a. Structural Isomers

b. Diastereomers

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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4.7: Optical Activity and Racemic Mixtures

Learning Objective

- define and explain the lack of optical activity of racemic mixtures
- determine the percent composition of an enantiomeric mixture from polarimetry data and the for specific rotation formula

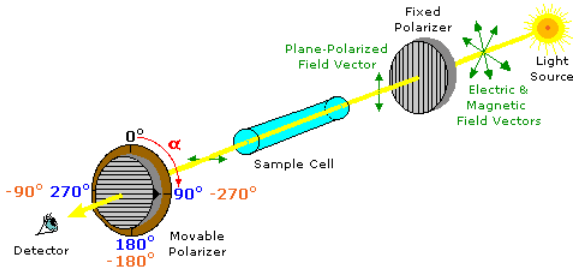
Racemic Mixtures (Racimates)

A *racemic mixture* is a 50:50 mixture of two enantiomers. Racemic mixtures were an interesting experimental discovery because two optically active samples can be combined in a 1:1 ratio to create an optically INACTIVE sample. Polarimetry is used to measure optical activity. The history and theoretical foundation are discussed below.

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**, shown in the diagram below.



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 (α = 0º). If the analyzer is turned 90º to the plane of initial polarization, all the light will be blocked from reaching the detector.

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 +81° (or +243°) while the negative rotation would change to –81°, 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 and carvone enantiomers discussed earlier have the following specific rotations.

Carvone from caraway: $[\alpha]_D$ = +62.5°	this isomer may be referred to as (+)-carvone or *d*-carvone
Carvone from spearmint: $[\alpha]_D$ = –62.5°	this isomer may be referred to as (–)-carvone or *l*-carvone
Lactic acid from muscle tissue: $[\alpha]_D$ = +2.5°	this isomer may be referred to as (+)-lactic acid or *d*-lactic acid
Lactic acid from sour milk: $[\alpha]_D$ = –2.5°	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 in the following equation).

$CH_3CH{=}CHCH_3$ + HBr	⟶	(±) $CH_3CH_2CHBrCH_3$

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%.

$$\%\ optical\ purity = \frac{specific\ rotation\ of\ mixture}{specific\ rotation\ of\ pure\ enantiomer} \times 100$$

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 %.

Example

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?

Solution

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.

$$\text{Rotation } (R/S \text{ Mix}) = [\text{Fraction}(S) \times \text{Rotation } (S)] + [\text{Fraction}(R) \times \text{Rotation } (R)]$$

Let Fraction (*S*) = x, therefore Fraction (*R*) = 1 – x

$$\text{Rotation } (R/S \text{ Mix}) = x[\text{Rotation } (S)] + (1 - x)[\text{Rotation } (R)]$$

$-23 = x(+61) + (1 - x)(-61)$

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.

$$ee = [(\%\text{ more abundant enantiomer} - 50) \times 100]/50$$

$$= [68.9 - 50) \times 100]/50 = 37.8\%$$

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.

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 in this technique are known as '

Exercise 1

A sample with a concentration of 0.3 g/mL was placed in a cell with a length of 5 cm. The resulting rotation at the sodium D line was +1.52°. What is the $[\alpha]_D$?

Solution

5 cm = 0.5 dm

$[\alpha]_D = \alpha/(c \times l) = +1.52/(0.3 \times 0.5) = +10.1°$

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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4.8: 6.8 Resolution (Separation) of Enantiomers

Learning Objective

- explain how to resolve (separate) a pair of enantiomers

Introduction and Overview

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.

Chiral Resolution

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.

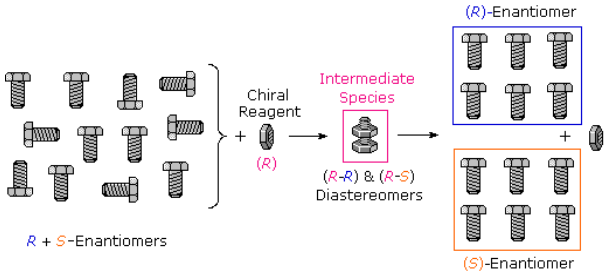


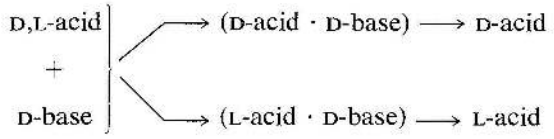
Figure 5.8.1:

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.

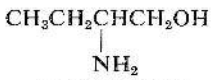
Because the physical properties of enantiomers are identical, they seldom can be separated by simple physical methods, such as fractional crystallization or distillation. It is only under the influence of another chiral substance that enantiomers behave differently, and almost all methods of resolution 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

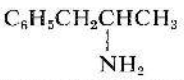
The most commonly used procedure for separating enantiomers is to convert them to a mixture of diastereomers that will have different physical properties: melting point, boiling point, solubility, and so on (Section 5-5). For example, if you have a racemic or D,L mixture of enantiomers of an acid and convert this to a salt with a chiral base having the D configuration, the salt will be a mixture of two diastereomers, (D acid . D base) and (L acid . D 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 acid regenerated from each salt will be either exclusively the D or the L enantiomer:



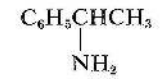
Resolution of chiral acids through the formation of diastereomeric salts requires adequate supplies of suitable chiral bases. Brucine, strychnine, and quinine frequently are used for this purpose because they are readily available, naturally occurring chiral bases. Simpler amines of synthetic origin, such as 2-amino- 1 -butanol, amphetamine, and 1 -phenylethanamine, also can be used, but first they must be resolved themselves.



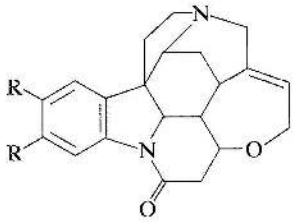
2-amino-1-butanol



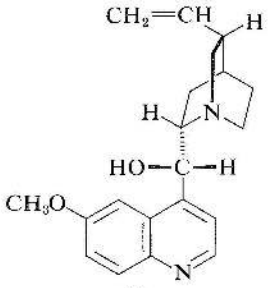
1-phenyl-2-propanamine
(amphetamine)



1-phenylethanamine



R = H, strychnine
R = OCH_3, brucine



quinine
(antimicrobial)
(antimalarial)

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.

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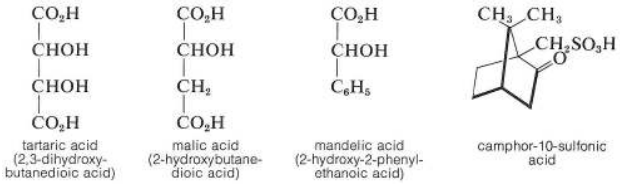
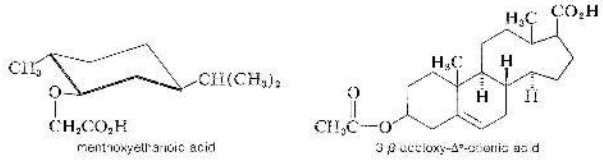


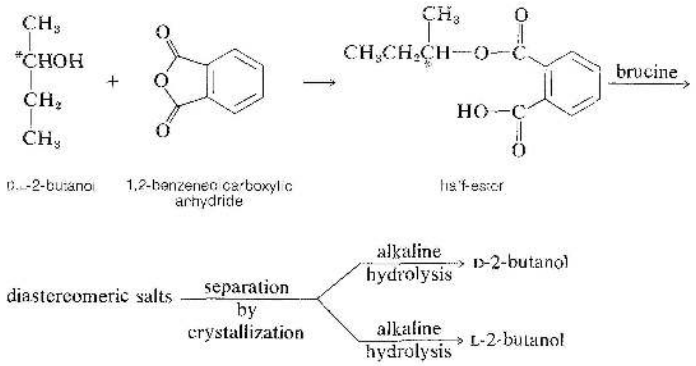
The principle is the same as for the resolution of a racemic acid with a chiral base, and the choice of acid will depend both on the ease of separation of the diastereomeric salts and, of course, on the availability of the acid for the scale of the resolution involved. Resolution methods of this kind 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:



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

Qne 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 effect 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 (Section 9-2), 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

A disadvantage of resolutions of this type is that the more reactive enantiomer usually is not recoverable from the reaction mixture.

The crystallization procedure employed by Pasteur for his classical resolution of (±)-tartaric acid (Section 5-1C) 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.

Even when a successful resolution is achieved, some significant problems remain. For instance, the resolution itself does not provide information on the actual configuration of the (+) or (-) enantiomer. This must be determined by other means (see Section 19-5). Also, it is not possible to tell the enantiomeric purity (optical purity) of the resolved enantiomers without additional information. This point is discussed further in the next section.

Exercise

1. Indicate the reagents you would 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.

1. 1 -phenyl-2-propanamine
2. 2,3-pentadienedioic acid
3. 1 -phenylethanol

Solutions:

1.

a. React 1-phenyl-2-propanamine racemic mixture with a chiral acid such as (+)-tartaric acid (*R*, *R*).

Reaction will produce a mixture of diastereomeric salts (i.e. *R*, *R*, *R* and *S*, *R*, *R*).

Separate diastereomers through crystallization.

Treat salt with strong base (e.g. KOH) to recover the pure enantiomeric amine.

b. React 2,3-pentadienedioic acid mixture with a chiral base such as (*R*)-1-phenylethylamine.

Reaction will produce a mixture of diastereomeric salts.

Separate diastereomers through crystallization.

Treat salt with strong acid (e.g. HCl) to recover the pure enantiomer acid.

c. React 1-phenylethanol mixture with 1,2-benzenedicarboxylic anhydride.

Reaction will produce a mixture of diastereomeric salts.

Separate diastereomers through crystallization.

Then alkaline hydrolysis treatment to recover the pure enantiomeric alcohol.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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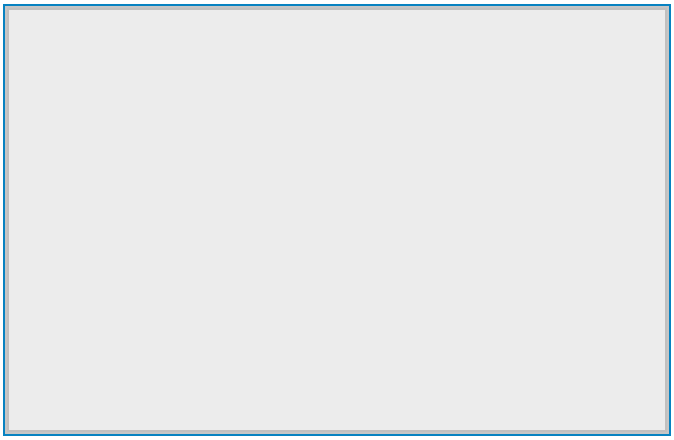
4.9: Stereochemistry of Molecules with Three or More Asymmetric Carbons

Learning Objective

- interpret the stereoisomerism of compounds with three or more chiral centers

Possible Number of Stereoisomers

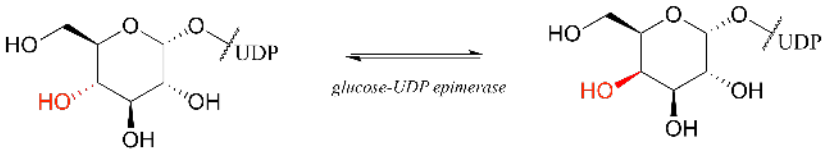
In general, a structure with *n* stereocenters will have 2^n different stereoisomers. (We are not considering, for the time being, the stereochemistry of double bonds – that will come later). For example, let's consider the glucose molecule in its open-chain form (recall that many sugar molecules can 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.

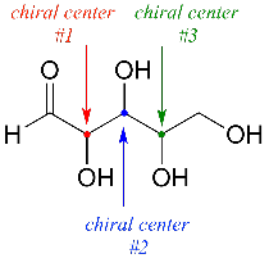
The epimer term is useful because in biochemical pathways, compounds with multiple chiral centers are isomerized at one specific center by enzymes known as **epimerases**. Two examples of epimerase-catalyzed reactions are below.

ribulose-5-phosphate xylulose-5-phosphate



glucose-UDP galactose-UDP

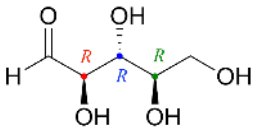
Now, let's extend our analysis to a sugar molecule with three chiral centers. Going through all the possible combinations, we come up with eight total stereoisomers - four pairs of enantiomers.



possible configurations:

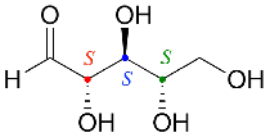
RRR RRS RSR RSS
SSS SSR SRS SRR

Let's draw the *RRR* stereoisomer. Being careful to draw the wedge bonds correctly so that they match the *RRR* configurations, we get:



RRR stereoisomer

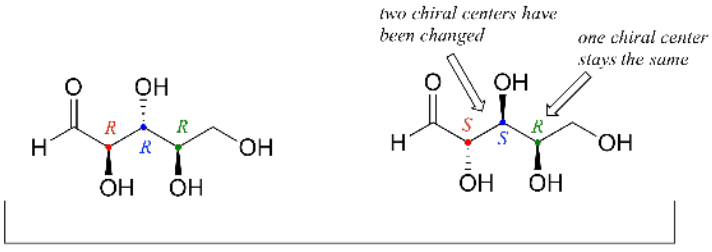
Now, using the above drawing as our model, drawing any other stereoisomer is easy. If we want to draw the enantiomer of *RRR*, we don't need to try to visualize the mirror image, we just start with the *RRR* structure and invert the configuration at *every* chiral center to get *SSS*.



SSS stereoisomer

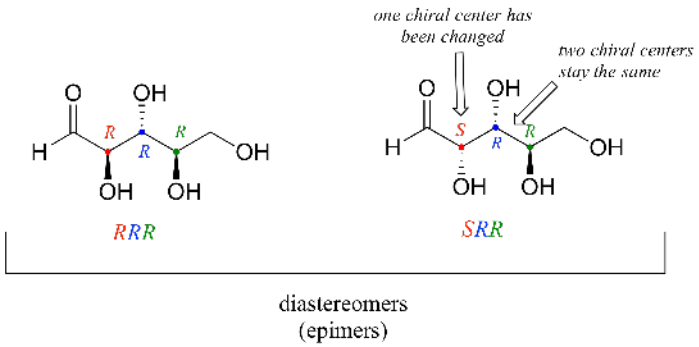
Try making models of *RRR* and *SSS* and confirm that they are in fact nonsuperimposable mirror images of each other.

There are six diastereomers of *RRR*. To draw one of them, we just invert the configuration of at least one, but not all three, of the chiral centers. Let's invert the configuration at chiral center 1 and 2, but leave chiral center 3 unchanged. This gives us the *SSR* configuration.



diastereomers

One more definition at this point: diastereomers which differ at only a single chiral center are called **epimers**. For example, *RRR* and *SRR* are epimers:



The *RRR* and *SSR* stereoisomers shown earlier are diastereomers but *not* epimers because they differ at *two* of the three chiral centers.

Example 4.9.1

1. Draw the structure of the *enantiomer* of the *SRS* stereoisomer of the sugar used in the previous example.
2. List (using the *XXX* format, not drawing the structures) all of the epimers of *SRS*.
3. List all of the stereoisomers that are diastereomers, but not epimers, of *SRS*.

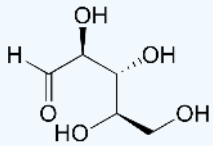
Solutions to exercises

Solution

Add text here.

Example 4.9.2

The sugar below is one of the stereoisomers that we have been discussing.



?

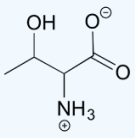
The only problem is, it is drawn with the carbon backbone in a different orientation from what we have seen. Determine the configuration at each chiral center to determine which stereoisomer it is.

Exercise 4.9.3

Draw the enantiomer of the xylulose-5-phosphate structure in the previous figure.

Exercise 4.9.4

The structure of the amino acid D-threonine, drawn without stereochemistry, is shown below. D-threonine has the (S) configuration at both of its chiral centers. Draw D-threonine, it's enantiomer, and its two diastereomers.

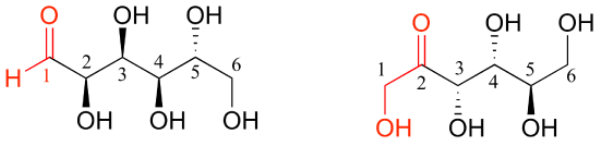


Answer

Solutions to exercises

Comparing Stereoisomerism with Structural Isomerism

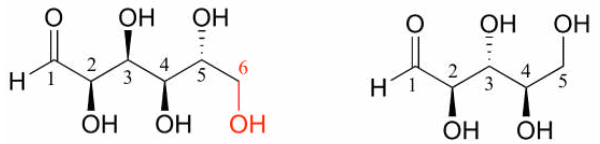
D-glucose and D-fructose are not stereoisomers, because they have different bonding connectivity: glucose has an aldehyde group, while fructose has a ketone. The two sugars do, however, have the same molecular formula, so by definition they are constitutional isomers.



D-glucose D-fructose

(constitutional isomers)

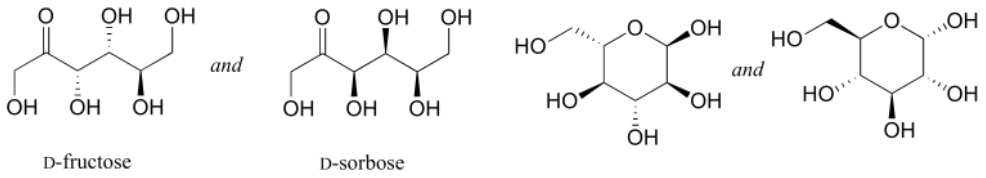
D-glucose and D-ribose are not isomers of any kind, because they have different molecular formulas.



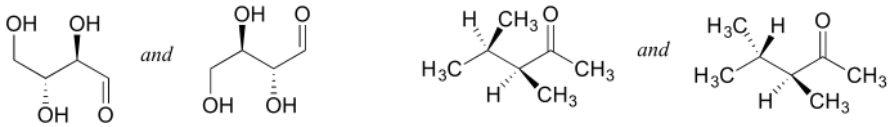
D-glucose D-ribose

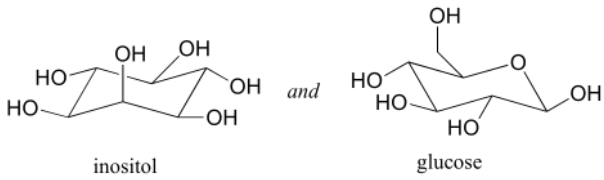
(not isomers)

Exercise 5: Identify the relationship between each pair of structures. Your choices are: not isomers, constitutional isomers, diastereomers but not epimers, epimers, enantiomers, or same molecule



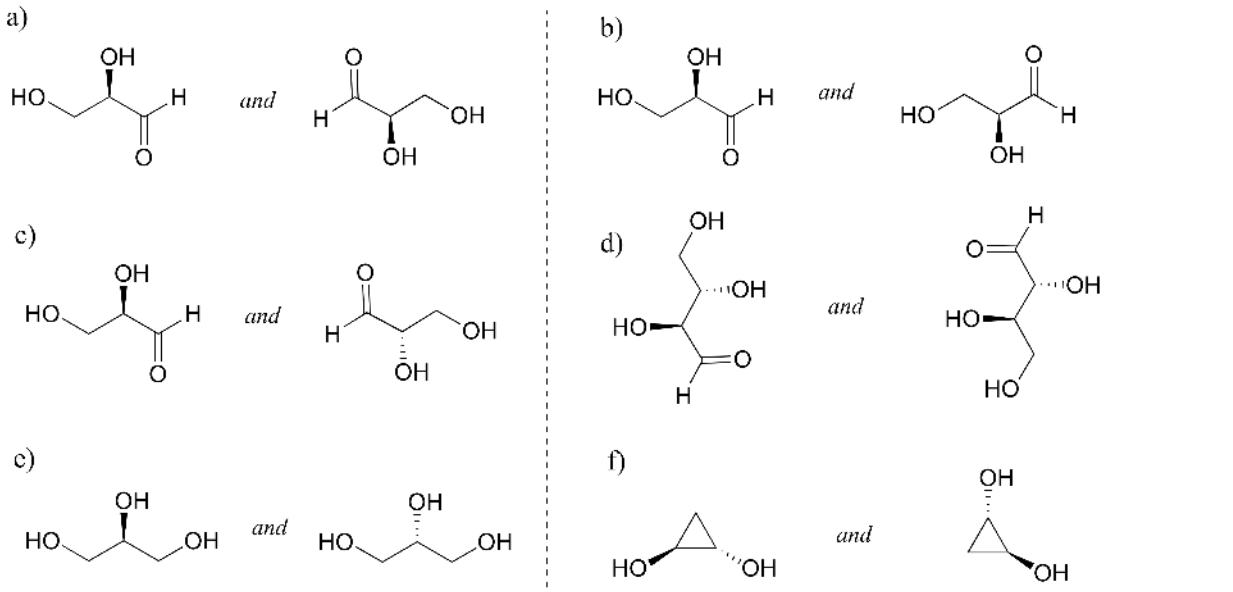
D-fructose D-sorbose





inositol glucose

Exercise 6: Identify the relationship between each pair of structures. *Hint* - figure out the configuration of each chiral center.



Solutions to exercises

Kahn Academy video tutorial on stereoisomeric relationships

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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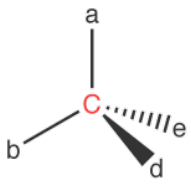
4.10: Absolute and Relative Configuration - the distinction

Learning Objective

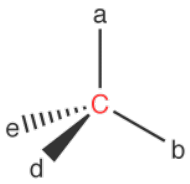
- compare and contrast absolute configuration with relative configuration

Absolute Configuration

The absolute configuration at a chiral center in a molecule is a time-independent and unambiguous symbolic description of the spatial arrangement of ligands (groups) bonded to the chiral center.



1



2

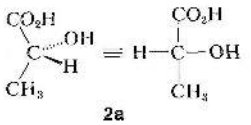
The chiral centers in 1 and 2 bear the same ligands: a,b,d, and e. However, 1 and 2 are not superimposable on each other, meaning that the arrangement of ligands around the chiral center in 1 and in 2 is different. 1 and 2 are mirror images of each other, meaning that the arrangement of ligands around the chiral center in 1 is the exact opposite of that in 2. Chiral centers in 1and 2 are said to have opposite absolute configurations.

According to R,S convention, if the absolute configuration at the chiral center in 1 is R, that at the chiral center in 2 is S or vice versa.

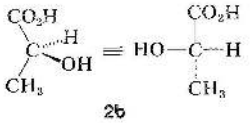
Relative Configuration

The relative configuration is the experimentally determined relationship between two enantiomers even though we may not know the absolute configuration. The sign of rotation of plane-polarized light by an enantiomer is not easily related to its configuration. This is true even for substances with very similar structures. Thus, given lactic acid, $\mathbf{CH_3CHOHCO_2H}$, with a specific rotation $\mathbf{+3.82°}$, and methyl lactate, $\mathbf{CH_3CHOHCO_2CH_3}$, with a specific rotation $\mathbf{-8.25°}$, we cannot tell from the rotation alone whether the acid and ester have the same or a different arrangement of groups about the chiral center. Their relative configurations have to be obtained by other means.

If we convert (+)-lactic acid into its methyl ester, we can be reasonably certain that the ester will be related in configuration to the acid, because esterification should not affect the configuration about the chiral carbon atom. It happens that the methyl ester so obtained is levorotatory, so we know that (+)-lactic acid and (−)-methyl lactate have the same relative configuration at the asymmetric carbon, even if they possess opposite signs of optical rotation. However, we still do not know the absolute configuration; that is, we are unable to tell which of the two possible configurations of lactic acid, **2*a*** or **2*b***, corresponds to the dextro or (+)-acid and which to the levo or (−)-acid:



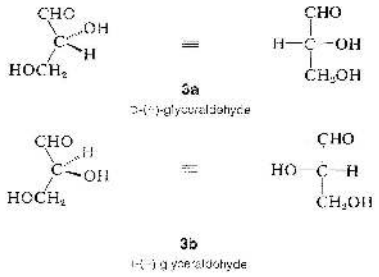
2a



2b

Until 1956, the absolute configuration of no optically active compound was known. Instead, configurations were assigned relative to a standard, *glyceraldehyde*, which originally was chosen by E. Fischer (around 1885) for the purpose of correlating the

configuration of carbohydrates. Fischer arbitrarily assigned the configuration **3*a*** to dextrorotatory glyceraldehyde, which was known as ***D*-(+)-glyceraldehyde**. The levorotatory enantiomer, **3*b***, is designated as ***L*-(−)-glyceraldehyde**. (If you are unsure of the terminology ***D*** and ***L***, or of the rules for writing Fischer projection formulas, review Sections 5-3C and 5-4.)



The configurations of many compounds besides sugars now have been related to glyceraldehyde, including **α**-amino acids, terpenes, steroids, and other biochemically important substances. Compounds whose configurations are related to ***D*-(+)-glyceraldehyde** are said to belong to the ***D*** series, and those related to ***L*-(−)-glyceraldehyde** belong to the ***L*** series.

At the time the choice of absolute configuration for glyceraldehyde was made, there was no way of knowing whether the configuration of (+)-glyceraldehyde was in reality **3*a*** or **3*b***. However, the choice had a **50%** chance of being correct, and we now know that **3*a***, the ***D*** configuration, is in fact the correct configuration of (+)-glyceraldehyde. This was established through use of a special x-ray crystallographic technique, which permitted determination of the absolute disposition of the atoms in space of sodium rubidium (+)-tartrate. The configuration of (+)-tartaric acid (Section 5-5) previously had been shown by chemical means to be opposite to that of (+)-glyceraldehyde. Consequently the absolute configuration of any compound now is known once it has been correlated directly or indirectly with glyceraldehyde. For example,

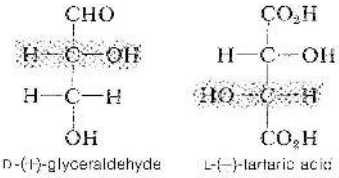
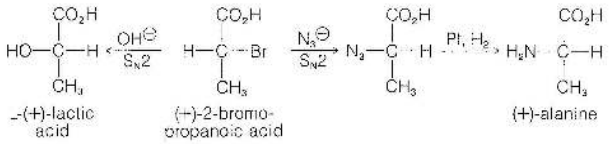
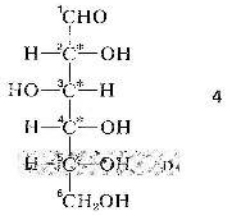


Figure below whereby the configuration of (+)-lactic acid is related to the amino acid (+)-alanine. Because (+)-lactic acid has been related to ***L*-(−)-glyceraldehyde**, it follows that the absolute configurations are ***L*-(+)-lactic acid** and ***L*-(+)-alanine**.



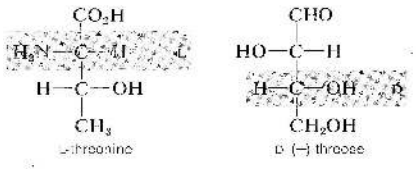
Chemical transformation showing how the configuration of natural (+)*-alanine has been related to* ***L*-(+)-*lactic acid and hence to ***L*-(−)-*glyceraldehyde. The transformations shown involve two* S_N2 *reactions, each of which is stereospecific and inverts the configuration (Section 8-5). Reduction of the azide group leaves the configuration unchanged.*

When there are several chiral carbons in a molecule, the configuration at one center usually is related directly or indirectly to glyceraldehyde, and the configurations at the other centers are determined relative to the first. Thus in the aldehyde form of the important sugar, (+)-glucose, there are *four* chiral centers, and so there are $2^4 = 16$ possible stereoisorners. The projection formula of the isomer that corresponds to the aldehyde form of natural glucose is **4**. By convention for sugars, the configuration of the *highest-numbered chiral carbon* is referred to glyceraldehyde to determine the overall configuration of the molecule. For glucose, this atom is C_5, next to the CH_2OH group, and has the hydroxyl group on the right. Therefore, naturally occurring glucose, which has a (+) rotation, belongs to the ***D*** series and is properly called ***D*-(+)-glucose**:



4

However, the configurations of α-amino acids possessing more than one chiral carbon are determined by the *lowest*-numbered chiral carbon, which is the carbon *alpha* to the carboxyl group. Thus, even though the natural α-amino acid, threonine, has exactly the same kind of arrangement of substituents as the natural sugar, threose, threonine by the amino-acid convention belongs to the L-series, whereas threose by the sugar convention belongs to the D-series:



A serious ambiguity arises for compounds such as the active tartaric acids. If the amino-acid convention is used, (+)-tartaric acid falls in the D series; by the sugar convention, it has the L configuration. One way out of this dilemma is to use the subscripts s and g to denote the amino-acid or carbohydrate conventions, respectively. Then the absolute configuration of (+)-tartaric acid can be designated as either D_s-(+)-tartaric acid of L_g-(+)-tartaric acid.

Contributors and Attributions

- Gamini Gunawardena from the OChemPal site (Utah Valley University)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition*. W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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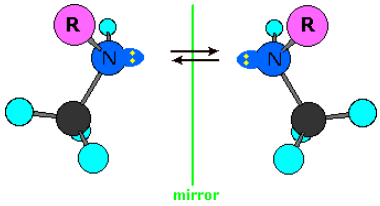
4.11: Chirality at Nitrogen, Phosphorus, and Sulfur

Learning Objective

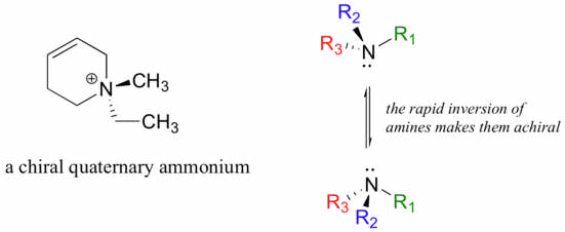
- interpret the stereoisomerism of compounds with nitrogen, phosphorus, or sulfur as chiral centers

Stereogenic Nitrogen

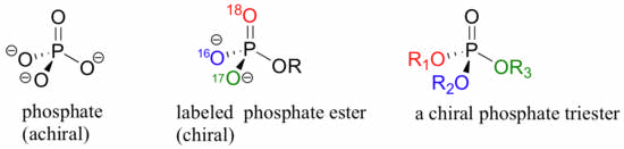
Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram (the remainder of the molecule is represented by R, and the electron pair is colored yellow). If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. 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. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of R and S configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. The take-home message is that nitrogen does not contribute to isolable stereoisomers.



Asymmetric quaternary ammonium groups are also chiral. Amines, however, are not chiral, because they rapidly invert, or turn 'inside out', at room temperature.



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.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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4.12: Biochemistry of Enantiomers

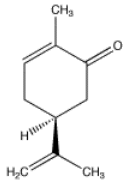
Learning Objective

- recognize and explain biochemical applications of chirality

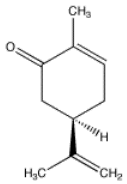
Some Chiral Organic Biomolecules

There are a number of important biomolecules that could occur as enantiomers, including amino acids and sugars. In most cases, only one enantiomer occurs (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 H2O, 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 H2O, misc EtOH, MeOH
$[\alpha]_D = -62.46°$

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.

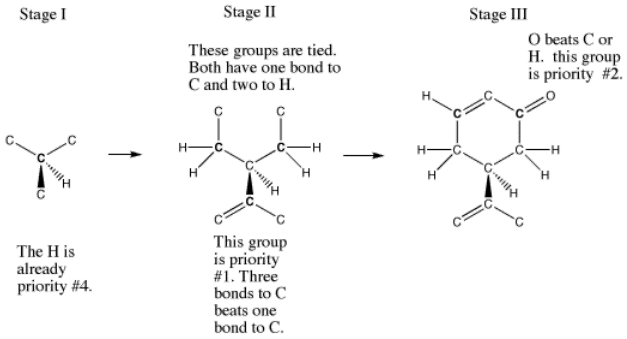
Note that (+)-carvone is the same thing as (S)-carvone. The (+) designation is based on its positive optical rotation value, which is experimentally measured. The (S) designation is determined by the Cahn-Ingold-Prelog rules for designating stereochemistry, which deal with looking at the groups attached to a chiral center and assigning priority based on atomic number. However, carvone's chiral center actually has three carbons attached to it; they all have the same atomic number. We need a new rule to break the tie.

- If two substituent groups have the same atomic number, go one bond further to the next atom.
- If there is a difference among the second tier of atoms, stop.
- The group in which you have encountered a higher atomic number gets the highest priority.
- If there is not a clear difference, proceed one additional bond to the next set of atoms, and so on, until you find a difference.

In carvone, this decision tree works as follows:

- The chiral center is connected to a H, a C, a C and a C.
- The H is lowest priority.
- One C eventually leads to a C=O. However, at the second bond from the chiral center, this C is connected to a C and two H's.
- A second C is also part of the six-membered ring, but the C=O is farther away in this direction. At the second bond from the chiral center, this C is connected to a C and two H's, just like the first one.
- The third C is part of a little three-carbon group attached to the six-membered ring. At the second bond from the chiral center, it is connected to only one H and has two bonds to another C (this is counted as two bonds to C and one to H).

- Those first two carbon groups are identical so far.
- However, the third group is different; it has an extra bond to C, whereas the others have an extra bond to H. C has a higher atomic number than H, so this group has higher priority.
- The second-highest priority is the branch that reaches the oxygen at the third bond from the chiral center.

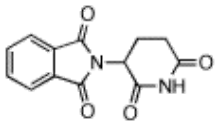


Comparing atoms step-by-step to assign configuration.

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 different shape complimentarity is not surprising, just as it isn't surprising that a left hand only fits into a left handed baseball glove and not into a right handed one.



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.

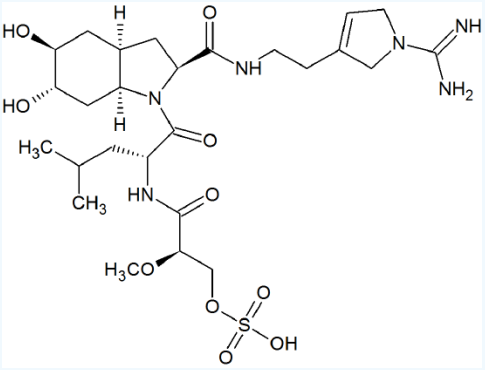
- Enantiomers may have very different biological properties.
- Obtaining enantiomerically pure compounds is very important in medicine and the pharmaceutical industry.

Exercises

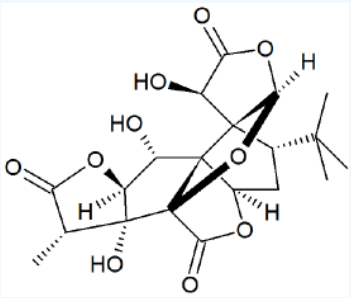
1. Draw the two enantiomeric forms of 2-butanol, $CH_3CH(OH)CH_2CH_3$. Label their configurations.

2. Sometimes, compounds have many chiral centers in them. For the following compounds, identify four chiral centers in each, mark them with asterisks, and identify each center as R or S configuration.

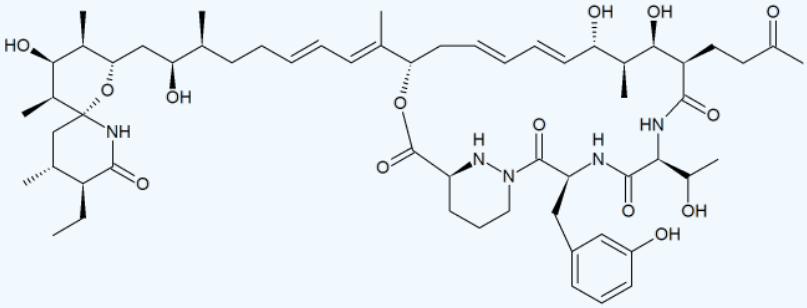
The following is the structure of dysinosin A, a potent thrombin inhibitor that consequently prevents blood clotting.



Ginkgolide B (below) is a secondary metabolite of the ginkgo tree, extracts of which are used in Chinese medicine.

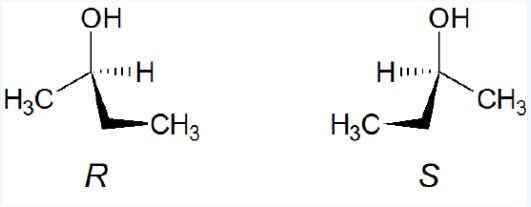


Sanglifehrin A, shown below, is produced by a bacteria that may be found in the soil of coffee plantations in Malawi. It is also a promising candidate for the treatment of organ transplant patients owing to its potent immuno-suppressant activity.

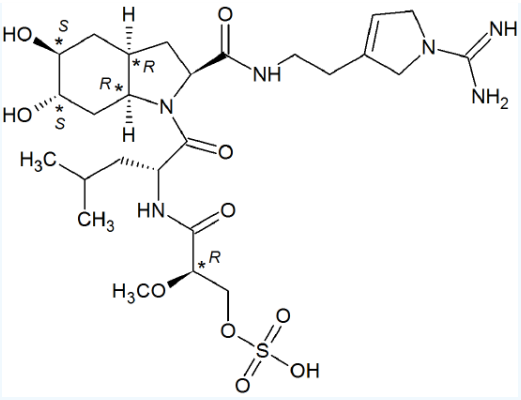


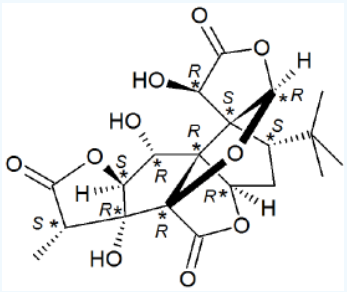
Solution

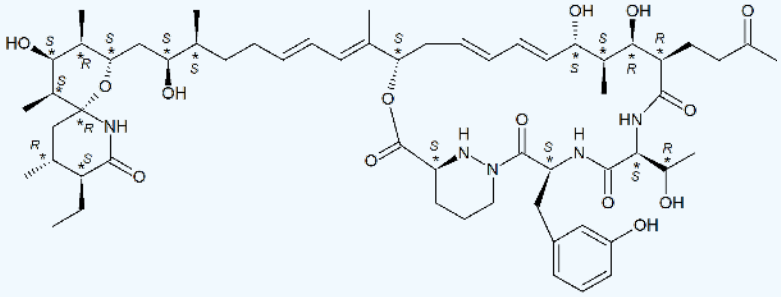
1.



2.







Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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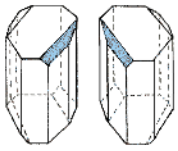
4.13: 6.13 The Discovery of Enantiomers

Learning Objective

- describe Jean Baptiste Biot and Louis Pasteur's contributions to the understanding of optical isomers

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.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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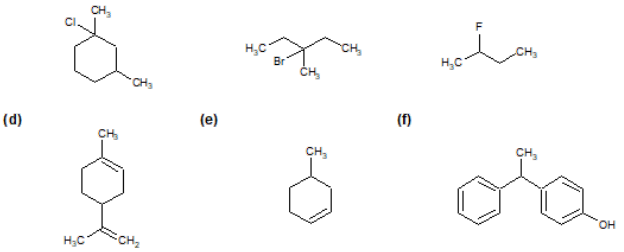
4.14: Additional Exercises

6-1 For the following compounds, star (*) each chiral center, if any.

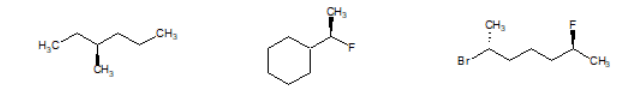
(a) (b) (c)



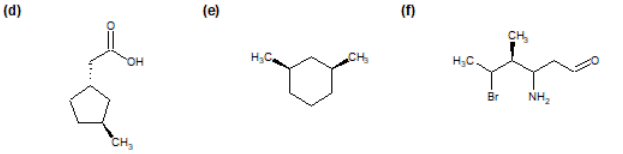
(d) (e) (f)

6-2 For the following compounds, identify the *R* or *S* configuration of each chiral carbon atom.

(a) (b) (c)



(d) (e) (f)



6-3 Draw out the following molecules, including stereocenters.

a) (2R,4S,6R)-2-bromo-6-chloro-4-methylheptane

b) (4R)-4-bromopent-1-ene

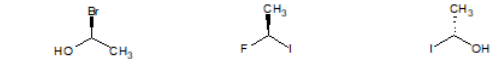
c) (1R,2R,3S)-1-fluoro-2,3-dimethylcyclohexane

d) (3S)-3-methylcyclopent-1-ene

(R) and (S) Nomenclature of Asymmetric Carbon Atoms

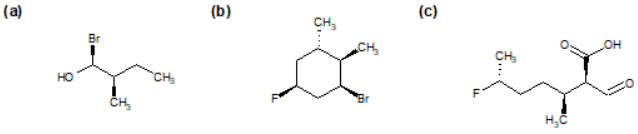
6-4 For the following compounds, assign *R* or *S* configurations for each stereocenter.

(a) (b) (c)

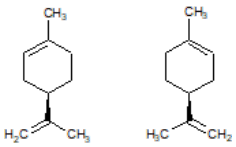


6-5 For the following compounds, assign *R* or *S* configurations for each stereocenter.

(a) (b) (c)

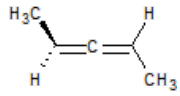


6-6 Identify each molecule as either (*R*)- or (*S*)-Limonene.



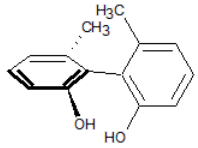
Chiral Compounds Without Asymmetric Atoms

6-7 Explain why the following compound is optically active.



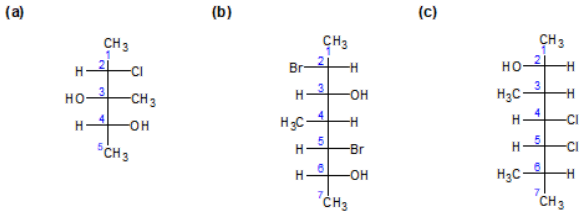
6-8 Does the following compound contain a chiral center? Is it a chiral molecule?

6-9 Why is this biaryl compound shown below considered chiral, despite having no chiral center?

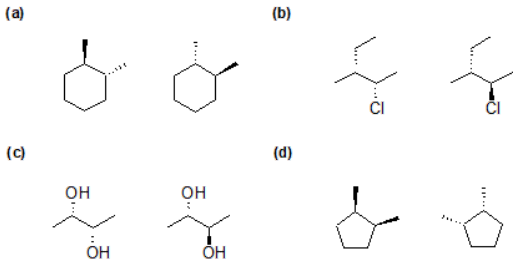


Fischer Projections and Diastereomers

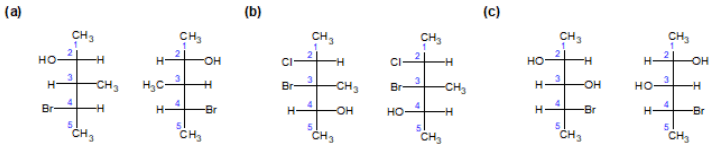
6-10 For the following Fischer projections, identify the configuration (*R* or *S*) of all chiral centers (some atoms may not be chiral centers).



6-11 For the following pairs of compounds, identify whether they are enantiomers, diastereomers, or the same compound.



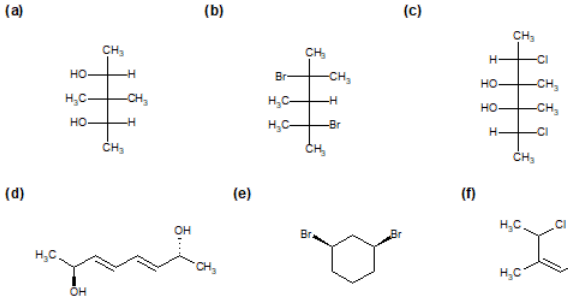
6-12 For the following pairs of compounds, identify whether they are enantiomers, diastereomers, or the same compound.



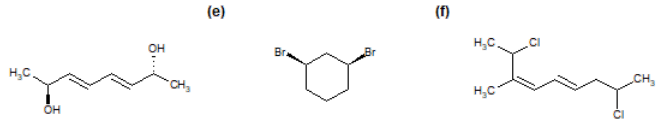
Meso Compounds

6-13 For the following compounds, identify whether they are meso or not meso.

(a) (b) (c)

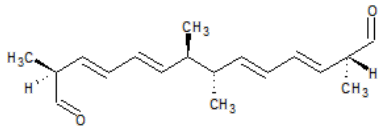


(d) (e) (f)



6-14 Are meso compounds optically active? Explain your answer.

6-15 Is the following compound meso or not meso?



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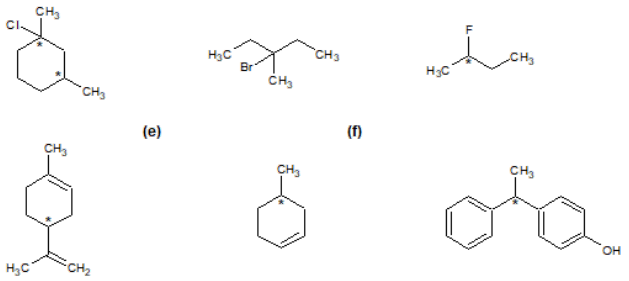
4.15: Solutions to Additional Exercises

Chirality

6-1

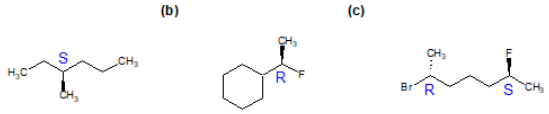
(a) (b) (c)



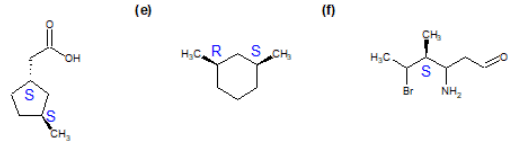
(d) (e) (f)

6-2

(a) (b) (c)

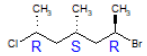


(d) (e) (f)



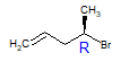
6-3

(a)



(2*R*,4*S*,6*R*)-2-bromo-6-chloro-4-methylheptane

(b)



(4*R*)-4-bromopent-1-ene

(c)

(1*R*,2*R*,3*S*)-1-fluoro-2,3-dimethylcyclohexane

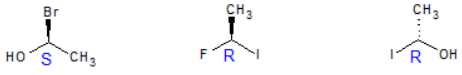
(d)

(3*S*)-3-methylcyclopent-1-ene

(R) and (S) Nomenclature of Asymmetric Carbon Atoms

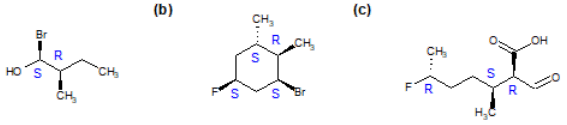
6-4

(a) (b) (c)

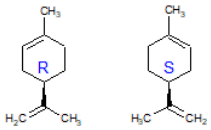


6-5

(a) (b) (c)



6-6



Chiral Compounds Without Asymmetric Atoms

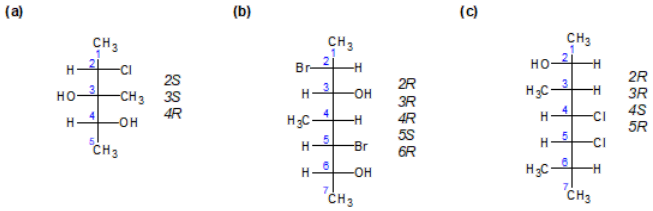
6-7 Though the molecule does not contain a chiral carbon, it is chiral as it is non-superimposable on its mirror image due to its twisted nature (the twist comes from the structure of the double bonds needing to be at 90° angles to each other, preventing the molecule from being planar). This allows it to be optically active.

6-8 The molecule does not contain a chiral center; however, it is a chiral molecule as it is non-superimposable on its mirror image.

6-9 In the case of this biaryl molecule, the large bulky substituents, located at the ortho positions relative to the sigma bond in the middle, experience enough steric interference with each other to create a large energy barrier to free rotation around the C-C sigma bond. Thus, the molecule cannot freely rotate to its other conformations and is non-superimposable on its mirror image.

Fischer Projections and Diastereomers

6-10



6-11

a) Enantiomers

b) Diastereomers

c) Diastereomers

d) Same compound

6-12

a) Enantiomers

b) Diastereomers

c) Diastereomers

Meso Compounds

6-13

a) Meso

b) Not meso

c) Meso

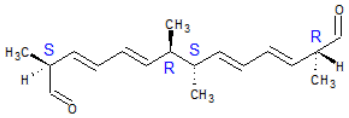
d) Meso

e) Meso

f) Not meso

6-14 Meso compounds are not optically active as they can be superimposed on their mirror images, making them achiral (which are not optically active). The stereocenters on one half of the molecule will rotate light one direction, while the other half of the molecule will rotate light the opposite direction, giving a net rotation of zero and making the molecule optically inactive.

6-15 The compound is meso, since the opposing stereocenters have opposite absolute configurations and if the molecule is rotated about the sigma bond in the middle, you can see that the two halves of the compound are mirror images of each other.



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CHAPTER OVERVIEW

5: An Introduction to Organic Reactions using Free Radical Halogenation of Alkanes

Learning Objectives

After reading the chapter and completing ALL the exercises and homework, a student can be able to:

- recognize and distinguish between the four major types of organic reactions (additions, eliminations, substitutions, and rearrangements) - refer to section 5.1
- accurately and precisely use reaction mechanism notation and symbols including curved arrows to show the flow of electrons - refer to section 5.2
- identify nucleophiles and electrophiles in polar reactions - refer to section 5.3
- perform calculations using the equation

$$\Delta G^{o} = -RT \ln K = -2.303 RT \log_{10} K \tag{5.1}$$

  and explain the relationship between equilibrium and free energy - refer to section 5.4
- calculate reaction enthalpies from bond dissociation energies - refer to section 5.5
- draw Reaction Energy Diagrams from the thermodynamic and kinetic data/information - refer to se5.6
- use a Reaction Energy Diagram to discuss transition states, Ea, intermediates & rate determining step - refer to section 5.6
- draw the transition states & intermediates of a reaction - refer to section 5.6
- describe the structure & relative stabilities of carbocations, free radicals and carbanions - refer to sections 5.7 - 5.9 respectively
- Explain the mechanism & energetics of the free-radical halogenation of alkanes - refer to section 5.10
- Predict the products of chlorination & bromination reactions of alkanes based on relative reactivity and selectivity - refer to section 5.11
- describe the similarities and differences between reactions performed in the lab with biochemical reactions - refer to section 5.12

5.1: Types of Organic Reactions
5.2: 5.2 Reaction Mechanism Notation and Symbols
5.3: the Dance of the Nucleophile and Electrophile
5.4: Describing a Reaction - Equilibrium and Free Energy Changes
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5.1: Types of Organic Reactions

Learning Objective

- recognize and distinguish between the four major types of organic reactions (additions, eliminations, substitutions, and rearrangements)

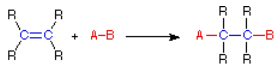
Introduction

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.

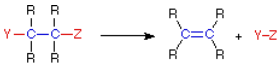
> *Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.*

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

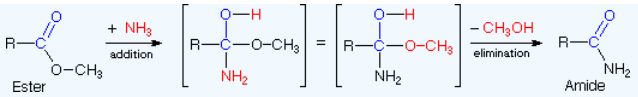
Rearrangement Reaction

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.

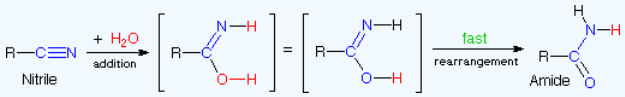
Example: substitution Reaction

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: Addition reaction

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

1. 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

1. A = Substitution; B = Elimination; C = Addition

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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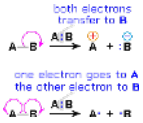
5.2: 5.2 Reaction Mechanism Notation and Symbols

Learning Objective

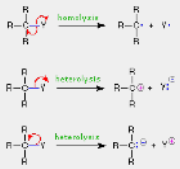
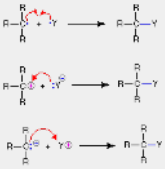
- accurately and precisely use reaction mechanism notation and symbols including curved arrows to show the flow of electrons

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**.

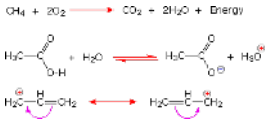
Bond-Breaking		Bond-Making
		

Other Arrow Symbols

Chemists also use arrow symbols for other purposes, and it is essential to use them correctly.

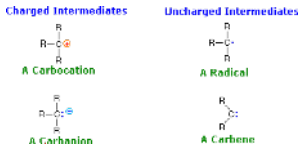
The Reaction Arrow	The Equilibrium Arrow	The Resonance Arrow

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.



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**.

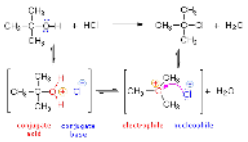
The importance of electrophile / nucleophile terminology comes from the fact that many organic reactions involve at some stage the bonding of a nucleophile to an electrophile, a process that generally leads to a stable intermediate or product. Reactions of this kind are sometimes called **ionic reactions**, 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

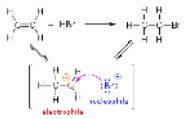
The principles and terms introduced in the previous sections can now be summarized and illustrated by the following three examples. Reactions such as these are called **ionic** or **polar** reactions, because they often involve charged species and the bonding together of **electrophiles and nucleophiles**. Ionic reactions normally take place in liquid solutions, where solvent molecules assist the formation of charged intermediates.

substitution



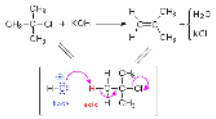
The substitution reaction shown on the left can be viewed as taking place in three steps. The first is an acid-base equilibrium, in of the alcohol. The resulting conjugate acid then loses water in a second step to give a carbocation intermediate. Finally, this e anion nucleophile to give the final product.

addition



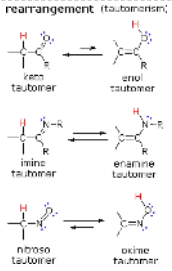
The addition reaction shown on the left can be viewed as taking place in two steps. The first step can again be considered an aci of the carbon-carbon double bond functioning as a base. The resulting conjugate acid is a carbocation, and this electrophile cc anion.

elimination



The elimination reaction shown on the left takes place in one step. The bond breaking and making operations that take place i arrows. The initial stage may also be viewed as an acid-base interaction, with hydroxide ion serving as the base and a hydrogen an acid.

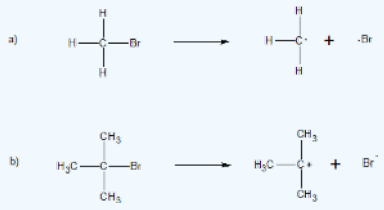
rearrangement (tautomerism)



There are many kinds of molecular rearrangements called isomerizations. The examples shown on the left are from an importar specifically, keto-enol tautomerization. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapic strongly favors one of the isomers (acetone, for example, is 99.999% keto tautomer). Even in such one-sided equilibria, evidenc comes from the chemical behavior of the compound. Tautomeric equilibria are catalyzed by traces of acids or bases that are gen

Exercise

1. Add curved arrows to explain the indicated reactivity and classify the reaction as "homolytic cleavage" or "heterolytic cleavage".



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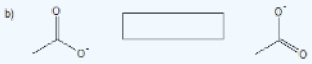
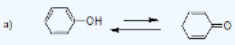
2. Add the correct arrow to each expression below using your knowledge of chemistry.

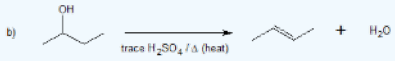
a)

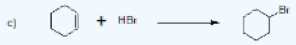
b) 

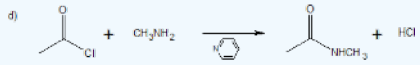
c)

3. Classify the following reactions as substituion, addition, elimination, or tautomerization (an example of isomerization).

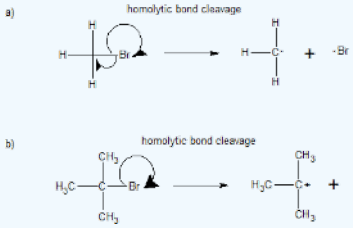
a) 

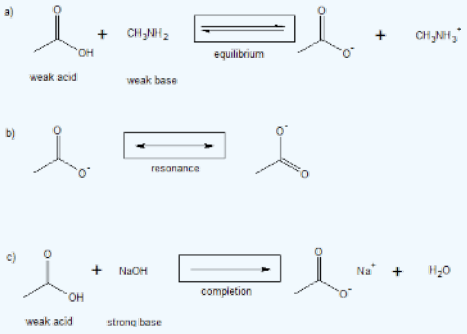
b) 

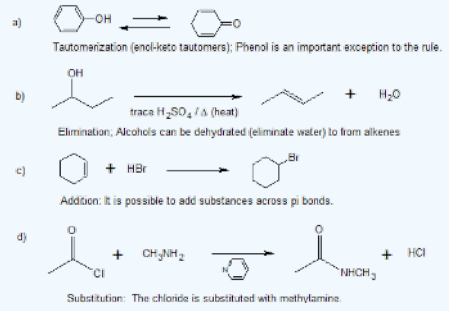
c) 

d) 

Answer

1. 

2. 

3. 

Contributors and Attributions

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5.3: the Dance of the Nucleophile and Electrophile

Learning Objective

- identify nucleophiles and electrophiles in polar reactions
- relate bond polarity to chemical reactivity

Nucleophiles and Electrophiles

The reactants of polar reactions are often called the "nucleophile" and "electrophile". These terms are related to Lewis acid-base notation, so it can be helpful to apply and transfer the knowledge and wisdom gained from this definiation of acid-base chemistry.

- Electrophile (Lewis Acid): An electron deficient atom, ion or molecule that has an affinity for an electron pair, and will bond to a base or nucleophile
- Nucleophile (Lewis Base): An atom, ion or molecule that has an electron pair that may be donated in bonding to an electrophile

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.

Enolate ions 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. Hydrocarbons carbons with pi bonds can also be nucleophiles. Reactions with carbon nucleophiles will be dealt with in later chapters In this chapter, 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: H_2O, NH_3, RNH_2, R_2NH, R_3N, ROH, RCO_2H. RSH, PR_3, $R_2C{=}CR_2$, and alkynes

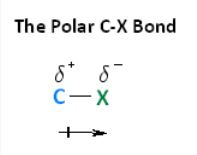
Charged Nucleophiles: RO^-, H_2N^-, RNH^-, R_2N^-, HS^-, RSe^-, Cl^-, Br^-, I^-, F^-, CN^-, N_3^-, OH^-, and RCO_2^-

Electrophiles

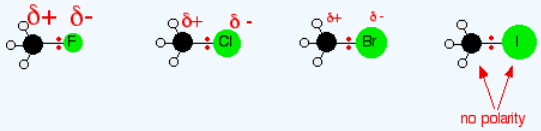
In the vast majority of polar reactions, the electrophilic atom is a carbon atom bonded to an electronegative atom, usually oxygen, nitrogen, sulfur, or a halogen. The concept of electrophilicity is relatively simple: an electron-poor atom with partial positive charge is an attractive target an electron-rich nucleophile. Electrophiles can be challenging to recognize because their partial positive charge is hidden in polar bonds and/or resonance. Allkyl halides and carbonyl groups are useful electrophiles for synthetic organic chemistry.

Electrophilicity of Alkyl Halides

With respect to electronegativity, halogens are more electronegative than carbons. This results in a carbon-halogen bond that is polarized. As shown in the image below, carbon atom has a partial positive charge, while the halogen has a partial negative charge.



Allkyl halides are useful electrophiles for synthetic organic chemistry. 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 following image shows the relative electronegativity of the halogens. 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 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

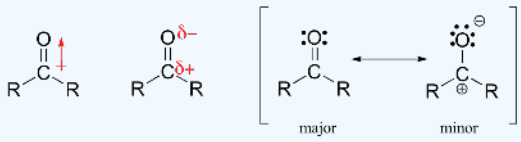
You might have thought that either of these would be more effective in the case of the carbon-fluorine bond with the quite large amounts of positive and negative charge already present. But that's not so - quite the opposite is true! The thing that governs the reactivity is the strength of the bonds which have to be broken. If is difficult to break a carbon-fluorine bond, but easy to break a carbon-iodine one. The relative electrophilicity of alkyl halides is summarized below.

Relative Electrophilicity R-I > R-Br > R-Cl > R-F

It is easier to break the weaker C-I bond.

Electrophilicity of the Carbonyl Group

The carbon atom of the carbonyl group (C=O) is electrophilic because the carbon-oxygen double bond is polar and one of the resonance contributors is ionized with a full positiv echarge on the carbonyl carbon. Oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Both of these factors combine to increase the electrophilicity of carbonyl groups. Carbonyl chemistry is studied in greater detail in the second semester of organic chemistry.



Exercise

1. Recognizing organic compounds as nucleophiles or electrophiles is an important first step in recognizing and learning patterns of chemical reactivity. Classify the following compounds as nucleophiles or electrophiles.

a) methoxide (CH_3O^-)

b) formaldehye (CH_2O)

c) bromocyclopentane

d) water

e) sodium cyanide

f) methanamine (CH_3NH_2)

Answer

a) charged nucleophile

b) electrophile (Carbonyl carbon has partial positive charge.)

c) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

d) neutral nucleophile

e) charge nucleophile (Don't let the cation distract us from the CN^-)

f) neutral nucleophile (The lone pair electrons on the nitrogen are nucleophilic in the same way they are Lewis bases (electron donators).

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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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5.4: Describing a Reaction - Equilibrium and Free Energy Changes

Learning Objective

- perform calculations using the equation

$$\Delta G^{o} = -RT \ln K = -2.303 RT \log_{10} K \tag{5.4.1}$$

and explain the relationship between equilibrium and free energy

Equilibrium Constant

For the hypothetical chemical reaction:

$$aA + bB \rightleftharpoons cC + dD \tag{5.4.2}$$

the equilibrium constant is defined as:

$$K_C = \frac{[C]^c[D]^d}{[A]^a[B]^b} \tag{5.4.3}$$

where the notation [A] signifies the molar concentration of species A. 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

$$\mathrm{CaH_2\,(s) + 2\,H_2O\,(g) \rightleftharpoons Ca(OH)_2\,(s) + 2\,H_2\,(g)} \tag{5.4.4}$$

is the following:

$$K_C = \frac{[H_2]^2}{[H_2O]^2} \tag{5.4.5}$$

Observe that the gas-phase species $\mathrm{H_2O}$ and $\mathrm{H_2}$ appear in the expression but the solids $\mathrm{CaH_2}$ and $\mathrm{Ca(OH)_2}$ 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

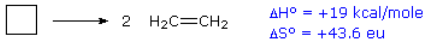
The interaction between enthalpy and entropy changes in chemical reactions is best observed by studying their influence on the equilibrium constants of reversible reactions. To this end a new thermodynamic function called Free Energy (or Gibbs Free Energy), symbol ΔG, is defined as shown in the first 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.

$$\Delta G^{o} = \Delta H^{o} - T\Delta S^{o} \tag{5.4.6}$$

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):

$$\Delta G^{o} = 19 \text{ kcal/mol} - 298(43.6) \text{ cal/mole} = 19 - 13 \text{ kcal/mole} = +6 \text{ kcal/mole}.$$

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),

$$\Delta G^{o} = 19\,kcal/mol - 473(43.6)\,cal/mole \tag{5.4.7}$$

$$= 19 - 20.6\,kcal/mole \tag{5.4.8}$$

$$= -1.6 kcal/mole. \tag{5.4.9}$$

This is now an **exergonic reaction**, and the thermal cracking of cyclobutane to ethene is known to occur at higher temperatures.

Label 'eq2' multiply defined

where R = 1.987 cal/ K mole T = temperature in K and K = equilibrium constant

Note

Equation 5.4.1 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.

Applications to Organic Reactions

The equation below can also be useful without performing any calculations.

Label 'eq2' multiply defined

Conceptually, this equation helps us compare the energetics of reaction mechanisms to predict the major products. For example, if ΔG° < 0, then K > 1, and products are favored over reactants. If ΔG° > 0, then K < 1, and reactants are favored over products. If ΔG° = 0, then K = 1, and the system is at equilibrium. Recognizing the underlying energetics of equilibrium, the stability of charged reactants and products can be used to predict reaction equilibrium. Reaction conditions can also be adjusted or controlled to shift the equilibrium in the desired direction by a range of experimental methods. A theoretical understanding of the reaction free energy and equilibrium helps us predict and design the optimum reaction conditions for a desired product.

Exercises

1. At 155°C, the equilibrium constant, K_{eq}, for the reaction

   $$\text{CH3CO2H} + \text{CH3CH2OH} <=> \text{CH3CO2CH2CH3} + \text{H2O} \tag{5.4.10}$$

   has a value of 4.0. Calculate $\Delta G°$ for this reaction at 155°C.

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

$$\Delta G^\circ = -RT \ln K_{eq} = -(8.314\ J \cdot K^{-1} \cdot mol^{-1})(428\ K) \ln(4.0) = -(8.314\ J \cdot K^{-1} \cdot mol^{-1})(428\ K)(1.386) = -4.9 \times 10^3\ J \cdot mol^{-1} = -4.9\ KJ \cdot mol^{-1}$$

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad \Delta S^\circ = (\Delta H^\circ - \Delta G^\circ)\, T = -631\ kJ - (-503\ kJ)\, 298\ K = -128\ kJ\ 298\ K = -0.430\ KJ \cdot mol^{-1} = -430\ J \cdot mol^{-1}$$

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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5.5: Homolytic Cleavage and Bond Dissociation Energies

Learning Objective

- calculate reaction enthalpies from bond dissociation energies

Introduction

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. *Solvation* is the interaction between solvent molecules and the ions or molecules dissolved in that solvent.

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

$$A-B \rightarrow A^{+} + B:^{-} \tag{5.5.1}$$

or

$$A-B \rightarrow A:^{-} + B^{+} \tag{5.5.2}$$

or homolytically, where one electron stays with each partner.

$$A-B \rightarrow A^{\bullet} + B^{\bullet} \tag{5.5.3}$$

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

$$BDE = \Delta_f H(A^{\bullet}) + \Delta_f H(B^{\bullet}) - \Delta_f H(A-B) \tag{5.5.4}$$

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: Chlorination of Methane

Consider the chlorination of methane

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{5.5.5}$$

the overall reaction thermochemistry can be calculated exactly by combining the BDEs for the bonds broken and bonds formed

$CH_4 \rightarrow CH_3\bullet + H\bullet$ BDE(CH_3-H)

$Cl_2 \rightarrow 2Cl\bullet$ BDE(Cl_2)\]

$H\bullet + Cl\bullet \rightarrow HCl$ -BDE(HCl)

$CH_3\bullet + Cl\bullet \rightarrow CH_3Cl$ -BDE(CH_3-Cl)

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{5.5.6}$$

$$\Delta H = BDE(R-H) + BDE(Cl_2) - BDE(HCl) - BDE(CH_3 - Cl) \tag{5.5.7}$$

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• → R• + HCl

The energy change for this step is equal to the difference in the BDEs in RH and HCl

$$\Delta H = BDE(R-H) - BDE(HCl) \tag{5.5.8}$$

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_0, kJ/mol	D_{298}, kJ/mol	R-H	D_0, 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-CH3)	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

$$D_o(A-B) = \frac{D_o(A-A) + D_o(B-B)}{2} + (X_A - X_B)^2 \tag{5.5.9}$$

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

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 \(\ce{{\sf{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}

2. Calculate $\Delta H°$ for the reactions given below.
   a. $CH_3CH_2OCH_3 + HI \rightarrow CH_3CH_2OH + CH_3I$
   b. $CH_3Cl + NH_3 \rightarrow CH_3NH_2 + HCl$

Answer

msub$CH_{4(g)} + 4\ F_{2(g)} \rightarrow CF_{4(g)} + 4HF_{(g)}\ \Delta H°=-416$ kcal

Bonds broken:

$$4 \text{ mol C-H bonds} \times \frac{(413 \text{ kJ})}{(1 \text{ mol})} = 1652 \text{ kJ}$$

$$4 \text{ mol F-F bonds} \times \frac{(155 \text{ kJ})}{(1 \text{ mol})} = 620 \text{ kJ}$$

Bonds formed:

$$4 \text{ mol C-F bonds} \times \frac{(x \text{ kJ})}{(1 \text{ mol})} = 4x \text{ kJ}$$

(where x = the average energy of one mole of C-F bonds in CF_4, expressed in kJ)

$$4 \text{ mol H-F bonds} \times \frac{(567 \text{ kJ})}{(1 \text{ mol})} = 2268 \text{ kJ}$$

$$\begin{aligned} \Delta H^\circ &= \Delta H^\circ(\text{bonds broken}) - \Delta H^\circ(\text{bonds formed}) \\ &= (1652 \text{ kJ} + 620 \text{ kJ}) - (4x + 2268 \text{ kJ}) \\ &= 1652 \text{ kJ} + 620 \text{ kJ} - 4x - 2268 \text{ kJ} \\ &= -1936 \text{ kJ} \end{aligned}$$

Thus,

$$\begin{aligned} 4x &= 1936 \text{ kJ} - 2268 \text{ kJ} + 620 \text{ kJ} + 1652 \text{ kJ} \\ &= 1940 \text{ kJ} \end{aligned}$$

and

$$\begin{aligned} x &= \frac{1940 \text{ kJ}}{4 \text{ mol}} \\ &= 385 \text{ kJ} \cdot \text{mol}^{-1} \end{aligned}$$

The average energy of a C-F bond in CF_4 is 385 kJ · mol^{-1}

2. $CH_3Cl + NH_3 \rightarrow CH_3NH_2 + HCl$

Reactant bonds broken	D	Product bonds formed	D
CH_3—Cl	351 kJ/mol	CH_3—NH_2	335 kJ/mol
NH_2—H	449 kJ/mol	H—Cl	432 kJ/mol
	800 kJ/mol		767 kJ/mol

$$\begin{aligned} \Delta H^\circ &= D_{\text{bonds broken}} + D_{\text{bonds formed}} \\ &= 800 \text{ kJ/mol} - 767 \text{ kJ/mol} \\ &= +33 \text{ kJ/mol} \end{aligned}$$

References

1. Gronert, S. *J. Org. Chem.* **2006**, *13*, 1209

Further Reading

MasterOrganicChemistry

Bond Strengths And Radical Stability

Contributors and Attributions

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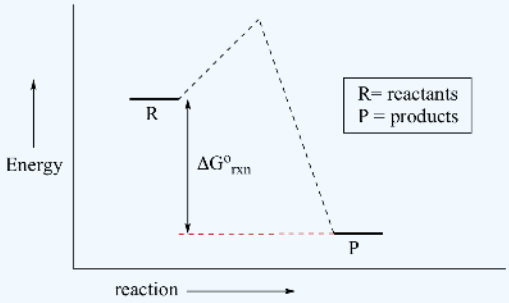
5.6: Reaction Energy Diagrams and Transition States

Learning Objective

- draw Reaction Energy Diagrams from the thermodynamic and kinetic data/information
- use a Reaction Energy Diagram to discuss transition states, Ea, intermediates & rate determining step
- draw the transition state of a reaction

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):

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{5.6.1}$$

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:

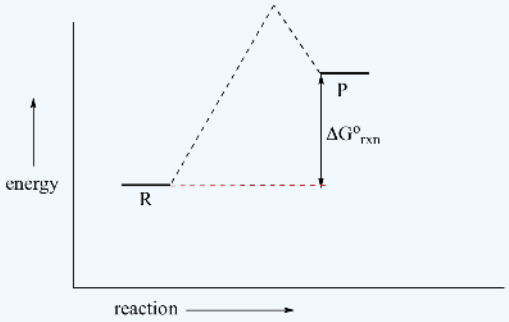
$$\Delta G^\circ = -RT \ln K_{eq} \tag{5.6.2}$$

where:

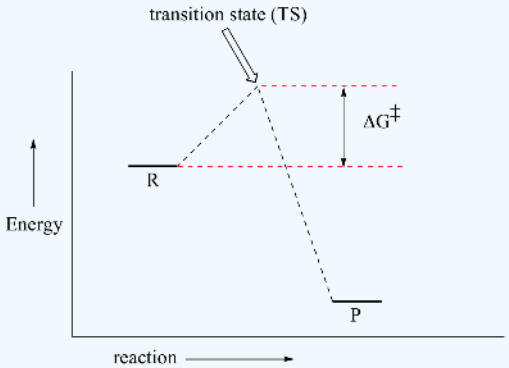
- K_{eq} = [product] / [reactant] at equilibrium
- R = 8.314 $J \times K^{-1} \times mol^{-1}$ *or* 1.987 $cal \times K^{-1} \times mol^{-1}$
- T = temperature in Kelvin (K)

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.

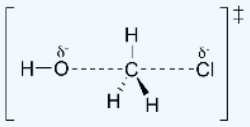


Now, let's move to kinetics. Look again at the energy diagram for exergonic reaction: although it is 'downhill' overall, it isn't a straight downhill run.



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'** ($\Delta G^{\ddagger}$). 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. 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:

$$CH_3Cl + HO^- \rightarrow CH_3OH + Cl^- \tag{5.6.3}$$



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:

rate = k[reactant 1][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 $\boldsymbol{K_{eq}}$:

$$A + B \rightleftharpoons AB \qquad K_{eq} = \frac{[AB]}{[A]\,[B]} = \frac{k_{forward}}{k_{reverse}}$$

This too should make some intuitive sense; if the forward rate constant is higher than the reverse rate constant, equilibrium should lie towards products.

Exercise

1. Which reaction is faster, $\Delta G^{\ddagger}$ = + 55 kJ/mol or $\Delta G^{\ddagger}$ = + 75 kJ/mol?

Answer

1. The + 55 kJ/mol reaction is the faster reaction.

Contributors and Attributions

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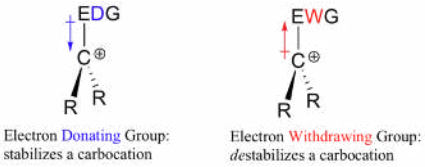
5.7: 5.7 Reactive Intermediates - Carbocations

Learning Objective

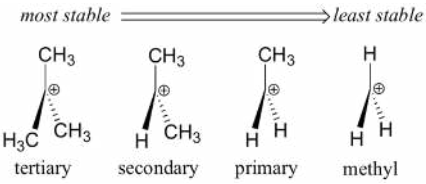
- describe the structure & relative stabilities of carbocations

Carbocations and their Stability

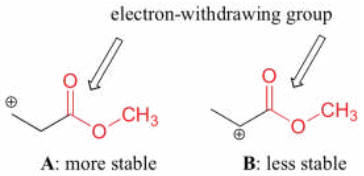
A **carbocation** is an ion with a positively-charged carbon atom. A carbocation is very electron-poor, and thus anything which donates electron density to the center of electron poverty will help to stabilize it. Conversely, a carbocation will be *destabilized* by an electron withdrawing group.



Alkyl groups are electron donating and carbocation-stabilizing because the electrons around the neighboring carbons are drawn towards the nearby positive charge, thus slightly reducing the electron poverty of the positively-charged carbon. What this means is that, in general, *more substituted carbocations are more stable*: a tert-butyl carbocation, for example, is more stable than an isopropyl carbocation. Primary carbocations are highly unstable and not often observed as reaction intermediates; methyl carbocations are even less stable.

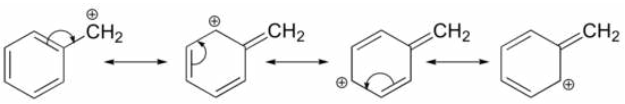


It is not accurate to say, however, that carbocations with higher substitution are *always* more stable than those with less substitution. Just as electron-donating groups can stabilize a carbocation, electron-withdrawing groups act to destabilize carbocations. Carbonyl groups are electron-withdrawing by inductive effects, due to the polarity of the C=O double bond. It is possible to demonstrate in the laboratory (see section 16.1D) that carbocation A below is more stable than carbocation B, even though A is a primary carbocation and B is secondary.



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.

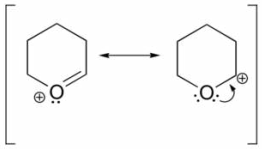
Stabilization of a carbocation can also occur through resonance effects, and as we have already discussed in the acid-base chapter, resonance effects as a rule are more powerful than inductive effects. Consider the simple case of a **benzylic** carbocation:



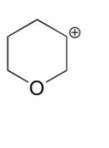
This carbocation is comparatively stable. In this case, electron donation is a resonance effect. Three additional resonance structures can be drawn for this carbocation in which the positive charge is located on one of three aromatic carbons. The positive charge is not isolated on the benzylic carbon, 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.

an allylic carbocation

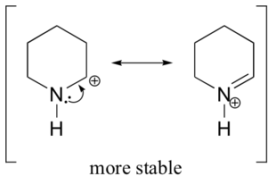
Because heteroatoms such as oxygen and nitrogen are more electronegative than carbon, you might expect that they would by definition be electron withdrawing groups that destabilize carbocations. In fact, the opposite is often true: if the oxygen or nitrogen atom is in the correct position, the overall 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:



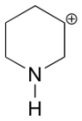
more stable



less stable
(no resonance delocalization)



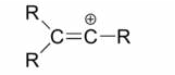
more stable



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.

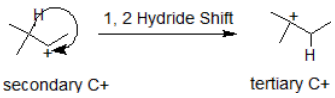
Finally, **vinylic** carbocations, in which the positive charge resides on a double-bonded carbon, are very unstable and thus unlikely to form as intermediates in any reaction.



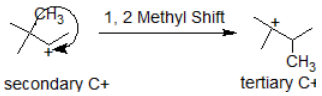
a vinylic carbocation
(very unstable)

Carbocation Rearrangements

Carbocations typically undergo rearrangement reactions from less stable structures to equally stable or more stable ones with rate constants in excess of 10^9/sec. This fact complicates synthetic pathways to many compounds, so it is important to look for carbocation rearrangements anytime they are formed. It is possible for either a neighboring hydrogen atom or methyl group to shift to the carbocation to create a more stable intermediate. In the 1,2-hydride shift shown below, the secondary carbocatin rearranges to a more stable tertiary carbocation. The numbers, 1,2- refer to the vicinal location of the rearrangement, not the nomenclature numbers.

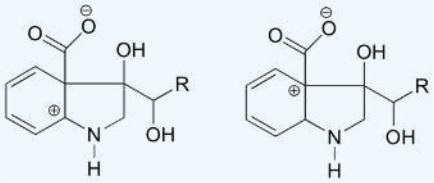


In this next example, the methyl group shifts to stabilize the carbocation.



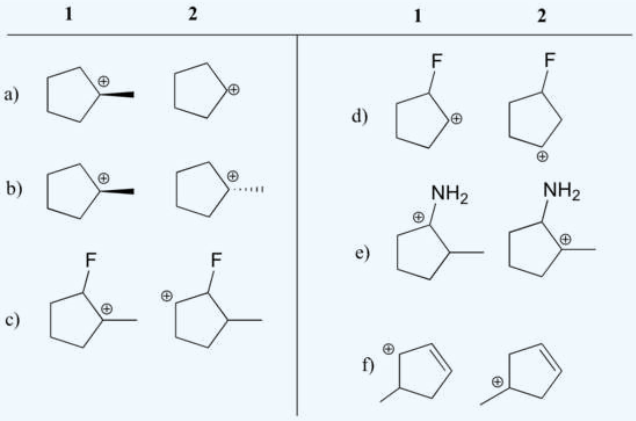
Exercise

1. In which of the structures below is the carbocation expected to be more stable? Explain.



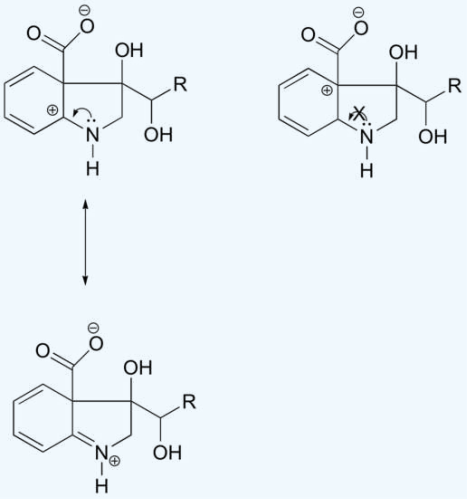
2. Draw a resonance structure of the crystal violet cation in which the positive charge is delocalized to one of the nitrogen atoms.

State which carbocation in each pair below is more stable, or if they are expected to be approximately equal. Explain your reasoning.

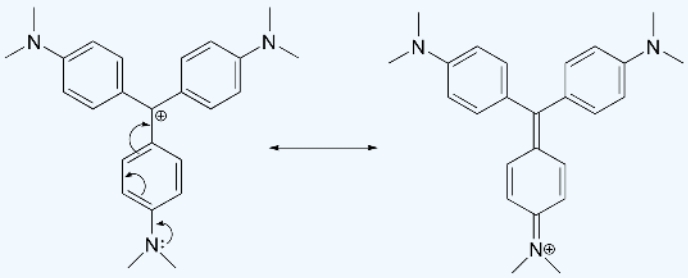


Answer

1. 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.



2.



3.

a) 1 (tertiary vs. secondary carbocation)

b) equal

c) 1 (tertiary vs. secondary carbocation)

d) 2 (positive charge is further from electron-withdrawing fluorine)

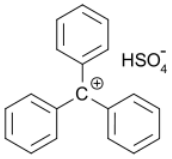
e) 1 (lone pair on nitrogen can donate electrons by resonance)

f) 1 (allylic carbocation – positive charge can be delocalized to a second carbon)

History

The history of carbocations dates back to 1891 when G. Merling[8] reported that he added bromine to tropylidene (cycloheptatriene) and then heated the product to obtain a crystalline, water-soluble material, C_7H_7Br. He did not suggest a structure for it; however, Doering and Knox[9] convincingly showed that it was tropylium (cycloheptatrienylium) bromide. This ion is predicted to be aromatic by Hückel's rule.

In 1902, Norris and Kehrman independently discovered that colorless triphenylmethanol gives deep-yellow solutions in concentrated sulfuric acid. Triphenylmethyl chloride similarly formed orange complexes with aluminium and tin chlorides. In 1902, Adolf von Baeyer recognized the salt-like character of the compounds formed.



He dubbed the relationship between color and salt formation halochromy, of which malachite green is a prime example.

Carbocations are reactive intermediates in many organic reactions. This idea, first proposed by Julius Stieglitz in 1899,[10] was further developed by Hans Meerwein in his 1922 study[11][12] of the Wagner-Meerwein rearrangement. Carbocations were also found to be involved in the S_N1 reaction, the \(E1\0 reaction, and in rearrangement reactions such as the Whitmore 1,2 shift. The chemical establishment was reluctant to accept the notion of a carbocation and for a long time the Journal of the American Chemical Society refused articles that mentioned them.

The first NMR spectrum of a stable carbocation in solution was published by Doering et al.[13] in 1958. It was the heptamethylbenzenium ion, made by treating hexamethylbenzene with methyl chloride and aluminium chloride. The stable 7-norbornadienyl cation was prepared by Story et al. in 1960[14] by reacting norbornadienyl chloride with silver tetrafluoroborate in sulfur dioxide at −80 °C. The NMR spectrum established that it was non-classically bridged (the first stable non-classical ion observed).

In 1962, Olah directly observed the tert-butyl carbocation by nuclear magnetic resonance as a stable species on dissolving tert-butyl fluoride in magic acid. The NMR of the norbornyl cation was first reported by Schleyer et al.[15] and it was shown to undergo proton-scrambling over a barrier by Saunders et al.[16]

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20. F.A. Carey, R.J. Sundberg Advanced Organic Chemistry Part A 2nd Ed.

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5.8: 5.8 Reactive Intermediates - Radicals

Learning Objective

- describe the structure & relative stabilities of free radicals

Radicals

In chemistry, a **radical** (more precisely, a **free radical**) is an atom, molecule, or ion that has unpaired valence electrons or an open electron shell, and therefore may be seen as having one or more "dangling" covalent bonds.

With some exceptions, these "dangling" bonds make free radicals highly chemically reactive towards other substances, or even towards themselves: their molecules will often spontaneously dimerize or polymerize if they come in contact with each other. Most radicals are reasonably stable only at very low concentrations in inert media or in a vacuum.

A notable example of a free radical is the hydroxyl radical (HO•), a molecule that is one hydrogen atom short of a water molecule and thus has one bond "dangling" from the oxygen. Two other examples are the carbene molecule (:CH2), which has two dangling bonds; and the superoxide anion (•O−2), the oxygen molecule O2 with one extra electron, which has one dangling bond. In contrast, the hydroxyl anion (HO−), the oxide anion (O2−) and thecarbenium cation (CH+3) are not radicals, since the bonds that may appear to be dangling are in fact resolved by the addition or removal of electrons.

Free radicals may be created in a number of ways, including synthesis with very dilute or rarefied reagents, reactions at very low temperatures, or breakup of larger molecules. The latter can be affected by any process that puts enough energy into the parent molecule, such as ionizing radiation, heat, electrical discharges, electrolysis, and chemical reactions. Indeed, radicals are intermediate stages in many chemical reactions.

Free radicals play an important role in combustion, atmospheric chemistry, polymerization, plasma chemistry, biochemistry, and many other chemical processes. In living organisms, the free radicals superoxide and nitric oxideand their reaction products regulate many processes, such as control of vascular tone and thus blood pressure. They also play a key role in the intermediary metabolism of various biological compounds. Such radicals can even be messengers in a process dubbed redox signaling. A radical may be trapped within a *solvent cage* or be otherwise bound.

Until late in the 20th century the word "radical" was used in chemistry to indicate any connected group of atoms, such as a methyl group or a carboxyl, whether it was part of a larger molecule or a molecule on its own. The qualifier "free" was then needed to specify the unbound case. Following recent nomenclature revisions, a part of a larger molecule is now called a functional group or substituent, and "radical" now implies "free". However, the old nomenclature may still occur in the literature.

Formation

The formation of radicals may involve breaking of covalent bonds homolytically, a process that requires significant amounts of energy. For example, splitting H_2 into 2H· has a $\Delta H°$ of +435 kJ/mol, and Cl_2 into 2Cl· has a $\Delta H°$ of +243 kJ/mol. This is known as the homolytic bond dissociation energy, and is usually abbreviated as the symbol $\Delta H°$. The bond energy between two covalently bonded atoms is affected by the structure of the molecule as a whole, not just the identity of the two atoms. Likewise, radicals requiring more energy to form are less stable than those requiring less energy. Homolytic bond cleavage most often happens between two atoms of similar electronegativity. In organic chemistry this is often the O-O bond in peroxide species or O-N bonds. Sometimes radical formation is spin-forbidden, presenting an additional barrier. However, propagation is a very exothermic reaction. Likewise, although radical ions do exist, most species are electrically neutral. Radicals may also be formed by single electron oxidation or reduction of an atom or molecule. An example is the production of superoxide by the electron transport chain. Early studies of organometallic chemistry, especially tetra-alkyl lead species by F.A. Paneth and K. Hahnfeld in the 1930s supported heterolytic fission of bonds and a radical based mechanism.

Depiction in chemical reactions

In chemical equations, free radicals are frequently denoted by a dot placed immediately to the right of the atomic symbol or molecular formula as follows:

$$Cl_2 \xrightarrow{UV} Cl\cdot + Cl\cdot$$

Chlorine gas can be broken down by ultraviolet light to form atomic chlorine radicals.

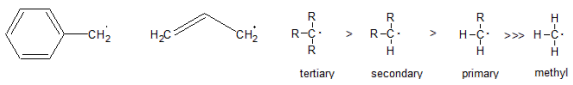
Radical reaction mechanisms use single-headed arrows to depict the movement of single electrons:

The homolytic cleavage of the breaking bond is drawn with a 'fish-hook' arrow to distinguish from the usual movement of two electrons depicted by a standard curly arrow. It should be noted that the second electron of the breaking bond also moves to pair up with the attacking radical electron; this is not explicitly indicated in this case.

Relative Stability

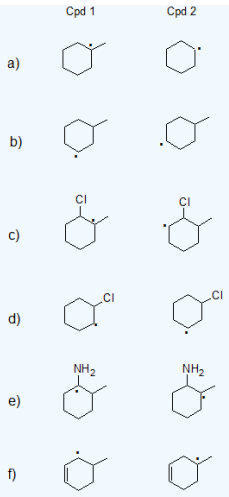
Radical alkyl intermediates are stabilized by similar physical processes to carbocations: as a general rule, the more substituted the radical center is, the more stable it is. This directs their reactions. Thus, formation of a tertiary radical ($R_3C\cdot$) is favored over secondary ($R_2HC\cdot$), which is favored over primary ($RH_2C\cdot$). Likewise, radicals next to functional groups such as carbonyl, nitrile, and ether are more stable than tertiary alkyl radicals.

Relative Stability of Carbon Radicals



Exercise

1. State which carbon radical (free radical) in each pair below is more stable or if they are expected to have comparable stability. Explain your reasoning.



Answer

1.

a) Cpd 1: Tertiary radicals are more stable than secondary radicals.

b) Cpds 1 and 2 are both secondary so they have comparable stability.

c) Cpd 1: Tertiary radicals are more stable than secondary radicals with similar effects from the Cl atom.

d) Cpd 2: Both compounds are secondary, but positive charge is further from electron-withdrawing chlorine on Cpd 2.

e) Cpd 1: Lone pair on nitrogen can donate electrons by resonance.

f) Cpd 1: Secondary allylic radicals are more stable than tertiary radicals. (Primary allylic radicals are comparable in stability to tertiary radicals.)

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5.9: Reactive Intermediates: Carbanions and Carbon Acids

Carbanions

A carbanion is an anion in which carbon has an unshared pair of electrons and bears a negative charge usually with three substituents for a total of eight valence electrons.[1] The carbanion exists in a trigonal pyramidal geometry. Formally, a carbanion is the conjugate base of a carbon acid.

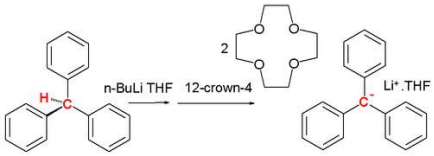
$$\mathbf{R_3C{-}H + B^- \rightarrow R_3C^- + H{-}B} \tag{5.9.1}$$

where B stands for the base. A carbanion is one of several reactive intermediates in organic chemistry.

A carbanion is a nucleophile, which stability and reactivity determined by several factors:

1. The inductive effect. Electronegative atoms adjacent to the charge will stabilize the charge;
2. Hybridization of the charge-bearing atom. The greater the s-character of the charge-bearing atom, the more stable the anion;
3. The extent of conjugation of the anion. Resonance effects can stabilize the anion. This is especially true when the anion is stabilized as a result of aromaticity.

A carbanion is a reactive intermediate and is encountered in organic chemistry for instance in the E1cB elimination reaction and in organometallic chemistry in for instance a Grignard reaction or in alkyl lithium chemistry. Stable carbanions do however exist. In 1984 Olmstead presented the lithium crown ether salt of the triphenylmethyl carbanion from triphenylmethane, n-butyllithium and 12-crown-4 at low temperatures:[2]



Adding n-butyllithium to triphenylmethane in THF at low temperatures followed by 12-crown-4 results in a red solution and the salt complex precipitates at −20 °C. The central C-C bond lengths are 145 pm with the phenyl ring propelled at an average angle of 31.2°. This propeller shape is less pronounced with a tetramethylammonium counterion.[3] One tool for the detection of carbanions in solution is proton NMR.[4] A spectrum of cyclopentadiene in DMSO shows four vinylic protons at 6.5 ppm and two methylene bridge protons at 3 ppm whereas the cyclopentadienyl anion has a single resonance at 5.50 ppm.

Carbon acids

Any molecule containing a C-H can lose a proton forming the carbanion. Hence any hydrocarbon containing C-H bonds can be considered an acid with a corresponding pKa value. Methane is certainly not an acid in its classical meaning yet its estimated pKa is 56. Compare this to acetic acid with pKa 4.76. The same factors that determine the stability of the carbanion also determine the order in pKa in carbon acids. These values are determined for the compounds either in water in order to compare them to ordinary acids, indimethyl sulfoxide in which the majority of carbon acids and their anions are soluble or in the gas phase. With DMSO the acidity window for solutes is limited to its own pKa of 35.5.

Table 1. Carbon acid acidities in pKa in DMSO [5]. Reference acids in bold.

name	formula	structural formula	pKa
Methane	**CH_4**		**~ 56**
Ethane	C_2H_6		~ 50
Anisole	C_7H_8O		~ 49
Cyclopentane	C_5H_{10}		~ 45
Propene	C_3H_6		~ 44
Benzene	C_6H_6		~ 43
Toluene	$C_6H_5CH_3$		~ 43
Dimethyl sulfoxide	$(CH_3)_2SO$		35.5
Diphenylmethane	$C_{13}H_{12}$		32.3
Aniline	**$C_6H_5NH_2$**		**30.6**
Triphenylmethane	$C_{19}H_{16}$		30.6
Xanthene	$C_{13}H_{10}O$		30
Ethanol	**C_2H_5OH**		**29.8**
Phenylacetylene	C_8H_6		28.8
Thioxanthene	$C_{13}H_{10}S$		28.6
Acetone	C_3H_6O		26.5
Acetylene	C_2H_2		25
Benzoxazole	C_7H_5NO		24.4
Fluorene	$C_{13}H_{10}$		22.6
Indene	C_9H_8		20.1
Cyclopentadiene	C_5H_6		18
Malononitrile	$C_3H_2N_2$		11.2
Hydrogen cyanide	HCN		9.2
Acetylacetone	$C_5H_8O_2$		8.95
Dimedone	$C_8H_{12}O_2$		5.23
Meldrum's acid	$C_6H_8O_4$		4.97
Acetic acid	**CH_3COOH**		**4.76**
Barbituric acid	$C_4H_2O_3(NH)_2$		4.01
Trinitromethane	$HC(NO_2)_3$		0.17
Fulminic acid	HCNO		-1.07
Carborane superacid	$HCHB_{11}Cl_{11}$		-9

Note that the anions formed by ionization of acetic acid, ethanol or aniline are not carbanions.

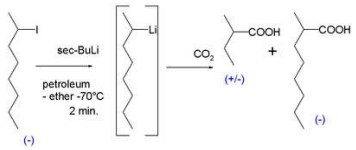
Starting from methane in Table 1, the acidity increases:

- when the anion is aromatic, either because the added electron causes the anion to become aromatic (as in indene and cyclopentadiene), or because the negative charge on carbon can be delocalized over several already-aromatic rings (as in triphenylmethane or the carborane superacid).
- when the carbanion is surrounded by strongly electronegative groups, through the partial neutralisation of the negative charge (as in malononitrile).
- when the carbanion is immediately next to a carbonyl group. The α-protons of carbonyl groups are acidic because the negative charge in the enolate can be partially distributed in the oxygen atom. Meldrum's acid and barbituric acid, historically named acids, are in fact a lactone and a lactam respectively, but their acidic carbon protons make them acidic. The acidity of carbonyl compounds is an important driving force in many organic reactions such as the aldol reaction.

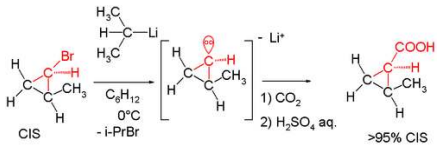
Chiral carbanions

With the molecular geometry for a carbanion described as a trigonal pyramid the question is whether or not carbanions can display chirality, because if the activation barrier for inversion of this geometry is too low any attempt at introducing chirality will end inracemization, similar to the nitrogen inversion. However, solid evidence exists that carbanions can indeed be chiral for example in research carried out with certain organolithium compounds.

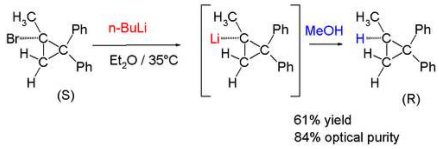
The first ever evidence for the existence of chiral organolithium compounds was obtained in 1950. Reaction of chiral 2-iodooctane with sec-butyllithium in petroleum ether at −70 °C followed by reaction with dry ice yielded mostly racemic 2-methylbutyric acid but also an amount of optically active 2-methyloctanoic acid which could only have formed from likewise optical active 2-methylheptyllithium with the carbon atom linked to lithium the carbanion:[6]



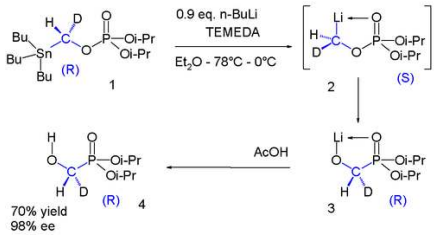
On heating the reaction to 0 °C the optical activity is lost. More evidence followed in the 1960s. A reaction of the cis isomer of 2-methylcyclopropyl bromide with sec-butyllithium again followed by carboxylation with dry ice yielded cis-2-methylcyclopropylcarboxylic acid. The formation of the trans isomer would have indicated that the intermediate carbanion was unstable.[7]



In the same manner the reaction of (+)-(S)-l-bromo-l-methyl-2,2-diphenylcyclopropane with n-butyllithium followed by quench with methanol resulted in product with retention of configuration:[8]



Of recent date are chiral methyllithium compounds:[9]



The phosphate **1** contains a chiral group with a hydrogen and a deuterium substituent. The stannyl group is replaced by lithium to intermediate **2** which undergoes a phosphate-phosphorane rearrangement to phosphorane **3** which on reaction with acetic acid givesalcohol **4**. Once again in the range of −78 °C to 0 °C the chirality is preserved in this reaction sequence.[10]

History

A carbanionic structure first made an appearance in the reaction mechanism for the benzoin condensation as correctly proposed by Clarke and Lapworth in 1907.[11] In 1904 Schlenk prepared Ph3C-NMe4+ in a quest for pentavalent nitrogen (fromTetramethylammonium chloride and Ph3CNa) [12] and in 1914 he demonstrated how triarylmethyl radicals could be reduced to carbonions by alkali metals.[13] The phrase carbanion was introduced by Wallis and Adams in 1933 as the negatively charged counterpart of the carbonium ion.[14][15]

External links

- Large database of Bordwell pKa values at www.chem.wisc.edu Link
- Large database of Bordwell pKa values at daecr1.harvard.edu Link

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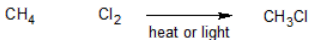
5.10: The Free-Radical Halogenation of Alkanes

Alkanes (the most basic 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 to form a haloalkane. This reaction is very important in organic chemistry because it opens a gateway to further chemical reactions.

Introduction

While the reactions possible with alkanes are few, there are many reactions that involve haloalkanes. In order to better understand the mechanism (a detailed look at the step by step process through which a reaction occurs), we will closely examine the chlorination of methane. When methane (CH_4) and chlorine (Cl_2) are mixed together in the absence of light at room temperature nothing happens. However, if the conditions are changed, so that either the reaction is taking place at high temperatures (denoted by Δ) or there is ultra violet irradiation, a product is formed, chloromethane (CH_3Cl).

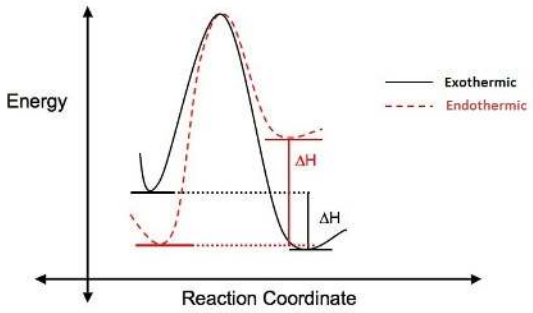


Energetics

Why does this reaction 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.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

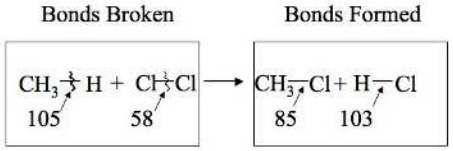
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed} \tag{5.10.1}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:



Change in enthalpy = (105 + 58) - (85 + 103)
= -25kcal/mol

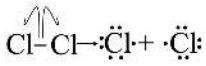
Since, the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically this reaction is favorable. In order to better understand this reaction we need to look at the mechanism (a detailed step by step look at the reaction showing how it occurs) by which the reaction occurs.

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism. The radical chain mechanism is characterized by three steps: **initiation**, **propagation** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining. The first propagation step uses up one of the products from initiation, and the second propagation step makes another one, thus the cycle can continue until indefinitely.

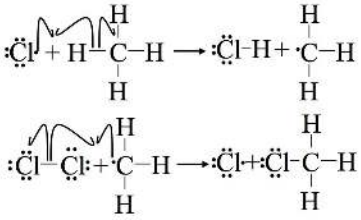
Step 1: Initiation

Initiation breaks the bond between the chlorine molecule (Cl_2). For this step to occur energy must be put in, this step is not energetically favorable. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy. It is important to note that this part of the mechanism cannot occur without some external energy input, through light or heat.

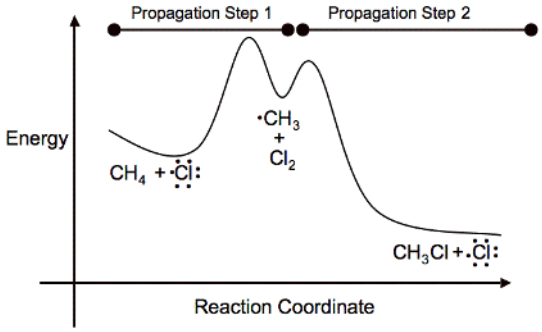


Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical combines with a hydrogen on the methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step more of the chlorine starting material (Cl_2) is used, one of the chlorine atoms becomes a radical and the other combines with the methyl radical.

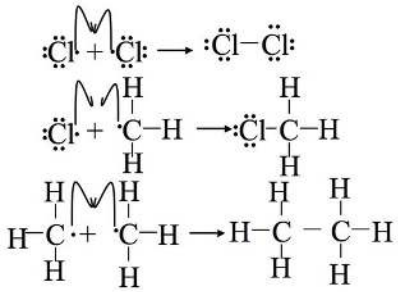


The first propagation step is endothermic, meaning it takes in heat (requires 2 kcal/mol) and is not energetically favorable. In contrast the second propagation step is exothermic, releasing 27 kcal/mol. Once the reaction is initiated, the exothermic energy released from the second propagation step provides the activation energy for the first propagation step creating a cyclic chain reaction following Le Chatelier's principle until termination.



Step 3: Termination

In the termination steps, all the remaining radicals combine (in all possible manners) to form more product (CH_3Cl), more reactant (Cl_2) and even combinations of the two methyl radicals to form a side product of ethane (CH_3CH_3).



Limitations of the Chlorination

The chlorination of methane or any other alkane does not necessarily stop after one chlorination. It may actually be very hard to get a monosubstituted chloromethane. Instead di-, tri- and even tetra-chloromethanes are formed. One way to avoid this problem is to use a much higher concentration of methane or other alkane in comparison to chloride. This reduces the chance of a chlorine radical running into a chloromethane and starting the mechanism over again to form a dichloromethane. Through this method of controlling product ratios one is able to have a relative amount of control over the product.

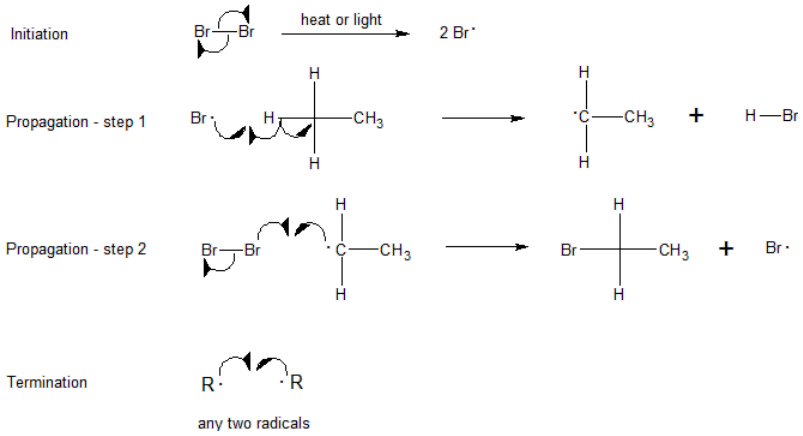
Exercises

1. Compounds other than chlorine and methane can react via free-radical halogenation. Write out the complete mechanism for the monobromination of ethane.
2. Explain how the energetically unfavorable first propagation step can continue to occur without the input of energy from an external source.
3. Which step of the radical chain mechanism requires outside energy? What can be used as this energy?
4. Use the table provided below to calculate the change in enthalpy for the monobromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Solutions

1.



2. The exothermic energy released from the second propagation step provides the activation energy for the first propagation step creating a cyclic chain reaction following Le Chatelier's principle until termination.

3. The initiation step requires energy from heat o lit. For maximum photoefficiency, the wavelength of light is correlated with bond being homolytically cleaved.

4. $\Delta H = (101 + 46) - (70 + 87)$ kcal/mol

References

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2. Phillips, Francis C. "# Researches upon the Chemical Properties of Gases." Researches upon the Chemical Properties of Gases 17 (1893): 149-236.

Outside Links

- Video of Mechanism: http://www.jbpub.com/organic-online/movies/chlormet.htm
- Wikipedia of Radical Chain Mechanism: en.Wikipedia.org/wiki/Free_radical_halogenation
- Wikipedia of Le Chatelier's Principle: en.Wikipedia.org/wiki/Le_Chatelier%27s_principle#Concentration

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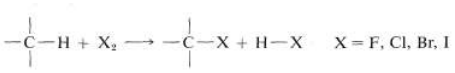
5.11: Reactivity and Selectivity

Comparing Reactivity

Given the knowledge that a particular reaction will proceed at a suitable rate, a host of practical considerations are necessary for satisfactory operation. These considerations include interference by possible side reactions that give products other than those desired, the ease of separation of the desired product from the reaction mixture, and costs of materials, apparatus, and labor. We shall consider these problems in connection with the important synthetic reactions discussed in this book.

The chlorination of saturated hydrocarbons can be induced by light, but also can be carried out at temperatures of about **300°** in the dark. Under such circumstances the mechanism is similar to that of light-induced chlorination, except that the chlorine atoms are formed by thermal dissociation of chlorine molecules. Solid carbon surfaces catalyze thermal chlorination, possibly by aiding in the cleavage of the chlorine molecules.

Direct monohalogenation of saturated hydrocarbons works satisfactorily only with chlorine and bromine. For the general reaction



the calculated ΔH^0 value is negative and very large for fluorine, negative and moderate for chlorine and bromine, and positive for iodine (see Table 4-7). With fluorine, the reaction evolves so much heat that it may be difficult to control, and products from cleavage of carbon-carbon as well as of carbon-hydrogen bonds may be obtained. The only successful, direct fluorination procedure for hydrocarbons involves diffusion of minute amounts of fluorine mixed with helium into liquid or solid hydrocarbons at low temperatures, typically **−78°** (Dry Ice temperature). As fluorination proceeds, the concentration of fluorine can be increased. The process is best suited for preparation of completely fluorinated compounds, and it has been possible to obtain in this way amounts of $(CF_3)_4C$ and $(CF_3)_3C-C(CF_3)_3$ from 2,2-dimethylpropane and 2,2,3,3-tetramethylbutane corresponding to **10-15%** yields based on the fluorine used.

Bromine generally is much less reactive toward hydrocarbons than chlorine is, both at high temperatures and with activation by light. Nonetheless, it usually is possible to brominate saturated hydrocarbons successfully. Iodine is unreactive.

Table: *Calculated Heat of Reaction for Halogenation fo Hydrocarbons*

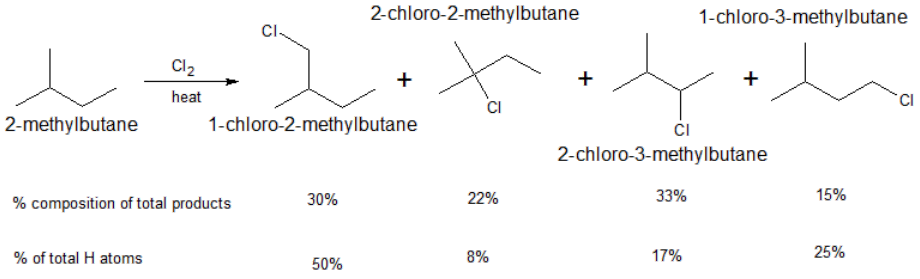
Halogen (X)	**ΔH^o (kcal/mole)[a]**
F	-116
Cl	-27
Br	-10
I	13
[a]Calculated from the bond energies of Table 4-3.	

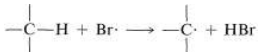
The chlorination of methane does not have to stop with the formation of chloromethane (methyl chloride). It is usual when chlorinating methane to obtain some of the higher chlorination products: dichloromethane (methylene chloride), trichloromethane (chloroform), and tetrachloromethane (carbon tetrachloride):

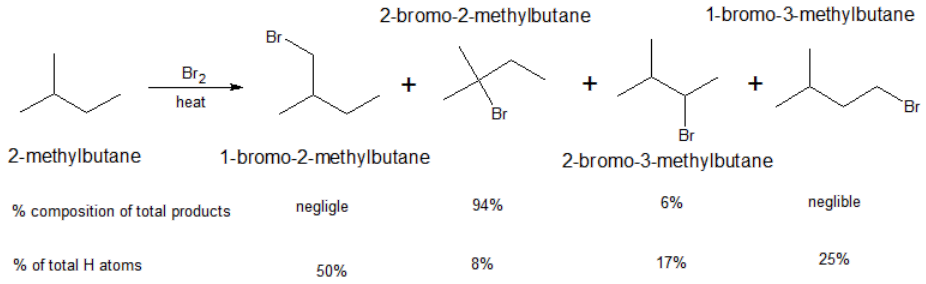
In practice, one can control the degree of substitution to a considerable extent by controlling the methane-chlorine ratio. For example, for monochlorination to predominate, a high methane-chlorine ratio is necessary such that the chlorine atoms react with CH_4 and not with CH_3Cl.

Selectivity in Alkane Halogenation

For propane and higher hydrocarbons for which more than one monosubstitution product is generally possible, difficult separation problems bay arise when a particular product is desired. For example, the chlorination of 2-methylbutane **3** at **300°** gives all four possible monosubstitution products. On a purely statistical basis, we may expect the ratio of products from 2-methylbutane to correlate with the number of available hydrogens at the various positions of substitution in the ratio 6:1:2:3 (**50%**:**8%**:**17%**:**25%**:). However, as can be seen from the strengths of bonds between hydrogen and primary, secondary, and tertiary carbons are not the same and we would expect the weaker $C-H$ bonds to preferentially react with $Cl\cdot$. As such, the proportion of the tertiary halide is about three times that expected on a statistical basis which is in accord with our expectation that the tertiary $C-H$ bond of 2-methylbutane should be the weakest of the $C-H$ bonds.



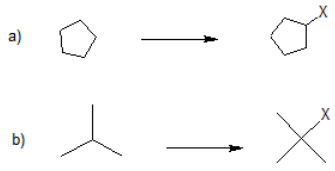
Bromine atoms are far more selective than chlorine atoms. This is not unexpected because  is endothermic, whereas corresponding reactions with a chlorine atoms usually are exothermic (data from Table 4-6). Bromine removes only those hydrogens that are relatively weakly bonded to a carbon atom. As predicted, attack of $Br\cdot$ on 2-methylbutane leads mostly to 2-bromo-2-methylbutane, some secondary bromide, and essentially no primary bromides:



When the structure of the alkane is symmetrical, then the fast reactivity of chlorination can be used for efficiency. When the structure of the alkane can produce a range of monohalogenated products, then the selectivity of bromination can be used to produce the most stable product in the greatest percentage.

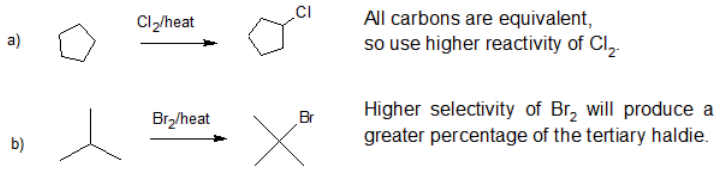
Exercises

1. Specify the optimum halogenation conditions (Cl_2/heat or Br_2/heat) to produce the indicated major product.



Solution

1.



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5.12: 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.

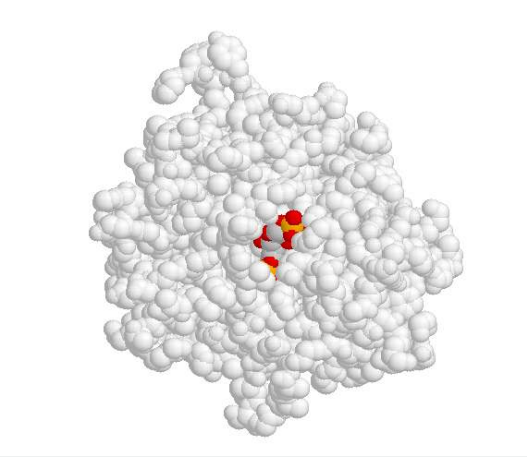
- enzyme

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.

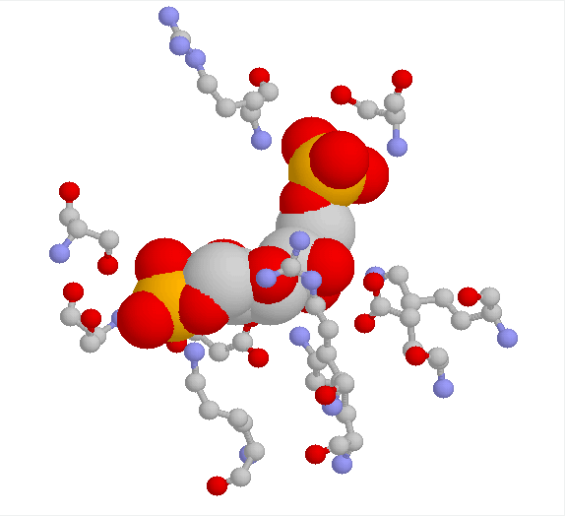
The active site

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.

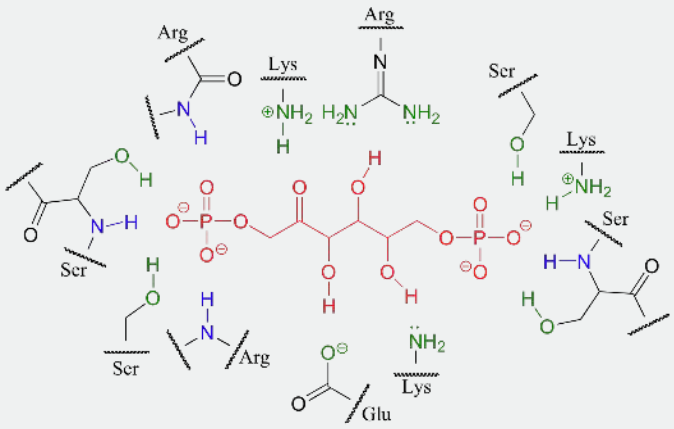


When the substrate binds to the active site, a large number of noncovalent interactions form with the amino acid residues that line the active site. The shape of the active site, and the enzyme-substrate interactions that form as a result of substrate binding, are *specific to the substrate-enzyme pair*: 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.



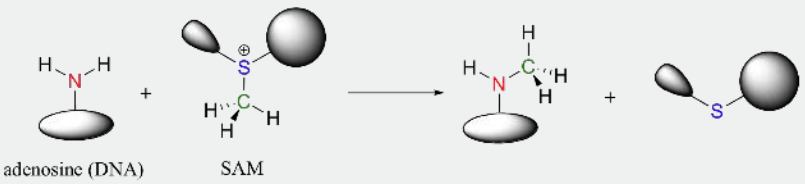
Below is a two-dimensional picture of the substrate (colored red) surrounded by hydrogen-bonding active site amino acids. Notice that both main chain and side chain groups contribute to hydrogen bonding: in this figure, main chain H-bonding groups are colored blue, and side chain H-bonding groups are 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.

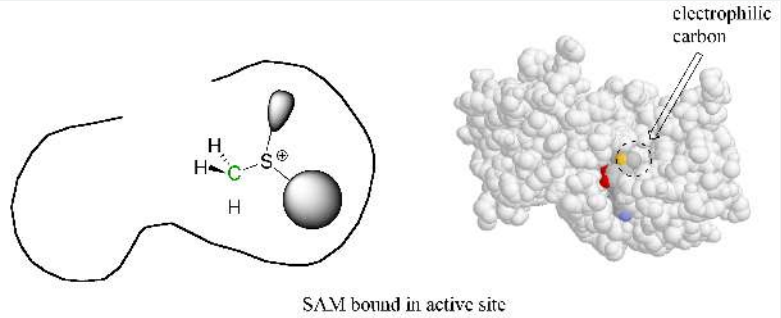
Transition state stabilization

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.

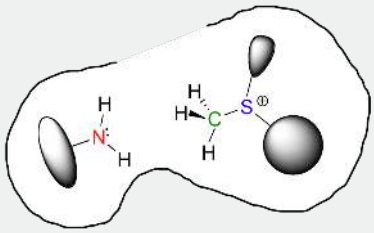
Here's where the enzyme's active site pocket comes into play. It is lined with various functional groups from the amino acid main and side chains, and has a very specific three-dimensional architecture that has evolved to bind to both of the substrates. If the SAM molecule, for example, diffuses into 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.



SAM bound in active site

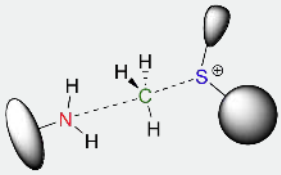
In a sense, SAM is moving from one solvent (water) to another 'solvent' (the active site), where many new energetically favorable interactions are possible. Remember: these new contacts between SAM and the active site groups are *highly specific* to SAM and SAM alone – no other molecule can 'fit' so 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').



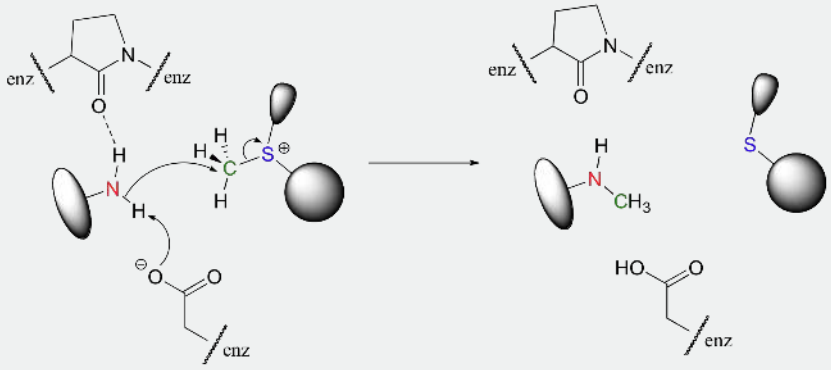
So now we have both substrates bound in the active site. But they are not just bound in any random orientation – they are specifically positioned relative to one another so that the nucleophilic nitrogen is held very close to the electrophilic carbon, with a free path of attack. What used to be a very 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.

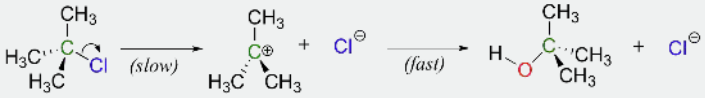


enzyme binds best to the transition state

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).

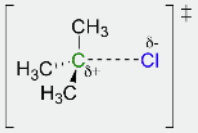


How does our picture of enzyme catalysis apply to multi-step reaction mechanisms? Although the two-step nucleophilic substitution reaction between *tert*-butyl chloride and hydroxide (section 6.1C) is not a biologically relevant process, let's pretend just for the sake of illustration that there is a hypothetical enzyme that catalyzes this reaction.



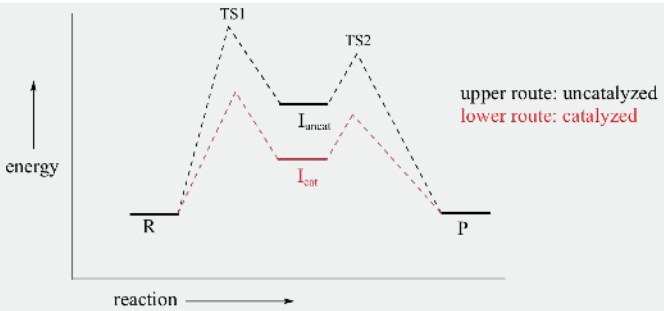
The same basic principles apply here: the enzyme binds best to the transition state. But therein lies the problem: there are two transition states! To which TS does the enzyme maximize its contacts?

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.



enzyme maximizes interactions with TS1

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.

Contributors and Attributions

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5.13: Additional Exercises

Kinetics and the Rate Equation

5-1 For a chemical reaction, what is the rate equation used to correlate?

5-2 Write the rate equation that describes the rate of the following reaction.

$$\boldsymbol{a}\mathbf{A} + \boldsymbol{b}\mathbf{B} \rightarrow \boldsymbol{c}\mathbf{C} + \boldsymbol{d}\mathbf{D}$$

5-3 What is the overall order of the following reaction with multiple reactants?

$$\text{Rate} = k\,[\text{A}]^1[\text{B}]^{1/2}$$

Halogenation of Alkanes

5-4 For the following compounds, give all possible monochlorinated derivatives.

(a)

(b)

(c)

(d)

(e)

(f)

5-5 For the following compounds, identify the major product of free-radical bromination.

(a)

(b)

(c)

(d)

5-6 Explain why radical bromination is significantly more selective than radical chlorination.

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5.14: Solutions to Additional Exercises

Kinetics and the Rate Equation

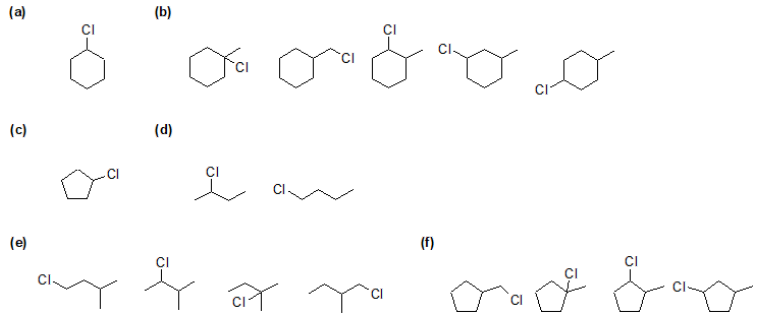
5-1 The rate equation is an experimentally derived equation that explains the relationship between the concentration of reactants and the rate of the reaction.

5-2 Rate = k [A]m[B]n

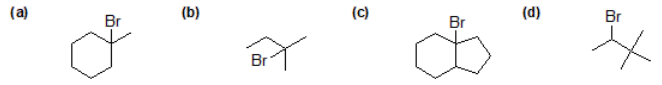
5-3 Overall order = 1.5

Halogenation of Alkanes

5-4



5-5



5-6 Radical bromination is more selective because of its slightly higher activation energy required to break a C-H bond during the propagation steps (when the bromine radical abstracts a proton from the substrate). Though the difference in activation energy is not huge (Cl = ~1 kcal/mol and Br = ~3 kcal/mol), it leads to a significant difference in selectivity.

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CHAPTER OVERVIEW

6: Alkyl Halides: Nucleophilic Substitution and Elimination

Learning Objectives

After reading the chapter and completing the exercises and homework, a student can be able to:

- classify alkyl halides - refer to section 7.1
- predict relative boiling points and solubility of alkyl halides - refer to section 7.1
- discuss the common uses of alkyl halides - refer to section 7.2
- specify the reagents for the most efficient synthesis of alkyl halides using free-radical halogenation of alkanes (Chapter 5) or allylic halogenation of alkenes with NBS - refer to section 7.3
- apply the alpha and beta labels to alkyl halides for substitution and elimination reactions - refer to section 7.4
- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N1, S_N2, E1 & E2 reactions - refer to sections 7.5, 7.6, 7.8, 7.13, and 7.15
- use Zaitsev's rule to predict major and minor products of elimination reactions including halocyclohexanes - refer to sections 7.14, 7.15, and 7.16
- predict the products and specify the reagents for S_N1, S_N2, E1 and E2 reactions with stereochemistry - refer to sections 7.6, 7.7, 7.9, 7.14, 7.15, 7.19
- propose mechanisms for S_N1, S_N2, E1 and E2 reactions - refer to sections 7.5, 7.6, 7.7, 7.8, 7.9, 7.13, 7.14, 7.15, 7.19
- draw, interpret, and apply Reaction Energy Diagrams for S_N1, S_N2, E1 and E2 reactions - refer to sections 7.5, 7.6, 7.7, 7.8, 7.9, 7.13, 7.14, 7.15, 7.19
- predict carbocation rearrangements in 1st order reactions - refer to section 7.10
- explain and apply Hammond's Postulate to substitution reactions - refer to section 7.11
- explain how the kinetic isotope effect (KIE) can be used to elucidate reaction mechanisms - refer to section 7.17
- distinguish 1st or 2nd order substitution and elimination reactions - refer to sections 7.12 and 7.18
- discuss the importance of leaving groups in biological substitution reactions - refer to section 7.20
- discuss enzymatic elimination reactions of histidine - refer to section 7.21

6.1: 7.1 Alkyl Halides - Structure and Physical Properties
6.2: Common Uses of Alkyl Halides
6.3: Preparation of Alkyl Halides
6.4: Reactions of Alkyl Halides: Substitution and Elimination
6.5: The Sn2 Reaction
6.6: Characteristics of the Sn2 Reaction
6.7: Stereochemistry of the SN2 Reaction
6.8: The Sn1 Reaction
6.9: Characteristics of the Sn1 Reaction
6.10: Rearrangements of the Carbocation and Sn1 Reactions
6.11: The Hammond Postulate and Transition States
6.12: Comparison of SN1 and SN2 Reactions
6.13: Characteristics of the E2 Reaction
6.14: Zaitsev's Rule
6.15: Characteristics of the E1 Reaction
6.16: E2 Regiochemistry and Cyclohexane Conformations
6.17: The E2 Reaction and the Deuterium Isotope Effect

6.18: Comparison of E1 and E2 Reactions
6.19: Comparing Substitution and Elimination Reactions
6.20: Biological Substitution Reactions
6.21: Biological Elimination Reactions
6.22: Additional Exercises
6.23: Solutions to Additional Exercises

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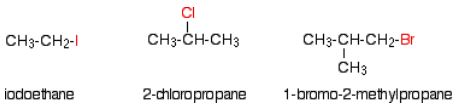
6.1: 7.1 Alkyl Halides - Structure and Physical Properties

Learning Objective

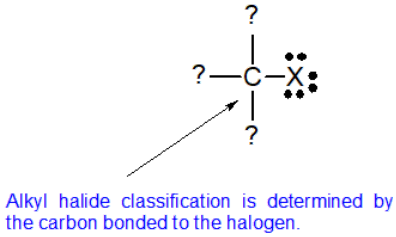
- classify alkyl halides
- predict relative boiling points and solubility of alkyl halides

Introduction

Alkyl halides are also known as haloalkanes. 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). We will only look at compounds containing one halogen atom like th compounds below.

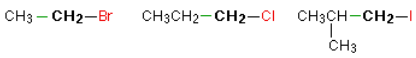


Alkyl halides fall into different classes depending on how the halogen atom is positioned on the chain of carbon atoms. Alkyl halides can be classified as primary, secondary, or tertiary. The chemical reactivity of alkyl halides is frequently discussed using alkyl halide classifications to help discern patterns and trends. Because the neutral bonding pattern for halogens is one bond and three lone pairs, the carbon and halogen always share a single bond. Alkyl halide classification is determined by the bonding pattern of the carbon atom bonded to the halogen as shown in the diagram below.



Primary alkyl halides

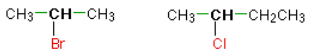
In a primary (1°) haloalkane, the carbon bonded to the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include thecompounds below.



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.

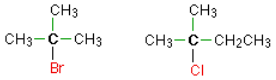
Secondary alkyl halides

In a secondary (2°) haloalkane, the carbon bonded with the halogen atom is joined directly to two other alkyl groups that can be the same or different. Some examples of secondary alkyl halides include thecompounds below.



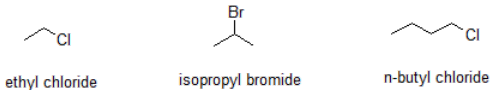
Tertiary alkyl halides

In a tertiary (3°) halogenoalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of same or different. Some examples of tertiary alkyl halides include thecompounds below.



Common Names

Many organic compounds are closely related to the alkanes and this similarity is incorporated into many common names. 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). The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the stem of the name of the halogen, with the ending *-ide*.

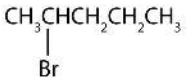


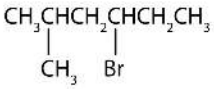
ethyl chloride | isopropyl bromide | n-butyl chloride

Examples

Give the common and IUPAC names for each compound.

1. $CH_3CH_2CH_2Br$
2. $(CH_3)_2CHCl$
3. Give the IUPAC name for each compound.

a) 

b) 

SolutionS

1. 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.
2. 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.
3. 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.

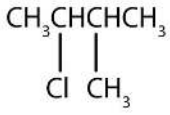
Exercise

1. Give common and IUPAC names for each compound.

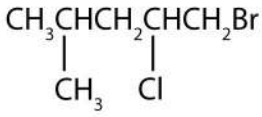
   a. CH_3CH_2I
   b. $CH_3CH_2CH_2CH_2F$

2. Give the IUPAC name for each compound.

a)



b)



Answer

1. a) ethyl iodide and iodoethane, respectively; Note the IUPAC name does not need a locator number because there is only one possible structure with two carbons and one iodine.

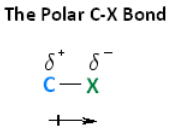
   b) butyl fluoride and 1-fluorobutane

2. a) 2-chloro-2-methylbutane

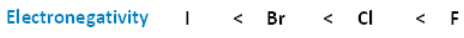
   b) 1-bromo-2-chloro-4-methylpentane

Halogens and the Character of the Carbon-Halogen Bond

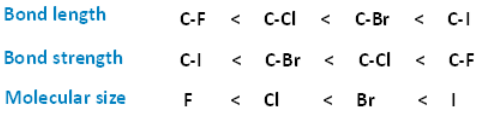
With respect to electronegativity, halogens are more electronegative than carbons. This results in a carbon-halogen bond that is polarized. As shown in the image below, carbon atom has a partial positive charge, while the halogen has a partial negative charge.



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.



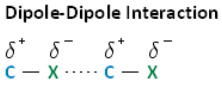
The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases and we get longer bonds, the strength of those bonds decreases.



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 incease 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.



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

Alkyl halides have little to no solubility in water in spite of the polar carbon-halogen bond. The attraction between the alkyl halide molecules is stronger than the attraction between the alkyl halide and water. Alkyl halides have little to no solubility in water, but be aware of densities. Polyhalogenated alkanes such as dichloromethane can have densities greater than water.

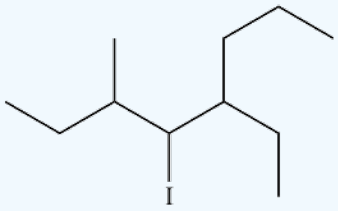
Solubility in organic solvents

Alkyl halides are soluble in most organic solvents. The London Dispersion forces play a dominant role in solubility.

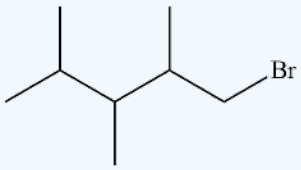
Exercises

Exercise

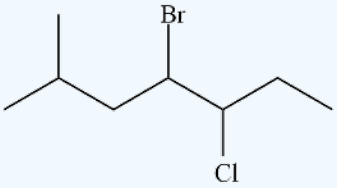
3. Classify (primary, secondary, tertiary, vicinal, or geminal) and give the IUPAC name for the following organohalides:



(A)



(B)



(C)

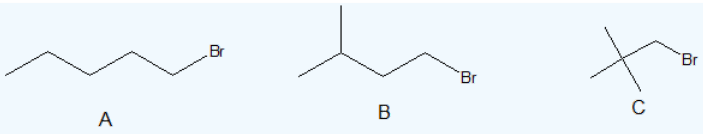
4. Classify (primary, secondary, tertiary, vicinal, or geminal) and draw the bond-line structures of the following compounds:

a) 2-Chloro-3,3-dimethylpentane

b) 1,1-Dichloro-4-isopropylcyclohexane

c) 3-bromo-3-ethylhexane

5. Arrange the following alkyl halides in order of decreasing boiling point.



6. Predict the solvent with great alkyl halide solubility.

a) water or hexane

b) water or 1-octanol

c) water or benzene

d) water or acetone

Solutions

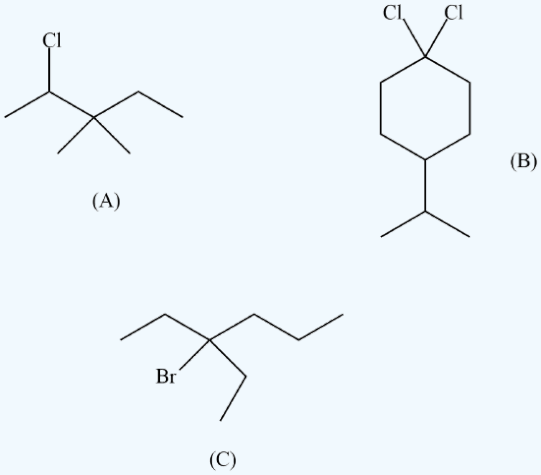
3.

a) secondary; 5-ethyl-4-iodo-3methyl-octane

b) primary; 1-bromo-2,3,4-trimethyl-pentane

c) vicinal dihalide; 4-bromo-5-chloro-2-methyl-heptane

4. (A) secondary; (B) geminal dichloride (C) tertiary



5. A > B > C

6.

a) hexane

b) benzene

c) 1-octanol

d) acetone

Alkyl halides have little to no solubility in water, but be aware of densities. Polyhalogenated alkanes can have densities greater than water.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
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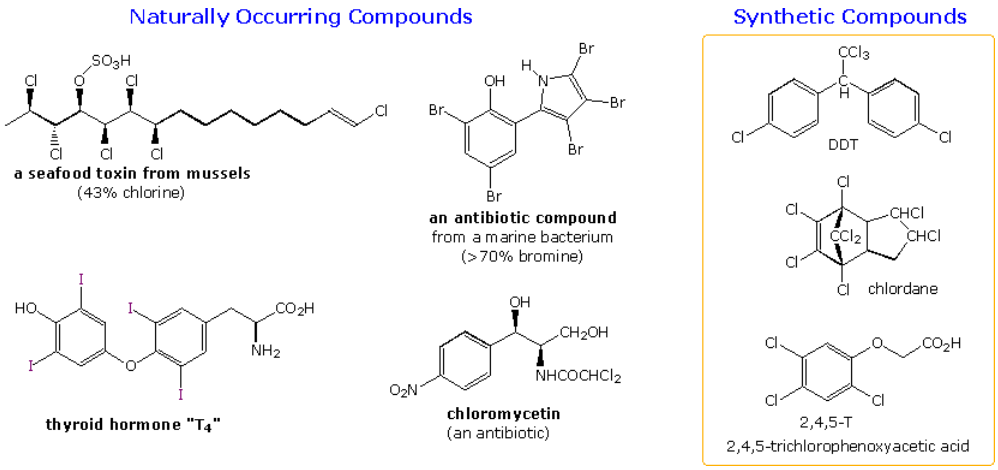
6.2: Common Uses of Alkyl Halides

Learning Objective

- Discuss the common uses of alkyl halides

Halogen containing organic compounds are relatively rare in terrestrial plants and animals. The thyroid hormones T_3 and T_4 are exceptions; as is fluoroacetate, the toxic agent in the South African shrub *Dichapetalum cymosum*, known as "gifblaar". However, the halogen rich environment of the ocean has produced many interesting natural products incorporating large amounts of halogen. Some examples are shown below.

The ocean is the largest known source for atmospheric methyl bromide and methyl iodide. Furthermore, the ocean is also estimated to supply 10-20% of atmospheric methyl chloride, with other significant contributions coming from biomass burning, salt marshes and wood-rotting fungi. Many subsequent chemical and biological processes produce poly-halogenated methanes.



Synthetic organic halogen compounds are readily available by direct halogenation of hydrocarbons and by addition reactions to alkenes and alkynes. Many of these have proven useful as intermediates in traditional synthetic processes. Some halogen compounds, shown in the box. have been used as pesticides, but their persistence in the environment, once applied, has led to restrictions, including banning, of their use in developed countries. Because DDT is a cheap and effective mosquito control agent, underdeveloped countries in Africa and Latin America have experienced a dramatic increase in malaria deaths following its removal, and arguments are made for returning it to limited use. 2,4,5-T and 2,4-D are common herbicides that are sold by most garden stores. Other organic halogen compounds that have been implicated in environmental damage include the polychloro- and polybromo-biphenyls (PCBs and PBBs), used as heat transfer fluids and fire retardants; and freons (e.g. CCl_2F_2 and other chlorofluorocarbons) used as refrigeration gases and fire extinguishing agents.

Alkyl halides provide nice examples for learning about two very important organic reaction mechanism types: nucleophilic substitution and beta-elimination. In learning about these mechanisms in the context of alkyl halide reactivity, we will also learn some very fundamental ideas about three main players in many organic reactions: nucleophiles, electrophiles, and leaving groups. We'll start with an overview of the substitution and elimination reactions which alkyl halides undergo.

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6.3: Preparation of Alkyl Halides

Learning Objective

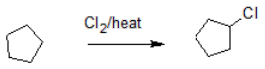
- specify the reagents for the most efficient synthesis of alkyl halides using free-radical halogenation of alkanes (Chapter 5) or allylic halogenation of alkenes with NBS

Free radical halogenation of alkanes

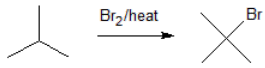
Free radical halogenation of alkanes is the substitution of a single hydrogen on the alkane for a single halogen to form a haloalkane. Light is required to initiate the radical formation and is a good example of a photochemical reaction. The simplest example is shown below for methane reacting with chlorine in the presence of light to form chloromethane and hydrogen chloride gas.

$$CH_4 + Cl_2 + \text{energy} \longrightarrow CH_3Cl + HCl \tag{6.3.1}$$

Free radical halogenation of alkanes has been thoroughly explained in chapter 5. The structure of the alkane is evaluated to choose between the high reactivity of chlorine (Cl_2) and the high selectivity of bromine (Br_2).



All carbons are equivalent, so use higher reactivity of Cl_2.



Higher selectivity of Br_2 will produce a greater percentage of the tertiary halide.

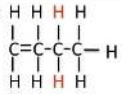
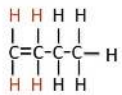
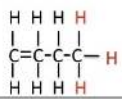
Allylic Bromination

When halogens are in the presence of unsaturated molecules such as alkenes, the expected reaction is addition to the double bond carbons resulting in a vicinal dihalide (halogens on adjacent carbons). The reaction is studied in a later chapter. To avoid halogen reactions at the alkene the halogen concentration is kept low enough that a substitution reaction occurs at the allylic position rather than addition at the double bond. The product is an allylic halide (halogen on carbon next to double bond carbons), which is acquired through a radical chain mechanism.

$$CH_2{=}CHCH_3 + X_{2\,(\text{low conc.})} \rightleftharpoons CH_2{=}CHCH_2X + HX$$

Why Substitution of Allylic Hydrogens?

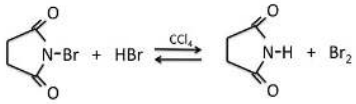
As the table below shows, the dissociation energy for the allylic C-H bond is lower than the dissociation energies for the C-H bonds at the vinylic and alkylic positions. This is because the radical formed when the allylic hydrogen is removed is resonance-stabilized. Hence, given that the halogen concentration is low, substitution at the allylic position is favored over competing reactions. However, when the halogen concentration is high, addition at the double bond is favored because a polar reaction out competes the radical chain reaction.

Type of Hydrogen	Dissociation Energy (DH^o)
allylic 	88 kcal/mol
vinylic 	106 kcal/mol
alkylic 	98 kcal/mol

Radical Allylic Bromination using NBS and light

Preparation of Bromine (low concentration)

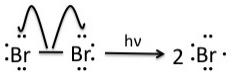
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



Allylic Bromination Mechanism

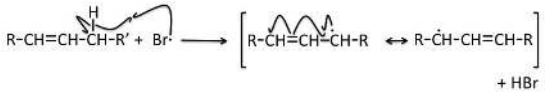
Step 1: Initiation

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.

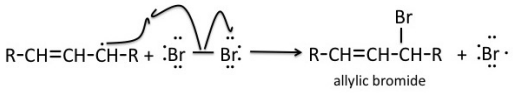


Step 2: Propagation

One bromine radical produced by homolytic cleavage in the initiation step removes an allylic hydrogen of the alkene molecule. A radical intermediate is generated, which is stabilized by resonance. The stability provided by delocalization of the radical in the alkene intermediate is the reason that substitution at the allylic position is favored over competing reactions such as addition at the double bond.

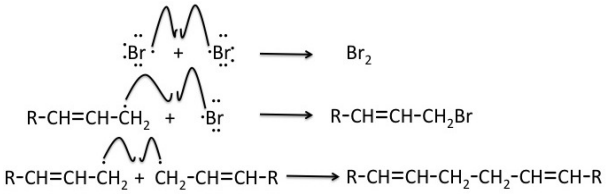


The intermediate radical then reacts with a Br_2 molecule to generate the allylic bromide product and regenerate the bromine radical, which continues the radical chain mechanism. If the alkene reactant is asymmetric, two distinct product isomers are formed.



Step 3: Termination

The radical chain mechanism of allylic bromination can be terminated by any of the possible steps shown below.



Radical Allylic Chlorination

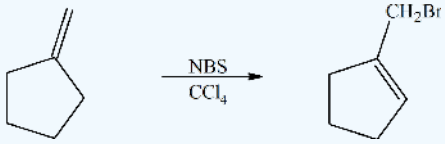
Like bromination, chlorination at the allylic position of an alkene is achieved when low concentrations of Cl_2 are present. The reaction is run at high temperatures to achieve the desired results.

Industrial Uses

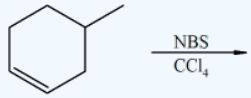
Allylic chlorination has important practical applications in industry. Since chlorine is inexpensive, allylic chlorinations of alkenes have been used in the industrial production of valuable products. For example, 3-chloropropene, which is necessary for the synthesis of products such as epoxy resin, is acquired through radical allylic chlorination (shown below).

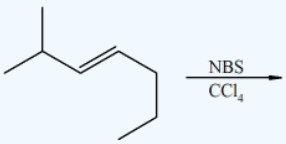
Exercises

Exercises

1. Predict the two products of the allylic chlorination reaction of 1-heptene.
2. What conditions are required for allylic halogenation to occur? Why does this reaction outcompete other possible reactions such as addition when these conditions are met?
3. Predict the product of the allylic bromination reaction of 2-phenylheptane. (Hint: How are benzylic hydrogens similar to allylic hydrogens?)
4. The reactant 5-methyl-1-hexene generates the products 3-bromo-5-methyl-1-hexene and 1-bromo-5-methyl-2-hexene. What reagents were used in this reaction?
5. 

6. Predict the products of the following reactions:





Solutions

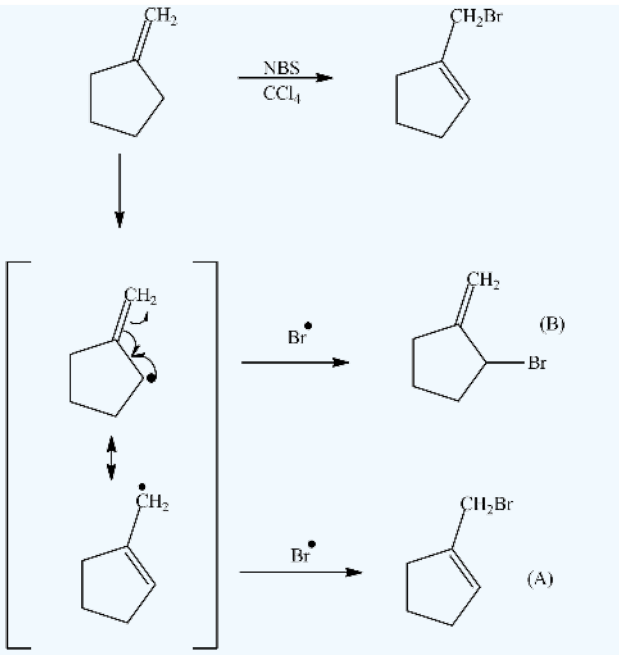
1. 3-chloro-1-heptene and 1-chloro-2-heptene

2. A low concentration of halide radical is sufficient for reaction at the allylic carbon without creating a reactivty environment for the pi bond of the alkene.

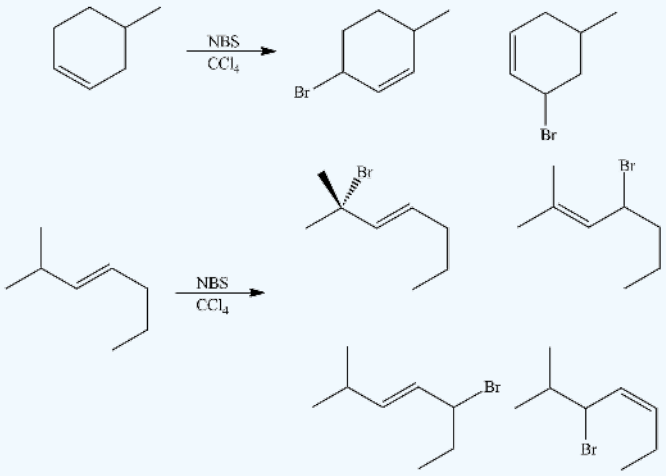
3. 2-bromo-2-phenylheptane

4. NBS with light

5. The product (A) is a 1° halogen which is more stable product even though the (B) had a better transition state with a 2° radical.



6.



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1. Djerassi, Carl. "Brominations with N-Bromosuccinimide and Related Compounds - The Wohl-Ziegler Reaction." Organic and Biomolecular Chemistry (2003). RSC Publishing. 9 June 2003. Royal Society of Chemistry. 25 Feb. 2009.
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3. Li, Chao-Jun, and Tak-Hang Chan. Organic Chemistry: Structure and Function. 5th ed. New York: W.H. Freeman and Company, 2007.

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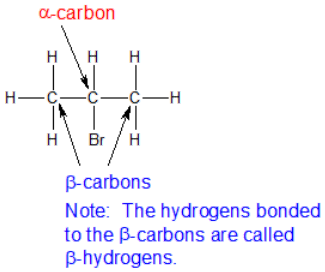
6.4: Reactions of Alkyl Halides: Substitution and Elimination

Learning Objective

- apply the alpha and beta labels to alkyl halides for substitution and elimination reactions - refer to section 7.4

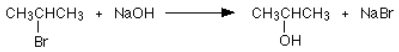
Alkyl Halide Structure and Reaction Language

The carbon bonded to a halide is called the alpha-carbon. The carbons bonded to the alpha-carbon are called beta-carbons. Carbon atoms further removed from the alpha carbon are named by continuing the Greek alphabet (alpha, beta, gamma, delta, etc). In discussing the reactions of alkyl halides, it can be effective to use the alpha- and beta- labels. The structure for 2-bromopropane is used below to illustrate the application of these terms.

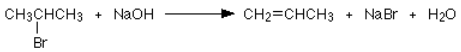


The Reactions - Nucleophilic Substitution and Elimination

Alkyl halides can undergo two major types of reactions - substitution and/or elimination. The substitution reaction is called a Nucleophilic Substitution reaction because the electrophilic alkyl halide forms a new bond with the nucleophile which substitutes for (replaces) the halogen at the alpha-carbon. Because carbon can only form four bonds, the halogen must leave and is called the "Leaving Group". Alkyl halides are excellent electrophiles because halogens share a polar bond with carbon, are polarizable, and form relatively stable leaving groups as halide anions. In the example below, 2-bromopropane is converted into propan-2-ol in a substitution reaction.



Allkyl halides can also undergo elimination reactions in the presence of strong bases. The elimination of a beta-hydrogen (hydrogen on a carbon vicinal to the alkyl halide carbon) and the halide produces a carbon-carbon double bond to form an alkene. In the example below, 2-bromopropane has undergone an elimination reaction to give an alkene - propene.

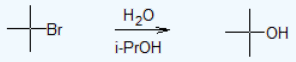


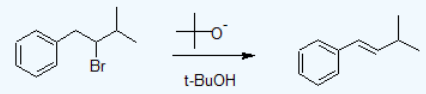
What decides whether you get substitution or elimination?

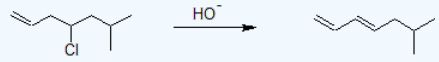
In the examples above, the reagents were the same for both substitution and elimination - the halogenoalkane and either sodium or potassium hydroxide solution. In all cases, you will get a mixture of both reactions happening - some substitution and some elimination. The product distribution depends on a number of factors. These factors will be explored in the remaining sections of this chapter. Depending on the structure of the alkyl halide, reagent type, reaction conditions, some reactions will only undergo only one pathway - substitution or elimination. While other alkyl halides will always produce a mixture of substitution and elimination products like the example above. The goal of efficient multiple-step synthetic pathways is to maximize the formation of a single product during each step. The reaction conditions explored in this chapter will be useful for future reactions we will study and learn.

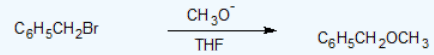
Exercise

1. Classify the following reactions as "Substitutions" or "Eliminations".

a) 

b) 

c) 

d) 

Answer

1. a) substitution

   b) elimination

   c) elimination

   d) substitution

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Jim Clark (Chemguide.co.uk)

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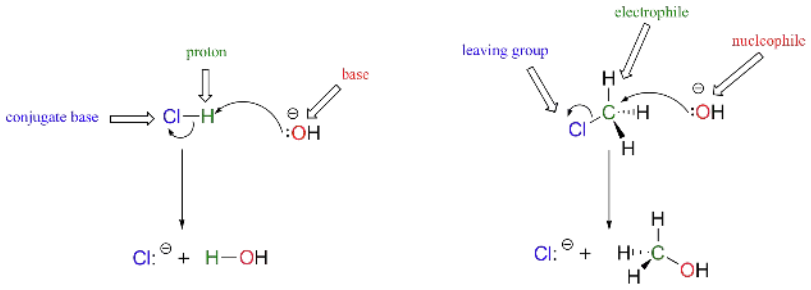
6.5: The Sn2 Reaction

Learning Objectives

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N2 reactions
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for S_N2 reactions

Introduction

In many ways, the proton transfer process of 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) reacts with an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base.

In the next few sections, we are going to be discussing some general aspects of nucleophilic substitution reactions, and in doing so it will simplify things greatly if we can use some abbreviations and generalizations before we dive into real examples.

What is a nucleophile (Nu)?

Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. Nucleophilic functional groups are those which have electron-rich atoms able to donate a pair of electrons to form a new covalent bond. Nucleophiles can be negatively charged and some that are neutral with lone pair electrons. 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.

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.

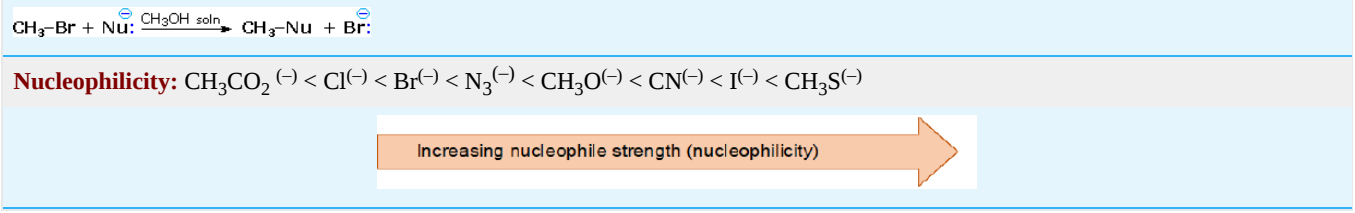
Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the pKa of the corresponding 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 an acid-base equilibrium the weakest acid and the weakest base will predominate (they will necessarily be on the same side of the equilibrium). Learning the pKa values for common compounds provides a useful foundation on which to build an understanding of acid-base factors in reaction mechanisms.

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
pKa	-9	-7	-1.7	4.8	8	9.1	16	33	48

Increasing base strength

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:



What is a Leaving Group (X or LG)?

In a similar fashion, we will call the leaving group 'X' for halogens as is customary. For other reactions, it will be more accurate to abbreviate the leaving group as "LG". The context of the reaction will dictate the abbreviation. Leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. Therefore, in this general picture we will not include a charge designation on the 'X' or 'LG' species. In referring to the comparison between acid-base chemistry and substitution reactions, the stability of the leaving group is evaluated the same way we evaluate the stability of conjugate bases.

When comparing the reactivity of electrophiles that vary only in their leaving groups, then leaving group stability plays a dominant role. The electrophile with the more stable leaving group will be favored. The lower the electron density of the leaving group, the more stable it is. Neutral leaving groups are favoring over charged leaving groups. When comparing charged leaving groups, apply the concepts used to determine the relative stability of conjugate bases:

1) identity or identities of the atom(s) holding the charge

2) delocalization of the charge via resonance

3) inductive effects

4) orbital hybridization

What is an Electrophile (E)?

An electrophile accepts electrons analogous to a Lewis acid. Electrophiles (E) are sometimes protonated and sometimes neutral. Electrophiles can also be called "Substrates". Since nucleophiles, leaving groups, and electrons may be charged or neutral, we will not include charges on 'Nu' or 'X' (or 'LG') or 'E'.

We will generalize the three other groups bonded on the electrophilic alpha-carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Finally, in order to keep figures from becoming too crowded, we will use in most cases the line structure convention in which the central, electrophilic carbon is not drawn out as a 'C'.

Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction:

To recognize neutral electrophiles, we will need to identify polarity and/or resonance with compounds to create a partial positive charge to attract the nucleophile. The electrophilicity of alkyl halides comes from the polar carbon-halogen bond.

The common halogens being fluorine, chlorine, bromine and iodine. With the exception of iodine, these halogens have electronegativities significantly greater than carbon. Consequently, this functional group is polarized so that the carbon is electrophilic and the halogen is nucleophilic, as shown in the drawing on the right. Two characteristics other than electronegativity also have an important influence on the chemical behavior of these compounds. The first of these is covalent bond strength. The strongest of the carbon-halogen covalent bonds is that to fluorine. Remarkably, this is the strongest common single bond to carbon, being roughly 30 kcal/mole stronger than a carbon-carbon bond and about 15 kcal/mole stronger than a carbon-hydrogen bond. Because of this, **alkyl fluorides and fluorocarbons in general are chemically and thermodynamically quite stable**, and do not share any of the reactivity patterns shown by the other alkyl halides. The carbon-chlorine covalent bond is slightly weaker than a carbon-carbon bond, and the bonds to the other halogens are weaker still, the bond to iodine being about 33% weaker. The second factor to be considered is the relative stability of the corresponding halide anions, which is likely the form in which these electronegative atoms will be replaced. This stability may be estimated from the relative acidities of the H-X acids, assuming that the strongest acid releases the most stable conjugate base (halide anion). With the exception of HF (pK_a = 3.2), all the hydrohalic acids are very strong, small differences being in the direction HCl < HBr < HI.

Exercise

1. 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 nuclephile or electrophile, while other functional groups can react as either a nuclephile or electrophile depending on the reaction conditions. Classify the following compounds as nucleophiles, electrophiles, or leaving groups. More than one answer may be possible.

a) bromoethane

b) hydroxide

c) water

d) chlorocyclohexane

e) ethanol

f) bromide

Answer

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

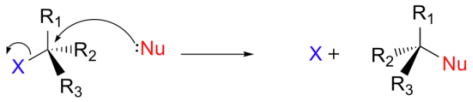
d) electrophile (Alkyl halides are always electrophiles - one reason they are an o-chem student's best friend.)

e) weak nucleophile, a poor electrophile without clever chemistry (stay tuned for future chapters), good leaving group

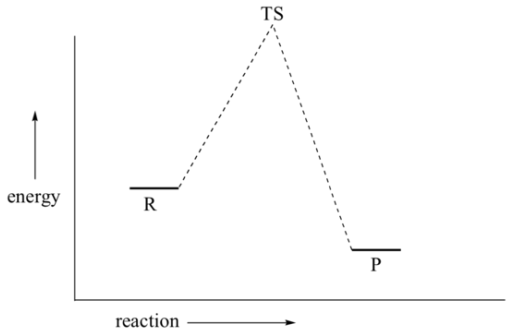
f) good nucleophile and a good leaving group

The S_N2 mechanism

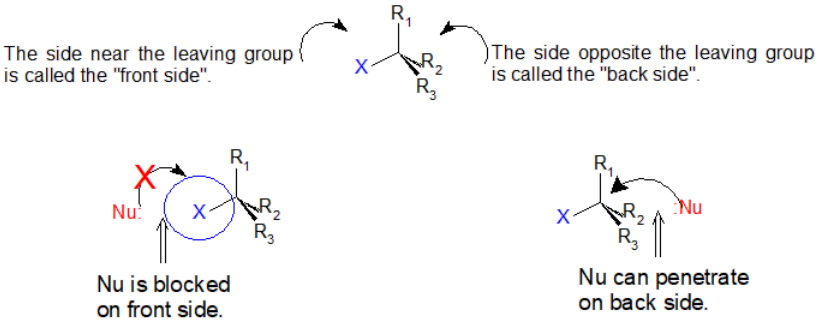
There are two mechanistic models for how an alkyl halide can undergo nucleophilic substitution, S_N2 and S_N1. The S_N2 reaction takes place in a single step with bond-forming and bond-breaking occurring simultaneously. (In all figures in this section, 'X' indicates a halogen substituent).



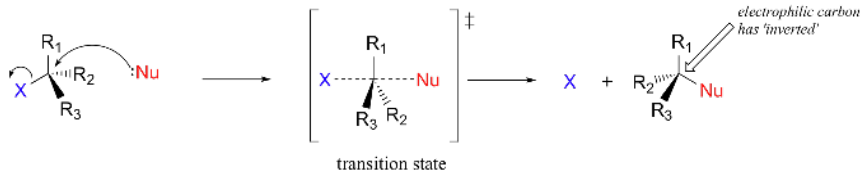
This is called an '**S_N2**' mechanism. In the term S_N2, S stands for 'substitution', the subscript N stands for 'nucleophilic', and the number 2 refers to the fact that it is a **bimolecular reaction**: the overall rate depends on a step in which two separate molecules (the nucleophile and the electrophile) collide. A potential energy diagram for this reaction shows the transition state (TS) as the highest point on the pathway from reactants to products.



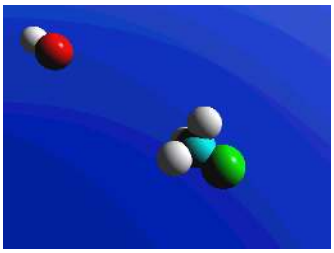
If you look carefully at the progress of the S_N2 reaction, you will realize something very important about the outcome. The nucleophile, being an electron-rich species, must react with the electrophilic carbon from the *back side* relative to the location of the leaving group. Approach from the front side simply doesn't work: the electron rich, leaving group blocks the way with electrostatic repulsion and steric hindrance.



The result of this backside penetration is that the stereochemical configuration at the central carbon *inverts* as the reaction proceeds. In a sense, the molecule is turned inside out. At the transition state, the electrophilic carbon and the three 'R' substituents all lie on the same plane.

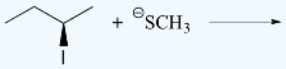


What this means is that S_N2 reactions whether enzyme catalyzed or not, are inherently stereoselective: when the substitution takes place at a stereocenter, we can confidently predict the stereochemical configuration of the product. Below is an animation illustrating the principles we have just learned, 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.



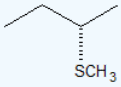
Exercise

2. Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.



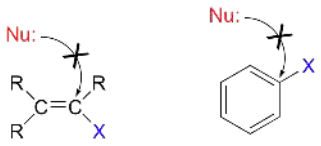
Solution

2.



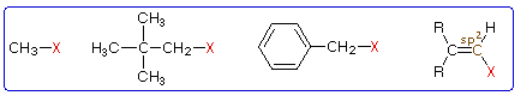
S_N2 Reactions Occur at sp^3 Carbons with a Leaving Group

One more important point must be made before continuing: nucleophilic substitutions as a rule occur at sp^3-hybridized carbons bonded to a leaving group. SN2 reactions can*not occur* where the leaving group is attached to an sp^2-hybridized carbon:

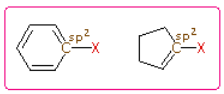


Bonds on sp^2-hybridized carbons are inherently shorter and stronger than bonds on sp^3-hybridized carbons, meaning that it is harder to break the C-X bond in these substrates. S_N2 reactions of this type are unlikely also because the (hypothetical) electrophilic carbon is protected from nucleophilic attack by electron density in the p bond. S_N1 reactions are highly unlikely, because the resulting carbocation intermediate, which would be sp-hybridized, would be very unstable (we'll discuss the relative stability of carbocation intermediates in a later section of this module).

For future reference when discerning between substitution and elimination reactions, evaluating the structure of the electrophile can eliminate possible products. **If the electrophilic carbon has no beta-hydrogens, then only substitution reactions can occur and elimination reactions are not possible** (of course carbocation rearrangements may need to be considered). The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds. It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).



no β-hydrogens



strained elimination product

Exercise

3. Predict which alkyl halides can undergo a S_N2 reaction.

a) C_6H_5Br

b) $CH_3CH_2CH_2Br$

https://chem.libretexts.org/@go/page/182904

c) CH_2CHBr

d) $CH_3CH_2CH_2CHBrCH_3$

Solutions

3.

a) No, aryl halide.

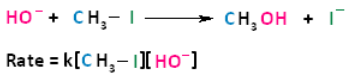
b) Yes, primary alkyl halide

c) No, vinyl halide

d) Yes, secondary alkyl halide

S_N2 Reaction Kinetics

In the term S_N2, the S stands for substitution, the N stands for nucleophilic, and 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.



$$HO^- + CH_3-I \longrightarrow CH_3OH + I^-$$

$$\text{Rate} = k[CH_3-I][HO^-]$$

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.

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 2\,\text{Rate}_1$$

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.

$$\text{Rate}_1 = k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4k[CH_3-I][HO^-]$$
$$\text{Rate}_2 = 4\,\text{Rate}_1$$

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

Exercise

4. The reaction below follows the SN2 mechanism.

$$CH_3Cl + NaOH \longrightarrow CH_3OH + NaCl$$

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 6×10^{-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.

Solutions

4.

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

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.6: Characteristics of the S_n2 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N2 reactions
- predict the products and specify the reagents for S_N2 reactions with stereochemistry
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for S_N2 reactions

Introduction

To understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation where X represents the leaving group (a halide for this chapter).

In order of decreasing importance, the factors impacting S_N2 reaction pathways are

1) structure of the alkyl halide

2) strength of the nucleophile

3) stability of the leaving group

4) type of solvent.

The bimolecular transition state of the S_N2 pathway means that sterics are a primary consideration. The orbitals of the nucleophile must be able to penetrate through the reaction solution and create orbital overlap with the orbitals of the electrophilic carbon. The sterics of this mechanism can be determined by applying the bonding theories for individual compounds and ions to the interaction of the nucleophile and electrophile. The strength of the nucleophile will also influence the reaction along with the stability of the leaving group. Solvents can have a subtle yet measurable effect on S_N2 pathway. *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. The role of the solvent is often misunderstood and consequently given way too much importance. Do not drown in the solvent. Solvation effects are less significant than the structure of the alkyl halide, the reactivity of the nucleophile, and the stability of the leaving group.

The following variables and observables can be used to study the S_N2 mechanism.

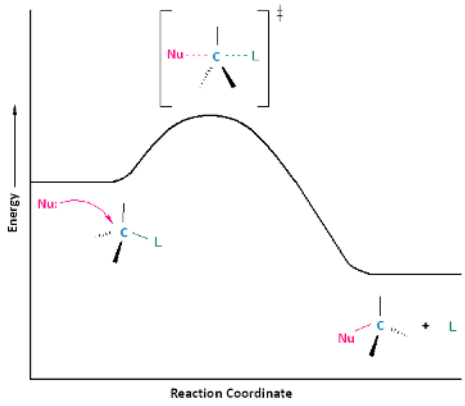
Variables	**R** change α-carbon from 1º to 2º to 3º if the α-carbon is a chiral center, set as (*R*) or (*S*) **X** change from Cl to Br to I (F is relatively unreactive) **Nu:** change from anion to neutral; change basicity; change polarizability **Solvent** polar vs. non-polar; protic vs. non-protic
Observables	**Products** substitution, elimination, no reaction. **Stereospecificity** if the α-carbon is a chiral center what happens to its configuration? **Reaction Rate** measure as a function of reactant concentration.

When several reaction variables may be changed, it is important to isolate the effects of each during the course of study. In other words: **only one variable should be changed at a time**, the others being held as constant as possible. For example, we can examine the effect of changing the halogen substituent from Cl to Br to I, using ethyl as a common R–group, cyanide anion as a common nucleophile, and ethanol as a common solvent. We would find a common substitution product, C_2H_5–CN, in all cases, but the speed or rate of the reaction would increase in the order: Cl < Br < I. This reactivity order reflects both the strength of the C–X bond, and the stability of $X^{(-)}$ as a leaving group, and leads to the general conclusion that alkyl iodides are the most reactive members of this functional class.

Bimolecular Nucleophilic Substitution Reactions Are Concerted

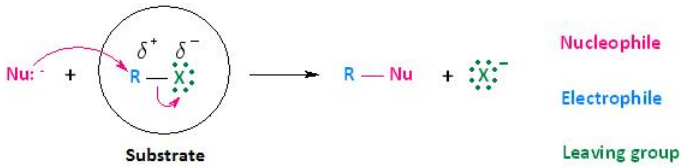
Bimolecular nucleophilic substitution (SN_2) reactions are **concerted**, meaning they are a **one step process**. The bond-making between the nucleophile and the electrophilic carbon occurs at the same time as the bond-breaking between the electophilic carbon and the halogen.

The potential energy diagram for an SN_2 reaction is shown below. The one-step mechanism means that only 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.

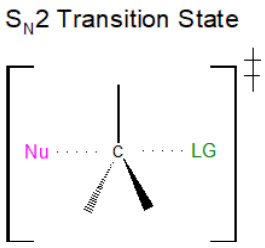


Alkyl halide (Substrate) Structure and SN2 Reaction Rates

Now that we have discussed the effects that the leaving group, nucleophile, and solvent have on biomolecular nucleophilic substitution (S_N2) reactions, it's time to turn our attention to how the substrate affects the reaction. Although the substrate, in the case of nucleophilic substitution of haloalkanes, is considered to be the entire molecule circled below, we will be paying particular attention to the alkyl portion of the substrate. In other words, we are most interested in the electrophilic center that bears the leaving group.

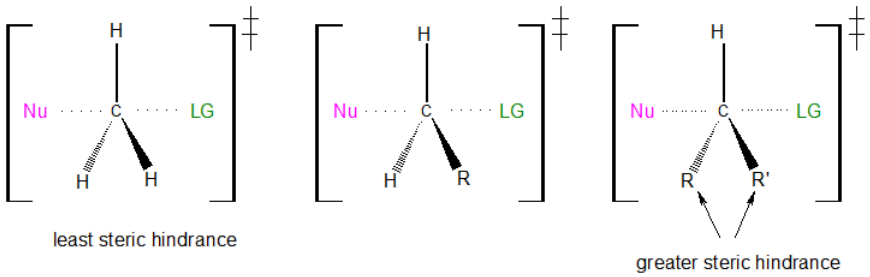


The S_N2 transition state is very crowded with a total of five groups around the electrophilic center, the nucleophile, the leaving group, and three substituents.



If each of the three substituents in this transition state were small hydrogen atoms, as illustrated in the first example below, there would be little steric repulsion between the incoming nucleophile and the electrophilic center, thereby increasing the ease at which the nucleophilic substitution reaction can occur. Remember, for the SN_2 reaction to occur, the nucleophile must be able to overlap orbitals with the electrophilic carbon center, resulting in the expulsion of the leaving group. 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 with the incoming nucleophile. If two of the hydrogens were replaced by R groups, there would be an even greater increase in steric repulsion with the incoming nucleophile.

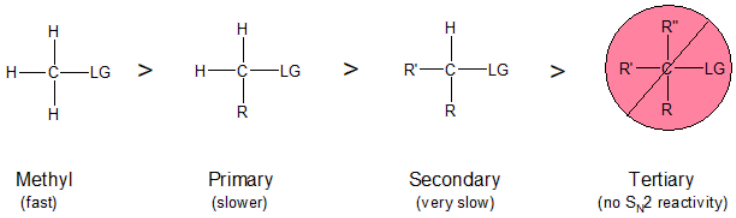
Alkyl Halide Structure and the S_N2 Transition State



How does steric hindrance affect the rate at which an SN_2 reaction will occur? As each hydrogen is replaced by an R group, the rate of reaction is significantly diminished. This is because the addition of one or two R groups shields the backside of the electrophilic carbon impeding nucleophilic penetration.

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.

Alkyl Halide Structure and S_N2 Relative Reactivity



Substitutes on Neighboring Carbons Slow Nucleophilic Substitution Reactions

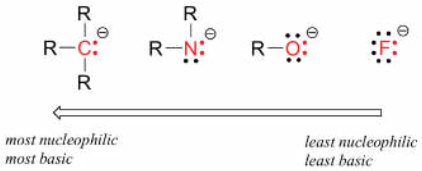
Previously we learned that adding R groups to the electrophilic carbon results in nucleophilic substitution reactions that occur at a slower rate. What if R groups are added to neighboring carbons? It turns out that the addition of substitutes on neighboring carbons will slow nucleophilic substitution reactions as well.

In the example below, 2-methyl-1-bromopropane 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.

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.

Nucleophilicity

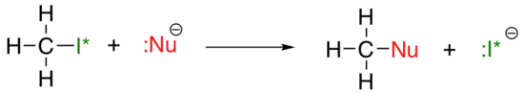
There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:



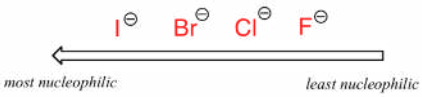
The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic 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).

The vertical periodic trend for nucleophilicity is somewhat more complicated because the solvent can influence the nucleophilicity trend in either direction. Let's take the simple example of the S_N2 reaction below:



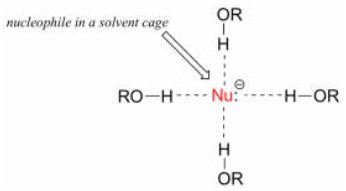
. . .where Nu^- is one of the halide ions: fluoride, chloride, bromide, or iodide, and the leaving group I* is a radioactive isotope of iodine (which allows us to distinguish the leaving group from the nucleophile when both are iodide). If this reaction is occurring in a **protic solvent** (that is, a solvent that has a hydrogen bonded to an oxygen or nitrogen - water, methanol and ethanol are the most important examples), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.



Relative nucleophilicity in a protic solvent

This of course, is opposite that of the vertical periodic trend for basicity, where iodide is the *least* basic. What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

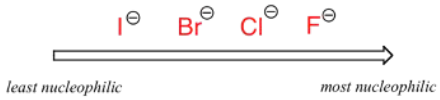
As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction occurring in a *protic* solvent like ethanol. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile:



In order for the nucleophile to react with the electrophile, it must break free, at least in part, from its solvent cage. The lone pair electrons on the larger, less basic iodide ion interact less tightly with the protons on the protic solvent molecules resulting in weaker

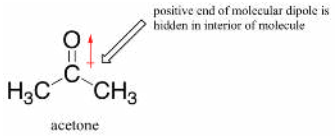
solvation - thus the iodide nucleophile is better able to break free from its solvent cage compared the smaller, more basic fluoride ion, whose lone pair electrons are bound more tightly to the protons of the solvent cage.

The picture changes if we switch to a **polar aprotic solvent**, such as acetone, in which there is a molecular dipole but *no hydrogens bound to oxygen or nitrogen*. Now, fluoride is the best nucleophile, and iodide the weakest.



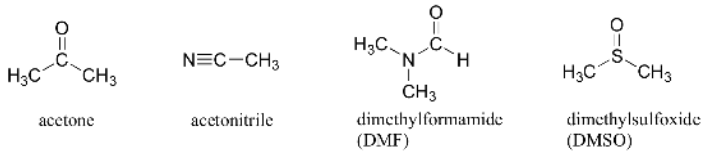
Relative nucleophilicity in a polar aprotic solvent

The reason for the reversal is that, with an aprotic solvent, the ion-dipole interactions between solvent and nucleophile are much weaker: the positive end of the solvent's dipole is hidden in the interior of the molecule, and thus it is shielded from the negative charge of the nucleophile.



A weaker solvent-nucleophile interaction means a weaker solvent cage for the nucleophile to break through, so the solvent effect is much less important, and the more basic fluoride ion is also the better nucleophile.

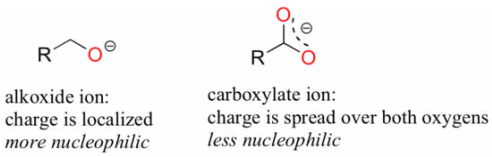
Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple - the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not 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).



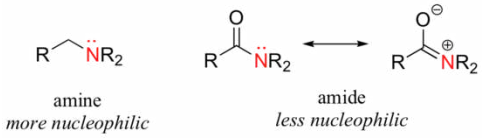
In biological chemistry, where the solvent is protic (water), the most important implication of the periodic trends in nucleophilicity is that thiols are more powerful nucleophiles than alcohols. The thiol group in a cysteine amino acid, for example, is a powerful nucleophile and often acts as a nucleophile in enzymatic reactions, and of course negatively-charged thiolates (RS^-) are even more nucleophilic. This is not to say that the hydroxyl groups on serine, threonine, and tyrosine do not also act as nucleophiles - they do.

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.



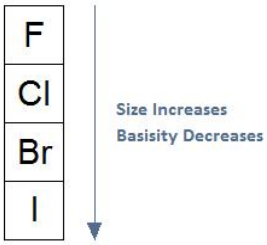
The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



The leaving group

The more stable the leaving group, the lower the transition state energy, the lower the activation energy, the faster the reaction rate. Evaluating leaving group stability is analogous to determining relative acidity by evaluating conjugate base stability. The considerations are the same: identity of the atom(s) and relative position on the periodic table, resonance delocalization, and electronegativity. Orbital hybridization is rarely relevant.

As Size Increases, Basicity Decreases, Leaving Group Stability Increases: 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.



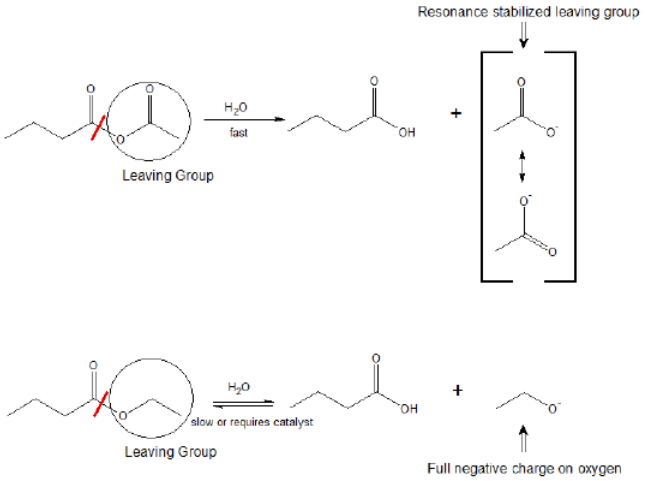
When evaluating halogens as leaving groups, the same trend is significant. Fluoride has the highest electron density and is considered the worst leaving group to the point of no reactivity. As move down the column, the leaving groups have lower electron density and greater stability with iodide considered an excellent leaving group.

Leaving Group Comparison

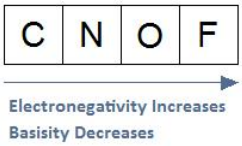
$F^- < Cl^- < Br^- < I^-$

worst fair good excellent

Resonance Decreases Basicity and Increases Leaving Group Stability: The formation of a resonance stabilized structure delocalizes the electrons over two or more atoms lowering the electron density of the leaving group and increases its stability. For halides as leaving groups there are no applications for this consideration, so we will look briefly at carbonyl chemistry to illustrate this effect. When comparing the hydrolysis rates of anhydrides and esters, anhydrides react spontaneously with water and undergo hydrolysis to form a resonance stabilized carboxylate ion. Whereas, ester hydrolysis is a much slower reaction and requires a catalyst to overcome the alkoxides as poor leaving groups. The details of these two reactions will be studied in greater detail later in this text.

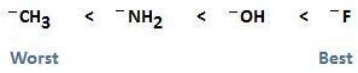


As Electronegativity Increases, Basicity Decreases and Leaving Group Stability Increases: In general, if we move from the left of the periodic table to the right of the periodic table as shown in the diagram below, electronegativity increases. As electronegativity increases, basicity will decrease, meaning a species will be less likely to act as base; that is, the species will be less likely to share its electrons.



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.

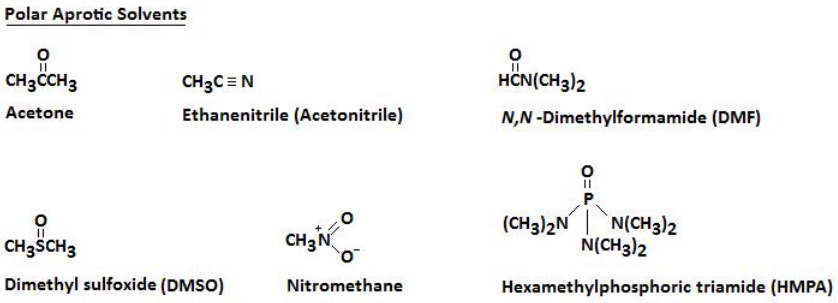
Leaving Groups Across a Period



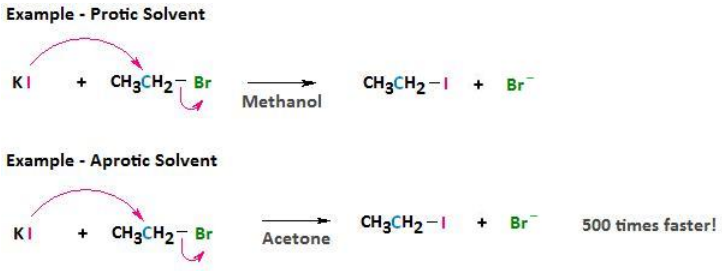
Solvent Effects on an S_N2 reaction

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 through strong solvation. WE can view the nucleophile as being locked in a solvent cage through the strong hydrogen-bond interactions between solvent protons and the reactive lone pairs on the nucleophile. 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. Below are several polar aprotic solvents that are commonly used in the laboratory:

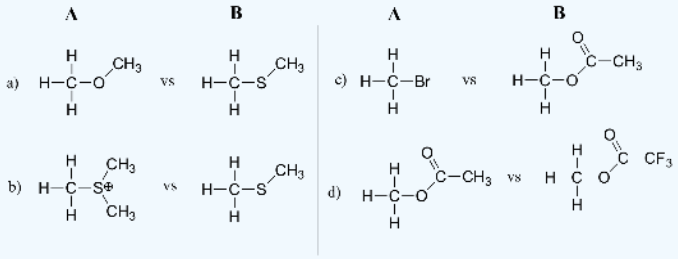


These aprotic solvents are polar but, because they do not form hydrogen bonds with the anionic nucleophile, there is a relatively weak interaction between the aprotic solvent and the nucleophile. By using an aprotic solvent we can raise the reactivity of the nucleophile. This can sometimes have dramatic 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 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?



Explanations to explain differences in chemical reactivity need to discuss structural and/or electrostatic differences between the reactants

a) Cpd B b/c it has a more stable leaving group.

The larger atomic size of S relative to O means the sulfide (CH_3S^-) will have a lower electron density than the alkoxide (CH_3O-).

b) Cpd A b/c it has a more stable leaving group.

The neutral leaving group, $(CH_3)_2S$, is more stable than the charged sulfie leaving group (CH_3S^-).

c) Cpd B b/c the leaving group is resonance stabilized delocalizing the negative charge over two oxygen atoms. d) Cpd B b/c the leaving group has inductive electron withdrawal stabilization from the three fluorine atoms in addition to the resonance stabilzation.

Exercise

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) $CH_3C{\equiv}C$-Li

d) NH_3

2. Which in the following pairs is a better nuceophile?

a) $(CH_3CH_2)_2N^-$ or $(CH_3CH_2)_2NH$

b) $(CH_3CH_2)_3N$ or $(CH_3CH_2)_3B$

c) H_2O or H_2S

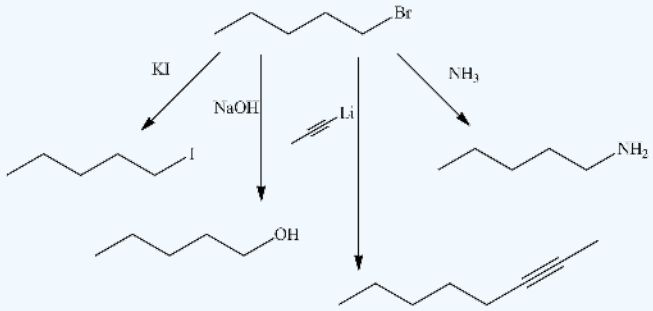
3. Order the following in increasing reactivity for an S_N2 reaction.

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?

Answer

1. (a) - (d)



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.

$$(CH_3CH_2)_3CCl \text{ -or- } (CH_3CH_2)_2CHCl \longrightarrow CH_3CH_2Br \longrightarrow CH_3CH_2OTos$$

4. They will decrease the reactivity of the reaction.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

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6.7: Stereochemistry of the SN2 Reaction

Learning Objective

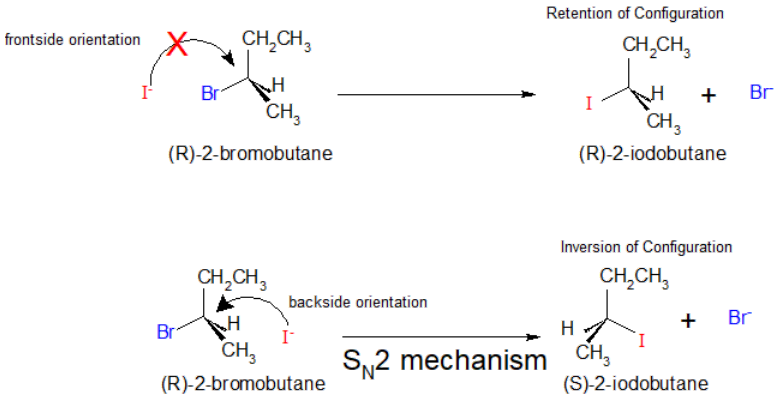
- predict the products and specify the reagents for $S_N2$reactions with stereochemistry
- propose mechanisms for S_N2 reactions
- draw and interpret Reaction Energy Diagrams for $S_N2$reactions

S_N2 Reactions Are Stereospecific

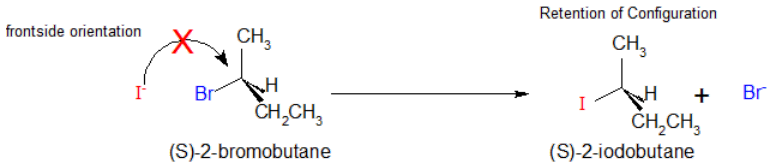
The S_N2 reaction is stereospecific like other concerted reactions.. A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. The nuclephile and electrophile must be correctly oriented for orbital overlap to occur and trigger chemical reactivity. Experimental observations show that all S_N2 reactions proceed with inversion of configuration; that is, the nucleophile will always penetrate from the backside in S_N2 reactions. To think about why this might be true, remember that the nucleophile has a lone pair of electrons to be shared with the electrophilic carbon center and the leaving group is going to take a lone pair of electrons with it upon leaving. Because like charges repel each other, the nucleophile will always proceed by a backside displacement mechanism.

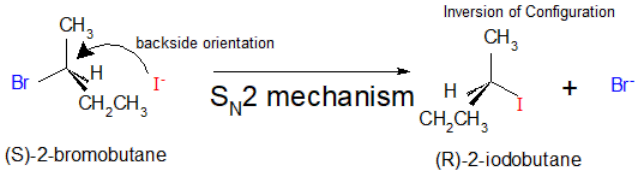
- **Frontside Orientation:** In a frontside orientation, the nucleophile approaches the electrophilic center on the same side as the leaving group. With frontside orientation, the stereochemistry of the product remains the same; that is, we have retention of configuration.
- **Backside Orientation:** In a backside orientation, the nucleophile approachss the electrophilic center on the side that is opposite to the leaving group. With backside orientation, the stereochemistry of the product does not stay the same. There is inversion of configuration.

For example, if the substrate is an R enantiomer, a frontside nucleophilic orientation results in retention of configuration, and the formation of the R enantiomer. A backside nucleophilic orientation results in inversion of configuration, and the formation of the S enantiomer.



Conversely, if the substrate is an S enantiomer, a frontside nucleophilic orientation results in retention of configuration, and the formation of the S enantiomer. A backside nucleophilic orientation results in inversion of configuration, and the formation of the R enantiomer.





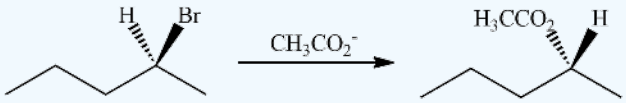
Empirically, S_N2 reactions that begin with the R enantiomer as the substrate will form the S enantiomer as the product. Those that begin with the S enantiomer as the substrate will form the R enantiomer as the product. This concept of retention and inversion of configuration can also be applied to substrates that can exist as geometric isomers (*cis* and *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

1. Predict the product of a nucleophilic substitution of (S)-2-bromopentane reacting with $CH_3CO_2^-$, Show stereochemistry.

Answer

1.



Contributors and Attributions

- Racheal Curtis (UCD)

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6.8: The Sn1 Reaction

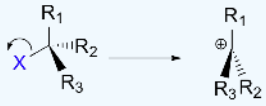
Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N1 reactions
- predict the products and specify the reagents for S_N1 reactions with stereochemistry
- propose mechanisms for S_N1 reactions
- draw and interpret Reaction Energy Diagrams for S_N1 reactions

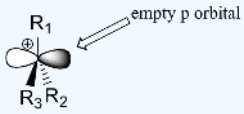
The SN1 mechanism with Stereochemistry

A second model for a nucleophilic substitution reaction is called the '**dissociative**' or '**S_N1**' mechanism. In many cases, the nucleophile is the solvent, so this mechanism can also be called "solvolysis".

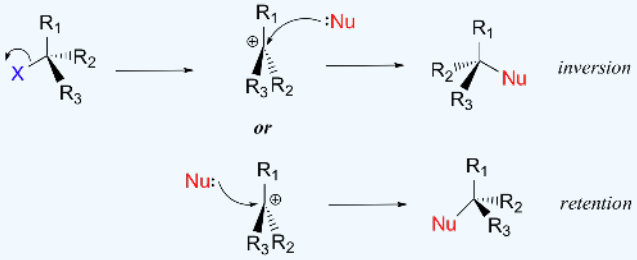
Step1: In the S_N1 mechanism, the carbocation forms when the C-X bond breaks *first*, before the nucleophile approaches



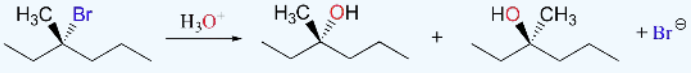
Th carbocation has a central carbon with only three bonds and bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



Step 2: The nucleophile reacts with the empty, 'electron hungry' *p* orbital of the carbocation to form a new bond and return the carbon to tetrahedral geometry. Because of this trigonal planar geometry, the nucleophile can approach the carbocation from either lobe of the empty p orbital (aka either side of the carbocation). 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* of the product occurs during SN1 reactions if the electrophilic carbon is chiral. If the intermediate from a chiral alkyl halide survives long enough to encounter a random environment, the products are expected to be racemic (a 50:50 mixture of enantiomers). On the other hand, if the departing halide anion temporarily blocks the front side, or if a nucleophile is oriented selectively at one or the other face, then the substitution might occur with predominant inversion or even retention of configuration.



As an example, the tertiary alkyl bromide below, (S)-3-bromo-3-methylhexane, would be expected to form a racemic mix of *R*- and *S*-3-methyl-3-hexanol after an S_N1 reaction with water as the nucleophile.

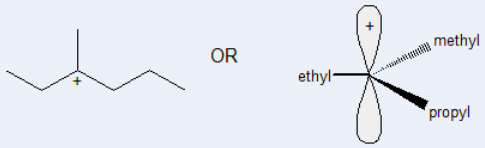


Exercise

1. Draw the structure of the intermediate in the two-step nucleophilic substitution reaction (S_N1) above.

Solution

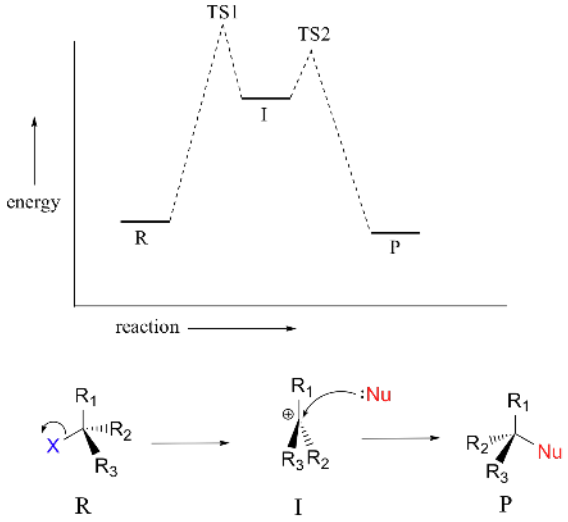
1.



When interpretting bond-line structures, it is useful to visualize the electronic structure with an unhibridized, empty p orbital extending perpendicaular to the alkyl groups.

The S_N1 Reaction Energy Diagram

The S_N1 reaction is an example of a two-step reaction with a reaction intermediate. Evaluating reactive intermediates is a very important skill in the study of organic reaction mechanisms. 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.

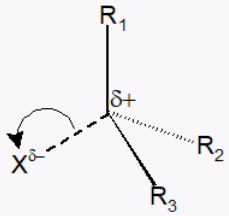


Exercise

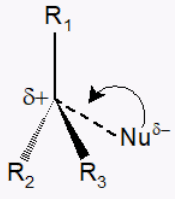
2. Draw structures representing transition state 1 (TS1) and transition state 2 (TS2) in the reaction above. Use the solid/dash wedge convention to show three dimensions.

Solution

2.



TS1 (transition state 1)



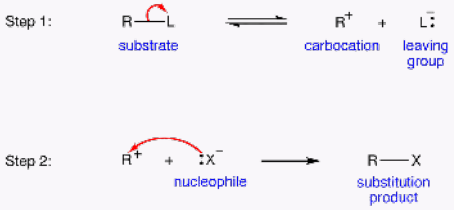
TS2 (transition state 2)

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 two 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* 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.

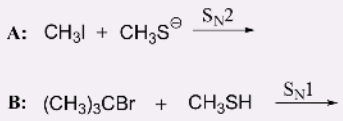
$$\text{rate} = k\,[\text{substrate}]$$

Because an S_N1 reaction is first order overall the concentration of the nucleophile does not affect the rate. The implication is that the nucleophile does not participate in the rate limiting step or any prior steps, which suggests that the first step is the rate limiting step. 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.

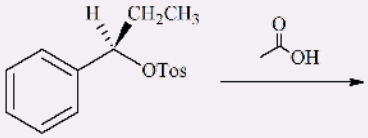


Exercise

3. 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.



4. Give the products of the following S_N1 reaction. Show stereochemistry.

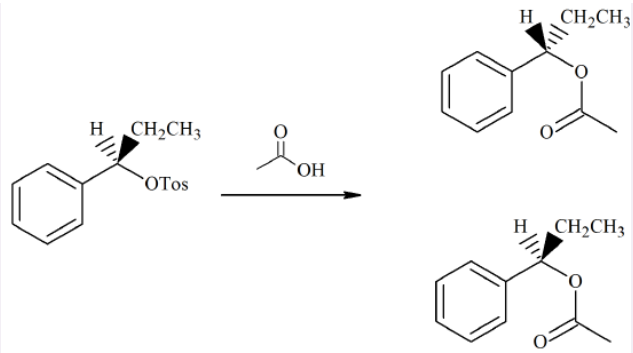


Solution

3. 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.

4.



Contributors and Attributions

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6.9: Characteristics of the Sn1 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for S_N1 reactions
- predict the products and specify the reagents for S_N1 reactions with stereochemistry
- propose mechanisms for S_N1 reactions
- draw and interpret Reaction Energy Diagrams for S_N1 reactions

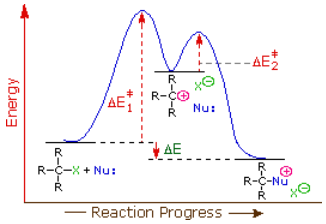
In order of decreasing importance, the factors impacting S_N1 reaction pathways are

1. structure of the alkyl halide
2. stability of the leaving group
3. type of solvent.

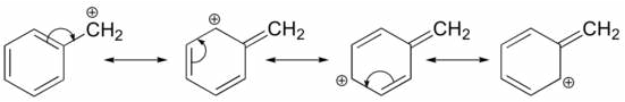
The unimolecular transition state of the S_N1 pathway means that structure of the alkyl halide and stability of the leaving group are the primary considerations. Alkyl halides that can ionize to form stable carbocations are more reactive via the S_N1 mechanism. Because carbocation stability is the primary energetic consideration, stabilization of the carbocation via solvation is also an important consideration.

Alkyl Halide Structure and Carbocation Stability

The first order kinetics of S_N1 reactions suggest a two-step mechanism in which the rate-determining step consists of carbocation formation from the ionization of the alkyl halide as shown in the diagram below. In this mechanism, the carbocation is a high-energy intermediate the bonds immediately to nearby nucleophiles. The only reactant that is undergoing change in the first (rate-determining) step is the alkyl halide, so we expect such reactions would be unimolecular and follow a first-order rate equation. Hence the name **S_N1** is applied to this mechanism.



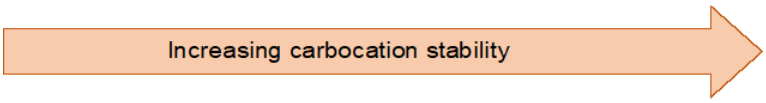
The Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate: the more stable the carbocation, the lower the activation energy, the faster the reactivity. Therefore, carbocation stability is a primary consideration in S_N1 reactions. Carbocations can be stabilized by delocalizing the charge via resonance and through inductive electron donation of alkyl groups. Carbocations can also stabilize by rearrangement via 1,2-hydride or 1,2-methyl shifts. Carbocation rearrangements are explained in a subsequent section of this chapter.



Benzyl Carbocation

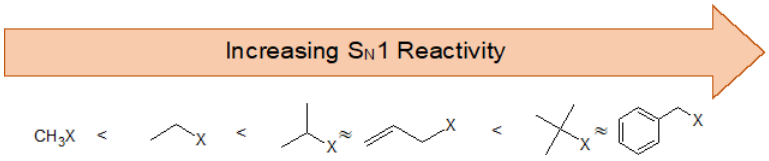
an allylic carbocation

The relative stability of carbocations is summarized below.



Carbocation Stability	$CH_3^{(+)}$	<	$CH_3CH_2^{(+)}$	<	$(CH_3)_2CH^{(+)}$	≈	$CH_2{=}CH{-}CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$(CH_3)_3C^{(+)}$

Consequently, we expect that 3º-alkyl halides will be more reactive than their 2º and 1º-counterparts in reactions that follow an S_N1 mechanism. This is opposite to the reactivity order observed for the S_N2 mechanism. Allylic and benzylic halides are exceptionally reactive by either mechanism. This trend is summarized in the diagram below.



Effects of Leaving Group

An S_N1 reaction speeds up with a good leaving group. This is because the leaving group is involved in the rate-determining step. A good leaving group wants to leave so it breaks 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.

A good leaving group is a weak base because weak bases can hold the charge. They're happy to leave with both electrons and in order for the leaving group to leave, it needs to be able to accept electrons. Strong bases, on the other hand, donate electrons which is why they can't be 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 whos leaving-group ability increases as you go down the column.

The two reactions below is the same reaction done with two different leaving groups. One is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.

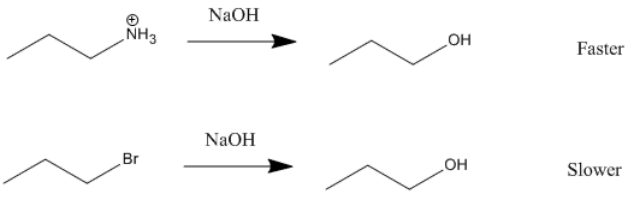


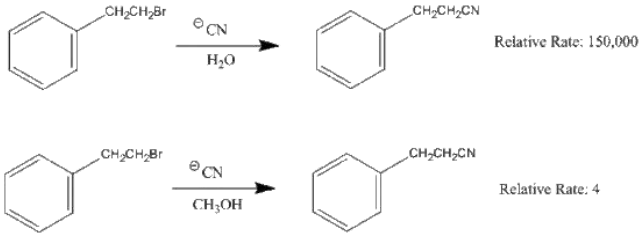
Figure below)

Methyl Sulfate Ion Mesylate Ion Triflate Ion Tosylate Ion

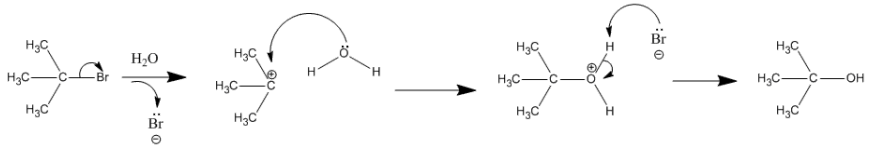
$CH_3SO_4^{2-}$ $CH_3SO_3^{2-}$ $CF_3SO_3^{2-}$ $CH_3C_6H_4SO_3^{2-}$

Solvent Effects on the S_N1 Reaction

To facilitate the charge separation of the ionization reaction in the first step, a good ionizing solvent is needed. Two solvent characteristics will be particularly important - the polarity and the solvating power. The **dielectric constant, ε,** measures polarity of solvent molecules and their ability to orient themselves between ions to attenuate (reduce) the electrostatic force one ion exerts on the other. The higher the dielectric constant the more polar the substance and in the case of SN1 reactions, the faster the rate. A dielectric constant below 15 is usually considered non-polar. Solvents having high dielectric constants, such as water (ε=81), formic acid (ε=58), dimethyl sulfoxide (ε=45) & acetonitrile (ε=39) are generally considered better ionizing solvents than are some common organic solvents such as ethanol (ε=25), acetone (ε=21), methylene chloride (ε=9) & ether (ε=4). Below is the same reaction conducted in two different solvents. The relative reaction rate in water (ε=81) is 150,000 times faster than in methanol (ε=33).



Solvation refers to the solvent's ability to stabilize ions by encasing them in a sheath of weakly bonded solvent molecules. Anions are solvated by partial positive charges of hydrogen-bonding solvents. Cations are often best solvated by the nucleophilic sites on a solvent molecule (e.g. oxygen & nitrogen atoms). The interaction of the carbocations with these nucleophilic solvents may be strong enough to form covalent bonds to carbon, thus converting the intermediate to a substitution product and creating the reaction name "solvolysis". When solvolysis occurs with water, the actions are called "hydrolysis reactions" as shown in the reaction below.



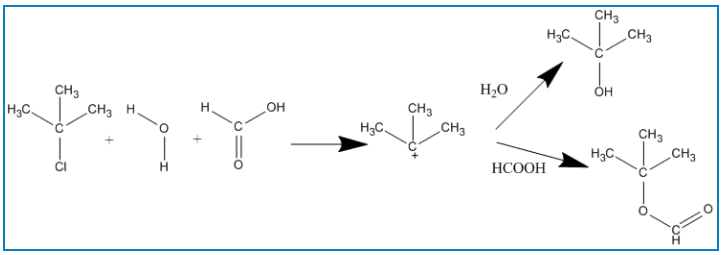
Polar Protic and Polar Aprotic Solvents

Protic solvents contain polarized hydrogen. Whereas, aprotic solvents do NOT contain polarized hydrogen. For S_N2 reactions, solvation of the nucleophile by polar protic solvents slows the reaction rate. However, in S_N1 reaction the nucleophile is not a part of the rate-determining step so this concern is not relevant. In fact, polar protic solvents actually speed up the rate of S_N1 reactions because the polar solvent helps stabilize the transition state and carbocation intermediate. Since the carbocation is unstable, anything that can stabilize this even a little will speed up the reaction. Polar aprotic solvents have a dipole moment, but their hydrogen is not highly polarized. Polar aprotic solvents are not used in S_N1 reactions because some of them can react with the carbocation intermediate and give an unwanted side-product. Rather, polar protic solvents are preferred for unimolecular substitution reactions.

Effects of Nucleophile

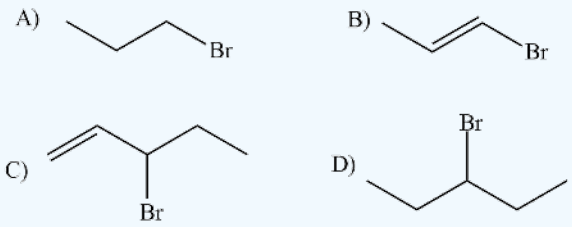
The strength of the nucleophile does not affect the reaction rate of S_N1 because the nucleophile is not involved in the rate-determining step. Since nucleophiles only participate in the fast second step, their relative molar concentrations rather than their nucleophilicities should be the primary product-determining factor. If a nucleophilic solvent such as water is used, its high concentration will assure that alcohols are the major product. 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. For example, if t-butylchloride reacts with a mixture of water and formic acid where the water and formic acid are competing nucleophiles, two different products are formed: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depends on the concentrations

and relative reactivities of the nucleophiles. With a higher electron density, water is considered the stronger nucleophile and the tertiary alcohol will be the major product if there are equal concentrations of competing nucleophiles.



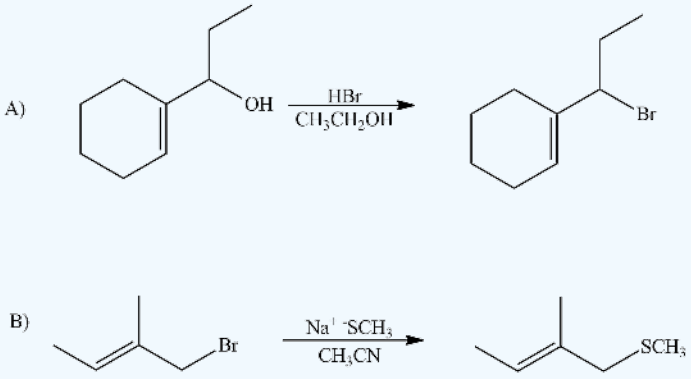
Exercises

1. Rank the following by increasing reactivity in an S_N1 reaction.



2. 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.

3. Label the following reactions as most likely occuring by an S_N1 or S_N2 mechanism. Suggest why.



Answers

1. Consider the stability of the intermediate, the carbocation.

A < D < B < C (most reactive)

2. They have the same intermediates when you look at the resonance forms.

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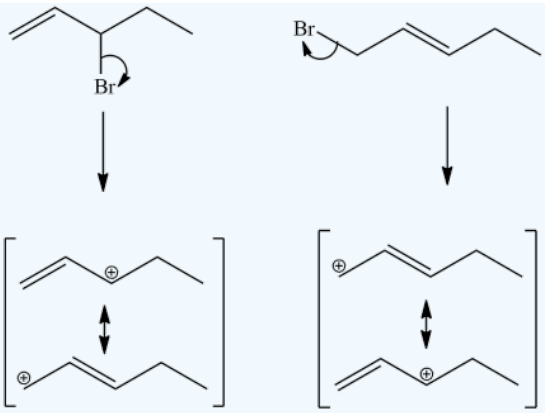

3. A – S_N1 *poor leaving group, protic solvent, secondary cation intermediate

B – S_N2 *good leaving group, polar solvent, primary position.

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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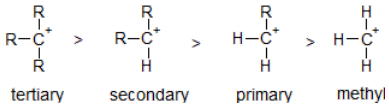
6.10: Rearrangements of the Carbocation and S_n1 Reactions

Learning Objective

- predict carbocation rearrangements in 1st order reactions

Whenever reactants like alkyl halides form carbocations, the carbocations are subject to a phenomenon known as carbocation rearrangement. A carbocation is highly reactive and holds the positive charge on carbon with a sextet rather than an octet. There are two types of rearrangements: hydride shift and alkyl shift. Rearrangements occur to create more stable carbocations. Reviewing carbocation stability from chapter 5 is helpful in identifying carbocations that can undergo rearrangement.

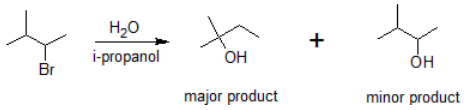
Relative Stability of Carbocations



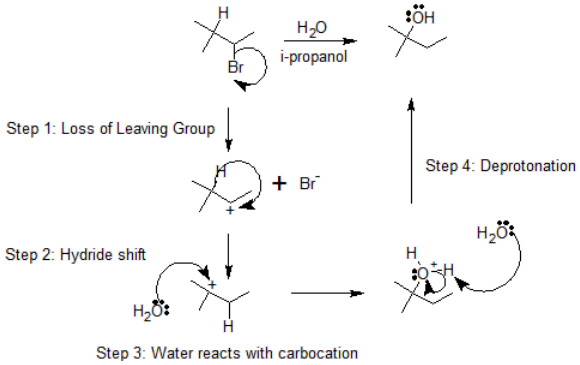
Once rearranged, the molecules can also undergo further unimolecular substitution (S_N1) or unimolecular elimination (E1). Nucleophilic reactions often produce two products, a major product and a minor product. The major product is typically the rearranged product that is more substituted (aka more stable). The minor product, in contract, is typically the normal product that is less substituted (aka less stable). Similarly, we will see in subsequent sections of this chapter that for the unimolecular elimination reaction, a more substituted alkene can form through carbocation rearrangements ("stay tuned for coming attractions").

Hydride Shift

The hydride shift can also be called the 1,2-Hydride Shift because rearrangements primarily occur between adjacent carbon atoms. The 1,2 are communicating that the carbons are vicinal (adjacent). These numbers have nothing to do with the nomenclature of the reactant. We can see the phenomenon of hydride shift in solvolysis (SN1) reactions like the example below.

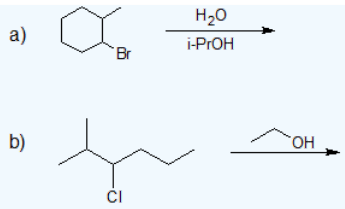


As shown in the following mechanism, the polarized carbon-chlorine bonds is heterolytically broken to produce a chloride ion and carbocation. The secondary carbocation undergoes a 1,2 hydride shift to produce the more stable tertiary carbocation. The oxygen of a water molecule acts as the nucleophile and reacts with the carbocation to form a protonated alcohol. The intermediate is deprotonated to form the final product, an alcohol. The mechanism for hydride shift occurs in *multiple steps* that includes various intermediates and transition states.

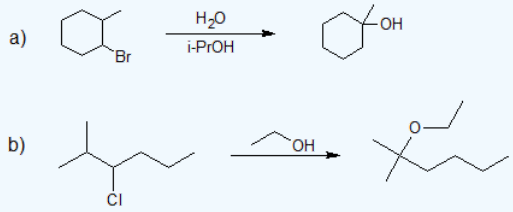


Exercise

1. Draw the bond-line structure for the major solvolysis product of each reaction.

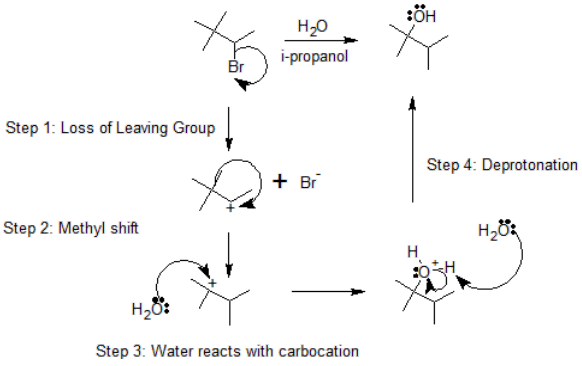


Answer



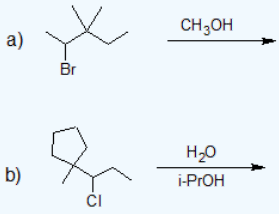
Alkyl Shift

Not all carbocations have suitable hydrogen atoms (either secondary or tertiary) that are on adjacent carbon atoms available for rearrangement. In this case, the reaction can undergo a different mode of rearrangement known as **alkyl shift** (or alkyl group migration). Alkyl Shift acts very similarily to that of hydride shift. Instead of the proton (H) that shifts with the nucleophile, we see an alkyl group that shifts with the nucleophile instead. The shifting group carries its electron pair with it to furnish a bond to the neighboring or adjacent carbocation. The shifted alkyl group and the positive charge of the carbocation switch positions on the molecule.

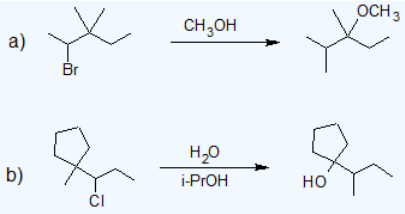


Exercise

2. Draw the bond-line structure for the major solvolysis product of each reaction.

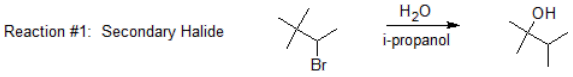


Answer

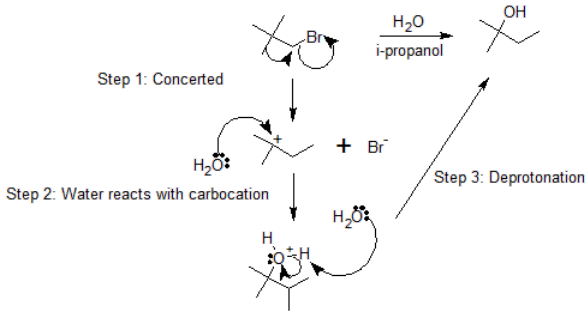


Alkyl Halide Classification and Carbocation Rearrangements

Reactions of tertiary carbocations react much faster than that of secondary carbocations and will form the major product almost exclusively. Alkyl shifts from a secondary carbocation to tertiary carbocation in S_N1 reactions occur by independent steps. When the alkyl halide is primary, then slight variations and differences between the two reaction mechanisms. In reaction #1, we see that we have a secondary substrate. This undergoes alkyl shift because it does not have a suitable hydrogen on the adjacent carbon. Once again, the reaction is similar to hydride shift. The only difference is that we shift an alkyl group rather than shift a proton, while still undergoing various intermediate steps to furnish its final product.

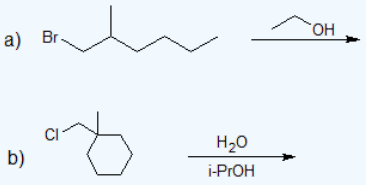


With reaction #2, on the other hand, we can say that it undergoes a *concerted* mechanism. In short, this means that everything happens in one step. This is because primary carbocations *cannot* be an intermediate and they are relatively difficult processes since they require higher temperatures and longer reaction times. After protonating the alcohol substrate to form the alkyloxonium ion, the water must leave *at the same time* as the alkyl group shifts from the adjacent carbon to skip the formation of the unstable primary carbocation.

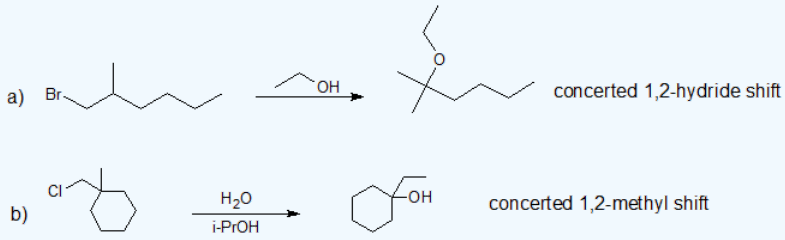


Exercise

3. Draw the bond-line structure for the major solvolysis product of each reaction.



Answer



1,3-Hydride and Greater Shifts

Typically, hydride shifts can occur at low temperatures. However, by heating the solutionf of a cation, it can easily and readily speed the process of rearrangement. One way to account for a slight barrier is to propose a 1,3-hydride shift interchanging the functionality of two different kinds of methyls. Another possibility is 1,2 hydride shift in which you could yield a secondary carbocation intermediate. Then, a further 1,2 hydride shift would give the more stable rearranged tertiary cation.

More distant hydride shifts have been observed, such as 1,4 and 1,5 hydride shifts, but these arrangements are too fast to undergo secondary cation intermediates.

Analogy

Carbocation rearrangements happen very readily and often occur in many organic chemistry reactions. Yet, we typically neglect this step. Dr. Sarah Lievens, a Chemistry professor at the University of California, Davis once said carbocation rearrangements can be observed with various analogies to help her students remember this phenomenon. For hydride shifts: "The new friend (nucleophile) just joined a group (the organic molecule). Because he is new, he only made two new friends. However, the popular kid (the hydrogen) glady gave up his friends to the new friend so that he could have even more friends. Therefore, everyone won't be as lonely and we can all be friends." This analogy works for alkyl shifts in conjunction with hydride shift as well.

References

1. Vogel, Pierre. Carbocation Chemistry. Amsterdam: Elsevier Science Publishers B.V., 1985.
2. Olah, George A. and Prakash, G.K. Surya. Carbocation Chemistry. New Jersey: John Wiley & Sons, Inc., 2004.
3. Vollhardt, K. Peter C. and Schore, Neil E. Organic Chemistry: Structure and Function. New York: Bleyer, Brennan, 2007.

Outside links

- en.Wikipedia.org/wiki/Carboca..._rearrangement
- Watch a short presentation on the carbocation rearrangement phenomenon

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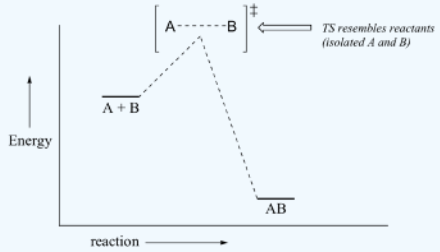
6.11: The Hammond Postulate and Transition States

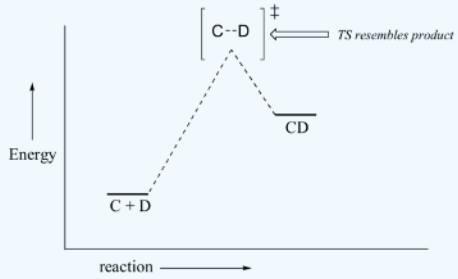
Learning Objective

- explain and apply Hammond's Postulate to substitution reactions

Now, back to transition states. Chemists are often very interested in trying to learn about what the transition state for a given reaction looks like, but addressing this question requires an indirect approach because the transition state itself cannot be observed. In order to gain some insight into what a particular transition state looks like, chemists often invoke the **Hammond postulate**, which states that *a transition state resembles the structure of the nearest stable species*. For an exergonic reaction, therefore, the transition state resembles the reactants more than it does the products.



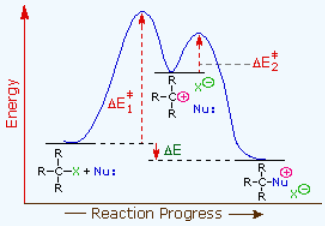
If we consider a hypothetical exergonic reaction between compounds A and B to form AB, the distance between A and B would be relatively large at the transition state, resembling the starting state where A and B are two isolated species. In the hypothetical endergonic reaction between C and D to form CD, however, the bond formation process would be much further along at the TS point, resembling the product.



The Hammond Postulate is a very simplistic idea, which relies on an assumption that potential energy surfaces are parabolic. Although such an assumption is not rigorously true, it is fairly reliable and allows chemists to make energetic arguments about transition states by employing arguments about the stability of a related species. Since the formation of a reactive intermediate is very reliably **endergonic**, arguments about the stability of reactive intermediates can serve as proxy arguments about transition state stability.

The Hammond Postulate and the SN1 Reaction

The Hammond postulate suggests that the activation energy of the rate-determining first step will be inversely proportional to the stability of the carbocation intermediate. The stability of carbocations is shown qualitatively below:



Carbocation Stability

$$\mathrm{CH_3(+) < CH_3CH_2(+) < (CH_3)_2CH(+) \approx\ CH_2{=}CH{-}CH_2(+)} \\ \mathrm{< C_6H_5CH_2(+) \approx\ (CH_3)_3C(+)} \tag{6.11.1}$$

Consequently, we expect that 3º-alkyl halides will be more reactive than their 2º and 1º-counterparts in reactions that follow an S_N1 mechanism. This is opposite to the reactivity order observed for the S_N2 mechanism. Allylic and benzylic halides are exceptionally reactive by either mechanism.

Contributors

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6.12: Comparison of SN1 and SN2 Reactions

Learning Objective

- distinguish 1st or 2nd order substitution reactions

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. These patterns of reactivity of summarized below.

Alkyl Halide Structure	Possible Substitution Reactions
methyl and primary	S_N2 only
secondary	S_N2 and S_N1
tertiary	S_N1 only
primary and secondary benzylic and allylic	S_N2 and S_N1
tertiary benzylic and allylic	S_N1 only
vinyl and aryl	NO reaction

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.

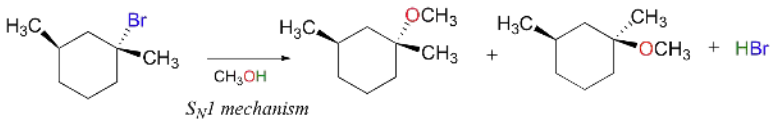
3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the transition state and carbocation intermediate. S_N1 reactions are called solvolysis reactions when the solvent is the nucleophile.

These patterns of reactivity are summarized in the table below.

Comparison between S_N2 and S_N1 Reactions

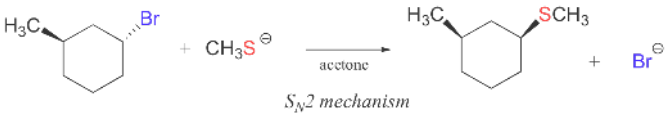
Reaction Parameter	S_N2	S_N1
alkyl halide structure	methyl > primary > secondary >>>> tertiary	tertiary > secodary >>>> primary > methyl
nucleophile	high concentration of a strong nucleophile	poor nucleophile (often the solvent)
mechanism	1-step	2-stp
rate limiting step	bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Nu]	rate = k[R-X]
stereochemisty	inversion of configuration	mixed configuration
solvent	polar aprotic	polar protic

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.



S_N1 mechanism

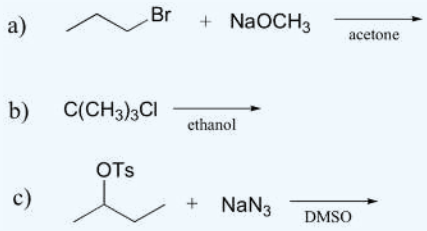
In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar protic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



S_N2 mechanism

Exercise

1. Determine whether each substitution reaction shown below is likely to proceed by an S_N1 or S_N2 mechanism and explain your reasoning.



Answer

a) S_N2 b/c primary alkyl halide with a strong nucleophile in a polar aprotic solvent.

b) S_N1 b/c tertiary alkyl halide with a weak nucleophile that is also the solvent (solvolysis).

c) S_N2 b/c secondary alkyl halides favor this mechanism when reacted with a strong nucleophile (and weak base) in a polar aprotic solvent.

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6.13: Characteristics of the E2 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for E2 reactions
- predict the products and specify the reagents for E2 reactions with stereochemistry
- propose mechanisms for E2 reactions
- draw and interpret Reaction Energy Diagrams for E2 reactions

In order of decreasing importance, the factors impacting E2 reaction pathways are

1) structure of the alkyl halide

2) strength of the base

3) stability of the leaving group

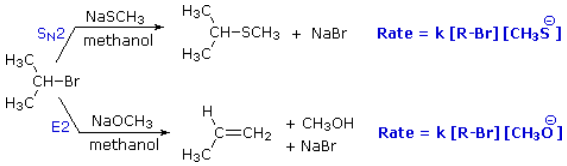
4) type of solvent.

The bimolecular transition state of the E2 pathway means that orientation of the base and leaving group are a primary consideration. Both the base and leaving group are electron rich and electrostatically repel each other forcing an anti-coplanar orientation between the base and leaving group. The structure of the alkyl halide must assume the orientation for an anti-coplar transition state. The strength of the base will also influence the reaction along with the stability of the leaving group. Solvents play a very minor role in E2 pathway.

Introduction

E2 reactions are typically seen with secondary and tertiary alkyl halides, but a hindered base is necessary with a primary halide. The mechanism by which it occurs is a single step **concerted** reaction with one transition state. The rate at which this mechanism occurs is second order kinetics, and depends on both the base and alkyl halide. A good leaving group is required because it is involved in the rate determining step. The leaving groups must be coplanar in order to form a pi bond; carbons go from sp^3 to sp^2 hybridization states.

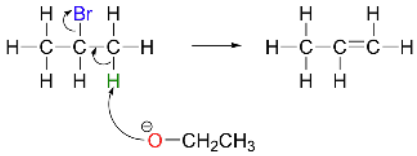
To get a clearer picture of the interplay of these factors involved in a a reaction between a nucleophile/base and an alkyl halide, consider the reaction of a 2º-alkyl halide, isopropyl bromide, with two different nucleophiles. In one pathway, a methanethiolate nucleophile substitutes for bromine in an S_N2 reaction. In the other (bottom) pathway, methoxide ion acts as a base (rather than as a nucleophile) in an elimination reaction. As we will soon see, the mechanism of this reaction is single-step, and is referred to as the E2 mechanism.



General Reaction

Below is a mechanistic diagram of an elimination reaction by the E2 pathway:

.



In this reaction, ethoxide ($CH_3CH_2O^-$) represents the base and Br representents a leaving group, typically a halogen. There is one transition state that shows the concerted reaction for the base attracting the hydrogen and the halogen taking the electrons from the bond. The product be both eclipse and staggered depending on the transition states. Eclipsed products have a synperiplanar transition

states, while staggered products have anticoplanar (antiperiplanar) transition states. Staggered conformation is usually the major product because of its lower energy confirmation.

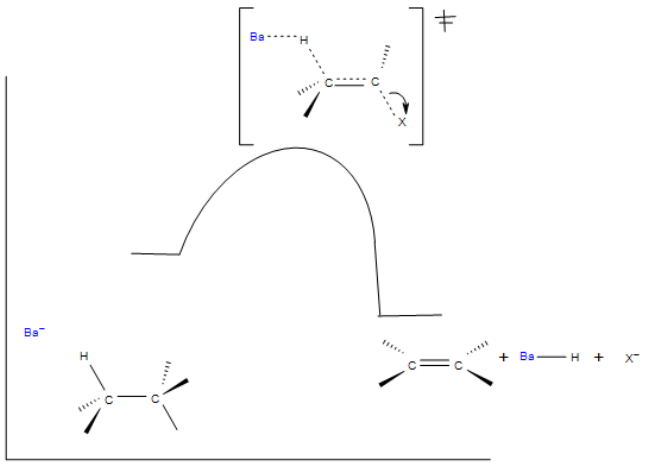
An E2 reaction has certain requirements to proceed:

- A strong base is necessary especially necessary for primary alkyl halides. Secondary and tertirary primary halides will procede with E2 in the presence of a base (OH^-, RO^-, R_2N^-)
- Both leaving groups should be on the same plane, this allows the double bond to form in the reaction. In the reaction above you can see both leaving groups are in the plane of the carbons.
- Follows Zaitsev's rule, the most substituted alkene is usually the major product.
- Hoffman Rule, a strically hindered base will result in the least substituted product.

E2 Reaction Coordinate

In the reaction energy diagram below, the base is represented as Ba^-. The bimolecular transition state determines the overall reaction rate. It is important to note the anti-coplanar orientation of the base and the leaving group. Both the base and leaving group are electron rich and electrostatically repel each other forcing an anti-coplanar orientation between the base and leaving group.

anti-coplanar transition state



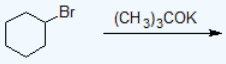
The Leaving Group Effect in E_2 Reactions

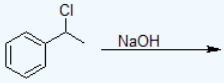
As Size Increases, The Electron Density Decrease, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

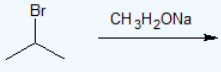
F	<	Cl	<	Br	<	I
Worst		Fair		Good		Excellent

Exercise

1. Ignoring the alkene stereochemistry show the elimination product(s) of the following compounds.

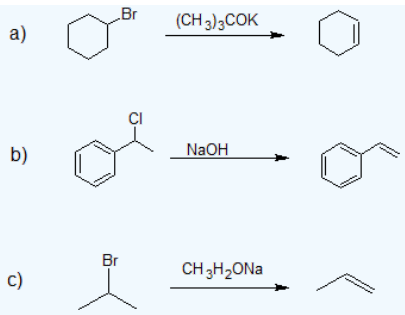
a) 

b) 

c) 

Answer

1.



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6.14: Zaitsev's Rule

Learning Objective

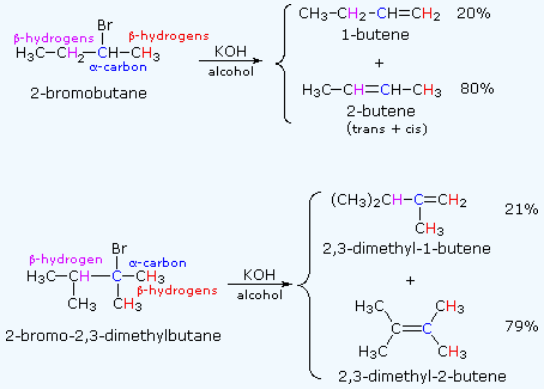
- use Zaitsev’s rule to predict major and minor products of elimination reactions

Zaisev's Rule and Regioselectivity

The prefix "regio" indicates the interaction of reactants during bond making and/or bond breaking occurs preferentially by one orientation. Because the beta-carbons of an alkyl halide may not be equivalent, there can be more than one possible elimination product. Zaitsev's Rule can be used to predict the regiochemistry of elimination reactions.

Zaitsev’s or Saytzev’s (anglicized spelling) rule is an empirical rule used to predict regioselectivity of beta-elimination reactions occurring via the E1 or E2 mechanisms. It states that in a regioselective E1 or E2 reaction the major product is the more stable alkene with the more highly substituted double bond as shown in the example below.

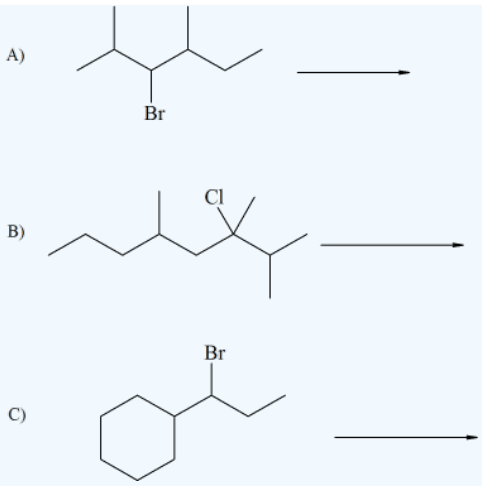
If two or more structurally distinct groups of beta-hydrogens are present in a given reactant, then several constitutionally isomeric alkenes may be formed by an E2 elimination. This situation is illustrated by the 2-bromobutane and 2-bromo-2,3-dimethylbutane elimination examples given below.



By using the strongly basic hydroxide nucleophile, we direct these reactions toward elimination. In both cases there are two different sets of beta-hydrogens available to the elimination reaction (these are colored red and magenta and the alpha carbon is blue). 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 1º-hydrogens (red) and two 2º-hydrogens (magenta) 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 1º-beta-hydrogens compared with one 3º-hydrogen. These results point to a strong regioselectivity favoring the more highly substituted product double bond, an empirical statement generally called the **Zaitsev Rule**.

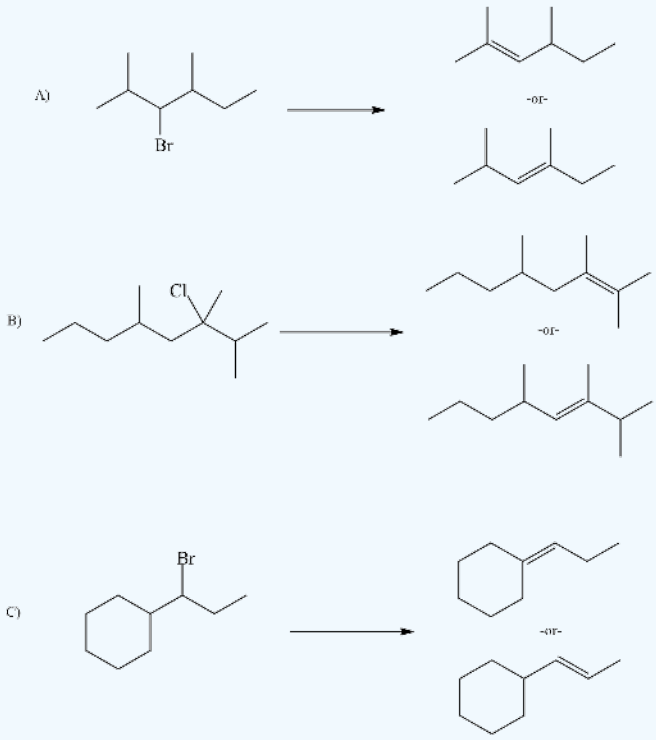
Exercise

1. Ignoring the alkene stereochemistry show the elimination product(s) of the following compounds:



Answer

1.



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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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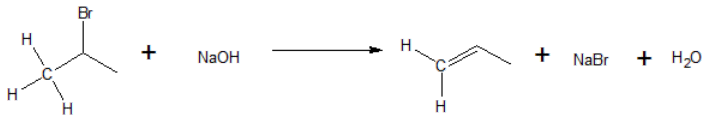
6.15: Characteristics of the E1 Reaction

Learning Objective

- determine the rate law & predict the mechanism based on its rate equation or reaction data for E1 reactions
- predict the products and specify the reagents for E1 reactions with stereochemistry
- propose mechanisms for E1 reactions
- draw and interpret Reaction Energy Diagrams for E1 reactions

General Reaction

Unimolecular Elimination (E1) is a reaction in which loss of the leaving group followed by removal of he beta-hydrogen 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 as the rate determining (slow) step, hence the name unimolecular. . Alkyl halides that can ionize to form stable carbocations are more reactive via the E1 mechanism. Because carbocation stability is the primary energetic consideration, stabilization of the carbocation via solvation is also an important consideration. Because carbocations are highly reactive, the strength of the base is not important and weak bases can be used. Since S_N1 and E1 reactions behave similarly, they often 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. Heating the reaction favors elimination over substitution.

In order of decreasing importance, the factors impacting E1 reaction pathways are

1) structure of the alkyl halide

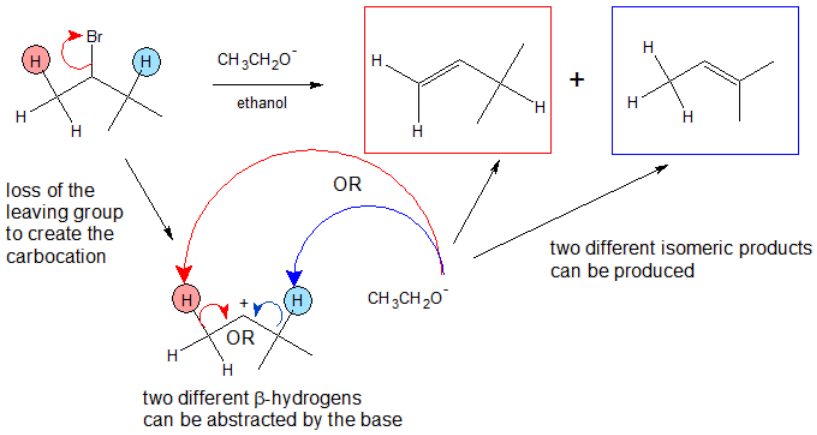
2) stability of the carbocation

3) type of solvent

4) strength of the base.

Mechanism for Alkyl Halides

As can be seen in the E1 mechanism below, the preliminary step is the leaving group (LG) leaving on its own. Because it takes the electrons in the bond along with it, the carbon that was attached to it loses its electron, making it a carbocation. Once it becomes a carbocation, a Lewis Base (B^-) deprotonates the intermediate carbocation at the beta position, which then donates its electrons to the neighboring C-C bond to form a double bond. Unlike E2 reactions, which require the 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 already left the molecule. The final product is an alkene along with the HB byproduct and leaving group salt.



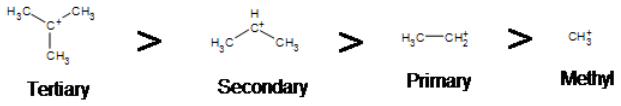
Once again, we see the two steps of the E1 mechanism.

1. A base deprotonates a beta carbon to form a pi bond.

In this case we see a mixture of products rather than one discrete one. This is the case because the carbocation has two nearby carbons that are capable of being deprotonated, but that only one forms a major product (more stable).

Reactivity

Due to the fact that E1 reactions create a carbocation intermediate, rules present in S_N1 reactions still apply.



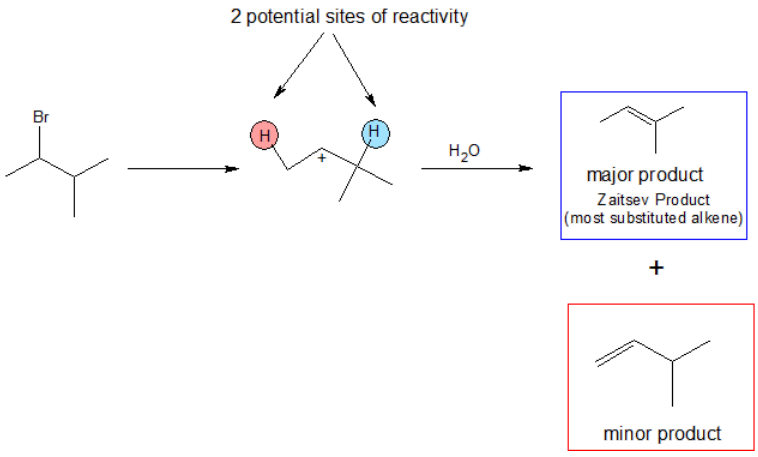
As expected, tertiary carbocations are favored over secondary, primary and methyl's. This is due to the phenomena of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing 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. Secondary and Tertiary carbons form more stable carbocations, thus this formation occurs quite rapidly.

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.

Regiochemistry & Stereochemistry of the E1 Reaction

The E1 reaction is regiospecific because it follows Zaitsev's rule that states the more substituted alkene is the major product. This infers that the hydrogen on the most substituted carbon is the most probable to be deprotonated, thus allowing for the most substituted alkene to be formed.

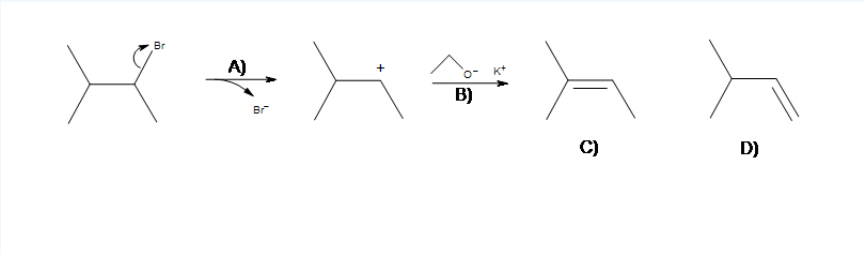
Unlike E2 reactions, the E1 reaction is not stereospecific. Thus, a hydrogen is not required to be anti-coplanar to the leaving group because the leaving group is gone. In the mechanism below, we can see two possible pathways for the reaction. Either one leads to a plausible resultant product, however, only one forms a major product. As stated by **Zaitsev's rule**, deprotonation of the most substituted carbon results in the most substituted alkene. This then becomes the most stable product due to hyperconjugation, and is also more common than the minor product.



Exercises

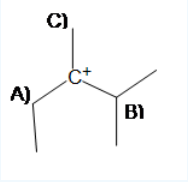
1. Which of these steps is the rate determining step (A or B)?

What is the major product formed (C or D)?

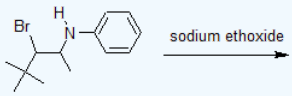


2. In order to produce the most stable alkene product, from which carbon should the base deprotonate (A, B, or C)?

If the carbocation were to rearrange, on which carbon would the positive charge go onto without sacrificing stability (A, B, or C)?



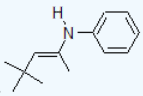
3) Predict the major product of the following reaction.



4) (True or False) – There is no way of controlling the product ratio of E1 / S_n1 reactions.

5) Explain why the presence of a weak base / nucleophile favors E1 reactions over E2.

Answer

1. A , C
2. B, B
3. 

4. False - They can be thermodynamically controlled to favor a certain product over another.

5. By definition, an E1 reaction is a Unimolecular Elimination reaction. This means the only rate determining step is that of the dissociation of the leaving group to form a carbocation. Since E2 is bimolecular and the nucleophilic attack is part of the rate determining step, a weak base/nucleophile disfavors it and ultimately allows E1 to dominate. (Don't forget about S_N1 which still pertains to this reaction simaltaneously).

Outside Links

- E1 reaction background: http://en.Wikipedia.org/wiki/E1_elimination

Outside Sources

1. McMurry, J., Simanek, E. Fundamentals of Organic Chemistry, 6th edition. Cengage Learning, 2007.

Contributors

- Satish Balasubramanian

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6.16: E2 Regiochemistry and Cyclohexane Conformations

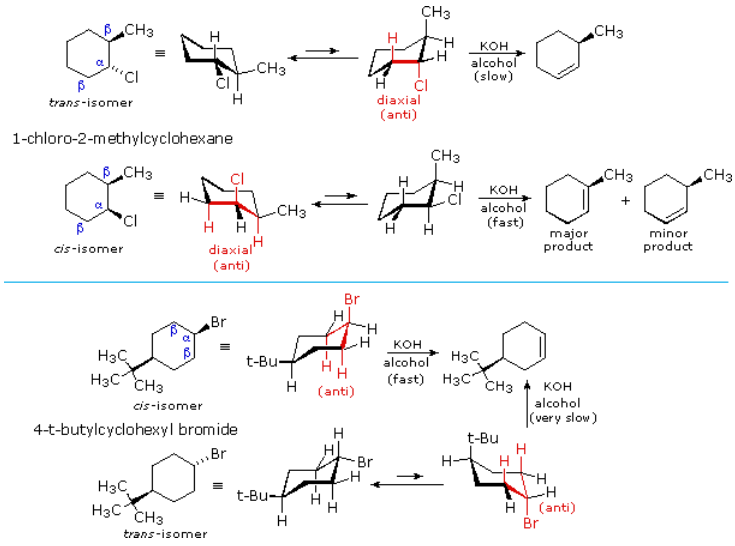
Learning Objective

- use Zaitsev's rule to predict major and minor products of elimination reactions including halocyclohexanes

Cyclohexane Conformation & Anti-coplanar Orientation

The concerted mechanism of the E2 reaction requires that the base and leaving group are orientated anti-coplanar to each other. When the beta-hydrogen and leaving group (halide for this chapter) are located on a 6-membered ring, then Zaitsev's Rule may not be followed. The beta-hydrogen and leaving group must both be in the axial position for the E2 reaction to occur. Consequently, E2 reactions of certain cycloalkyl halides show unusual rates and regioselectivity that are not explained by the principles thus far discussed. For example, trans-2-methyl-1-chlorocyclohexane reacts with alcoholic KOH at a much slower rate than does its cis-isomer. Furthermore, the product from elimination of the trans-isomer is 3-methylcyclohexene (not predicted by the Zaitsev rule), whereas the cis-isomer gives the predicted 1-methylcyclohexene as the chief product. These differences are described by the first two equations in the following diagram.

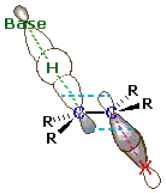
Unlike open chain structures, cyclic compounds generally restrict the spatial orientation of ring substituents to relatively few arrangements. Consequently, reactions conducted on such substrates often provide us with information about the preferred orientation of reactant species in the transition state. Stereoisomers are particularly suitable in this respect, so the results shown here contain important information about the E2 transition state.



The most sensible interpretation of the elimination reactions of 2- and 4-substituted halocyclohexanes is that this reaction prefers an **anti orientation** of the halogen and the beta-hydrogen which is attacked by the base. These anti orientations are colored in red in the above equations. The compounds used here all have six-membered rings, so the anti orientation of groups requires that they assume a diaxial conformation. The observed differences in rate are the result of a steric preference for equatorial orientation of large substituents, which reduces the effective concentration of conformers having an axial halogen. 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. Because of symmetry, the two axial beta-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 chlorine 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.

A similar analysis of the 1-chloro-2-methylcyclohexane isomers explains both the rate and regioselectivity differences. Both the chlorine and methyl groups may assume an equatorial orientation in a chair conformation of the trans-isomer, as shown in the top

equation. The axial chlorine needed for the E2 elimination is present only in the less stable alternative chair conformer, but this structure has only one axial beta-hydrogen (colored red), and the resulting elimination gives 3-methylcyclohexene. In the cis-isomer the smaller chlorine atom assumes an axial position in the more stable chair conformation, and here there are two axial beta hydrogens. The more stable 1-methylcyclohexene is therefore the predominant product, and the overall rate of elimination is relatively fast.

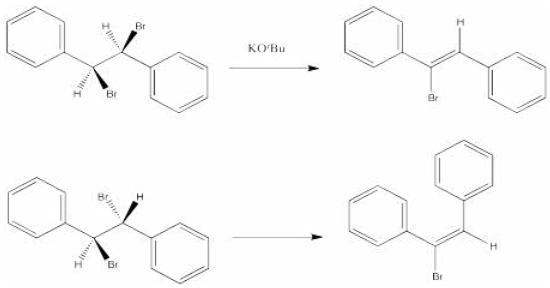


An orbital drawing of the anti-transition state is shown on the right. Note that the base attacks the alkyl halide from the side opposite the halogen, just as in the S_N2 mechanism. In this drawing the α and β carbon atoms are undergoing a rehybridization from sp^3 to sp^2 and the developing π-bond is drawn as dashed light blue lines. The symbol **R** represents an alkyl group or hydrogen. Since both the base and the alkyl halide are present in this transition state, the reaction is bimolecular and should exhibit second order kinetics. We should note in passing that a syn-transition state would also provide good orbital overlap for elimination, and in some cases where an anti-orientation is prohibited by structural constraints *syn*-elimination has been observed.

Alkyl Halide Chains

Instead, in an E2 reaction, stereochemistry of the double bond -- that is, whether the *E* or *Z* isomer results -- is dictated by the stereochemistry of the starting material, if it is diastereomeric. In other words, if the carbon with the hydrogen and the carbon with the halogen are both chiral, then one diastereomer will lead to one product, and the other diastereomer will lead to the other product.

The following reactions of potassium ethoxide with dibromostilbene (1,2-dibromo-1,2-diphenylethane) both occurred via an E2 mechanism. Two different diastereomers were used. Two different stereoisomers (*E* vs. *Z*) resulted.



Exercise

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

1. The *cis* isomer will react faster than the *trans*. The *cis* isomer has two possible perpendicular hydrogen in which it can eliminate from.

trans cis

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.17: The E2 Reaction and the Deuterium Isotope Effect

Learning Objective

- explain how the kinetic isotope effect (KIE) can be used to elucidate reaction mechanisms

Kinetic Isotope Effects

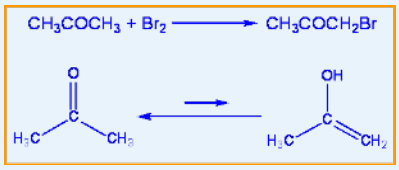
Kinetic Isotope Effects (KIEs) are used to determine reaction mechanisms by determining rate limiting steps and transition states and are commonly measured using NMR to detect isotope location or GC/MS to detect mass changes. In a KIE experiment an atom is replaced by its isotope and the change in rate of the reaction is observed. A very common isotope substitution is when hydrogen is replaced by deuterium. This is known as a deuterium effect and is expressed by the ratio k_H/k_D (as explained above). Normal KIEs for the deuterium effect are around 1 to 7 or 8. Large effects are seen because the percentage mass change between hydrogen and deuterium is great. Heavy atom isotope effects involve the substitution of carbon, oxygen, nitrogen, sulfur, and bromine, with effects that are much smaller and are usually between 1.02 and 1.10. The difference in KIE magnitude is directly related to the percentage change in mass. Large effects are seen when hydrogen is replaced with deuterium because the percentage mass change is very large (mass is being doubled) while smaller percent mass changes are present when an atom like sulfur is replaced with its isotope (increased by two mass units).

Primary KIEs

Primary kinetic isotope effects are rate changes due to isotopic substitution at a site of bond breaking in the rate determining step of a reaction.

Example

Consider the bromination of acetone: kinetic studies have been performed that show the rate of this reaction is independent of the concentration of bromine. To determine the rate determining step and mechanism of this reaction the substitution of a deuterium for a hydrogen can be made.



When hydrogen was replaced with deuterium in this reaction a $\frac{k_H}{k_D}$ of 7 was found. Therefore the rate determining step is the tautomerization of acetone and involves the breaking of a C-H bond. Since the breaking of a C-H bond is involved, a substantial isotope effect is expected.

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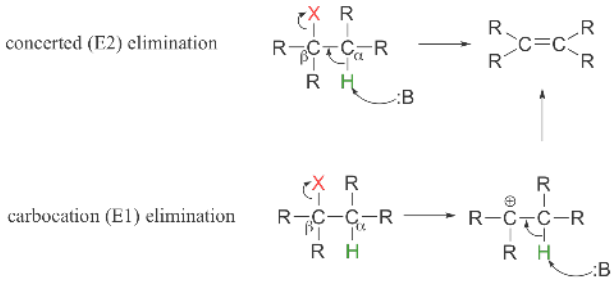
6.18: Comparison of E1 and E2 Reactions

Learning Objective

- distinguish 1st or 2nd order elimination reactions

Elimination reactions of alkyl halides can occur via the bimolecular E2 mechanism or unimolecular E1 mechanism as shown in the diagram below.



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.

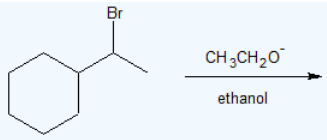
2) **The solvent**: good ionizing xolvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.

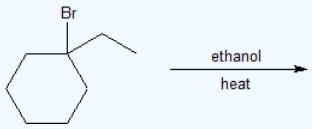
3) **The alkyl halide:** primary alkyl halides have the only structure useful in distinguishing between the E2 and E1 pathways. Since primary carbocations do not form, only the E2 mechanism is possible.

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	anti-coplanar bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Base]	rate = k[R-X]
stereochemisty	retained configuration	mixed configuration
solvent	not important	polar protic

Exercises

1. Predict the dominant elimination mechanism (E1 or E2) for each reaction below. Explain your reasoning.

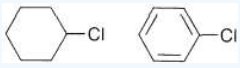
a) 

b) 

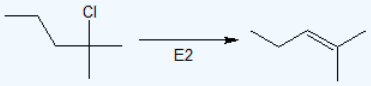
2. Which one of the following groups of compounds would eliminate **HCl** most readily on reaction with potassium hydroxide? Explain your reasoning, draw the bond-line structure and give the IUPAC name of the product.

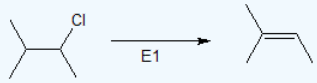
a) $(CH_3)_3CCl$ $CH_3CH_2CH_2CH_2Cl$ $CH_3CH(Cl)CH_2CH_3$

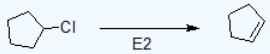
b) $(CH_3)_3CCH_2Cl$ $(CH_3)_2CHCH_2Cl$

c) 

3. Specify the reaction conditions to favor the indicated elimination mechanism.

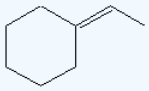
a) 

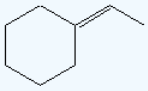
b) 

c) 

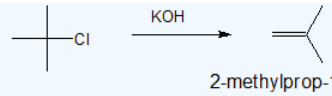
Answer

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) 

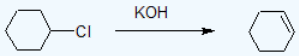
2-methylprop-1-ene

t-butyl chloride will react faster b/c it is a tertiary alkyl halide reacting with a strong base via the E2 mechanism.

b)

3-methylbut-1-ene

1-chloro-3-methyl butane will react faster since both reactants are primary alkyl halides and the reaction conditions favor the E2 mechanism, the reactant with less steric hindrance at the beta-hydrogen will react faster.

c) 

cyclohexene

The alkyl halide b/c aryl halides cannot undergo elimination reactions under these conditions.

3. 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

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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6.19: Comparing Substitution and Elimination Reactions

Learning Objective

- predict the products and specify the reagents for S_N1, S_N2, E1 and E2 reactions with stereochemistry
- propose mechanisms for S_N1, S_N2, E1 and E2 reactions
- draw, interpret, and apply Reaction Energy Diagrams for S_N1, S_N2, E1 and E2 reactions

Summary of Reaction Patterns

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, several variables must be considered, the most important being the structure of the alkyl group and the nature of the nucleophilic reactant.In general, in order for an S_N1 or E1 reaction to occur, the relevant carbocation intermediate must be relatively stable. Strong nucleophile favor substitution, and strong bases, especially strong hindered bases (such as tert-butoxide) favor elimination.

The nature of the halogen substituent on the alkyl halide is usually not very significant if it is Cl, Br or I. In cases where both S_N2 and E2 reactions compete, chlorides generally give more elimination than do iodides, since the greater electronegativity of chlorine increases the acidity of beta-hydrogens. Indeed, although alkyl fluorides are relatively unreactive, when reactions with basic nucleophiles are forced, elimination occurs (note the high electronegativity of fluorine).

The following table summarizes the expected outcome of alkyl halide reactions with nucleophiles. It is assumed that the alkyl halides have one or more beta-hydrogens, making elimination possible; and that low dielectric solvents (e.g. acetone, ethanol, tetrahydrofuran & ethyl acetate) are used. When a high dielectric solvent would significantly influence the reaction this is noted in red. Note that halogens bonded to sp^2 or sp hybridized carbon atoms do not normally undergo substitution or elimination reactions with nucleophilic reagents.

Nucleophile	**Anionic Nucleophiles** (Weak Bases: I^-, Br^-, SCN^-, N_3^-, $CH_3CO_2^-$, RS^-, CN^- etc.)	**Anionic Nucleophiles** (Strong Bases: HO^-, RO^-, NH_2^-, pK_a's > 15	**Neutral Nucleophiles** (H_2O, ROH, RSH, R_3N pK_a's ranging from -2 to pK_a's from -9 to 10 (left to right)
Alkyl Group			
Primary RCH_2–	Rapid S_N2 substitution. The rate may be reduced by substitution of β-carbons, as in the case of neopentyl.	Rapid S_N2 substitution. E2 elimination may also occur. *e.g.* $ClCH_2CH_2Cl + KOH$ ——> $CH_2=CHCl$	S_N2 substitution. (N ≈ S >>O)

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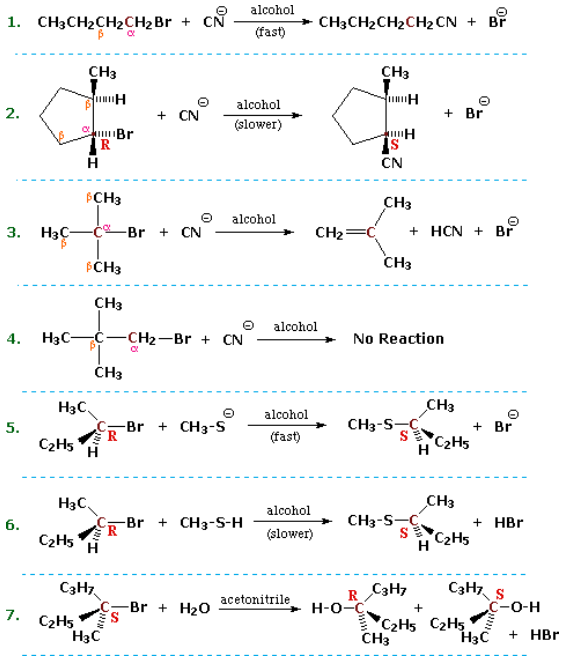
Secondary $R_2CH–$	S_N2 substitution and / or E2 elimination (depending on the basicity of the nucleophile). Bases weaker than acetate (pK_a = 4.8) give less elimination. The rate of substitution may be reduced by branching at the β-carbons, and this will increase elimination.	E2 elimination will dominate.	S_N2 substitution. (N ≈ S >>O) In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be formed slowly.
Tertiary $R_3C–$	E2 elimination will dominate with most nucleophiles (even if they are weak bases). No S_N2 substitution due to steric hindrance. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be expected.	E2 elimination will dominate. No S_N2 substitution will occur. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	E2 elimination with nitrogen nucleophiles (they are bases). No S_N2 substitution. In high dielectric ionizing solvents S_N1 and E1 products may be formed.

Allyl $H_2C=CHCH_2–$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides. E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.
Benzyl $C_6H_5CH_2–$	Rapid S_N2 substitution for 1º and 2º-halides. For 3º-halides a very slow S_N2 substitution or, if the nucleophile is moderately basic, E2 elimination. In high dielectric ionizing solvents, such as water, dimethyl sulfoxide & acetonitrile, S_N1 and E1 products may be observed.	Rapid S_N2 substitution for 1º halides (note there are no β hydrogens). E2 elimination will compete with substitution in 2º-halides, and dominate in the case of 3º-halides. In high dielectric ionizing solvents S_N1 and E1 products may be formed.	Nitrogen and sulfur nucleophiles will give S_N2 substitution in the case of 1º and 2º-halides. 3º-halides will probably give E2 elimination with nitrogen nucleophiles (they are bases). In high dielectric ionizing solvents S_N1 and E1 products may be formed. Water hydrolysis will be favorable for 2º & 3º-halides.

Experimental Observations

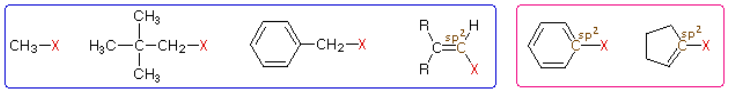
Experimental observations are reported for the following reactions. These reactions include a range of alkyl halide structures in a variety of reaction conditions to illustrate the reaction patterns summarized above. In describing these, it is useful to designate the halogen-

bearing carbon as **alpha** and the carbon atom(s) adjacent to it as **beta**, as noted in the first four equations shown below. Replacement or substitution of the halogen on the α-carbon (colored maroon) by a nucleophilic reagent is a commonly observed reaction, as shown in equations **1, 2, 5, 6 & 7** below. Also, since the electrophilic character introduced by the halogen extends to the β-carbons, and since nucleophiles are also bases, the possibility of base induced H-X elimination must also be considered, as illustrated by equation **3**. Finally, there are some combinations of alkyl halides and nucleophiles that fail to show any reaction over a 24 hour period, such as the example in equation **4**. For consistency, alkyl bromides have been used in these examples. Similar reactions occur when alkyl chlorides or iodides are used, but the speed of the reactions and the exact distribution of products will change.



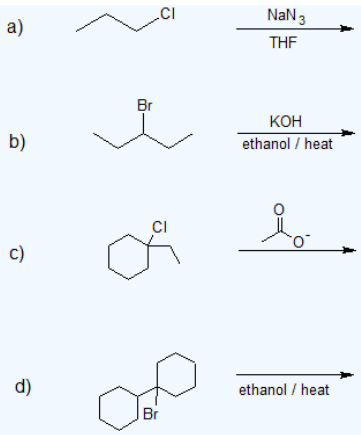
In order to understand why some combinations of alkyl halides and nucleophiles give a substitution reaction, whereas other combinations give elimination, and still others give no observable reaction, we must investigate systematically the way in which changes in reaction variables perturb the course of the reaction. The following general equation summarizes the factors that will be important in such an investigation.

Friendly Reminder: One conclusion, relating the structure of the R-group to possible products, should be immediately obvious. **If R- has no beta-hydrogens an elimination reaction is not possible**, unless a structural rearrangement occurs first. The first four halides shown on the left below do not give elimination reactions on treatment with base, because they have no β-hydrogens. The two halides on the right do not normally undergo such reactions because the potential elimination products have highly strained double or triple bonds. It is also worth noting that sp^2 hybridized C–X compounds, such as the three on the right, do not normally undergo nucleophilic substitution reactions, unless other functional groups perturb the double bond(s).



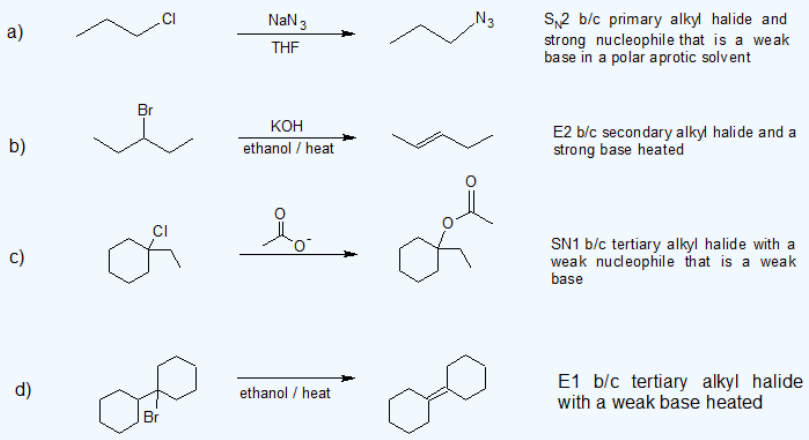
Exercise

1. Identify the dominant reaction mechanism (S_N1, S_N2, E1, or E2) and predict the major product for the following reactions.



Answer

1.



Contributors

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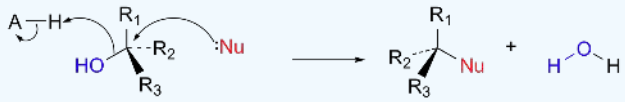
6.20: Biological Substitution Reactions

Objective

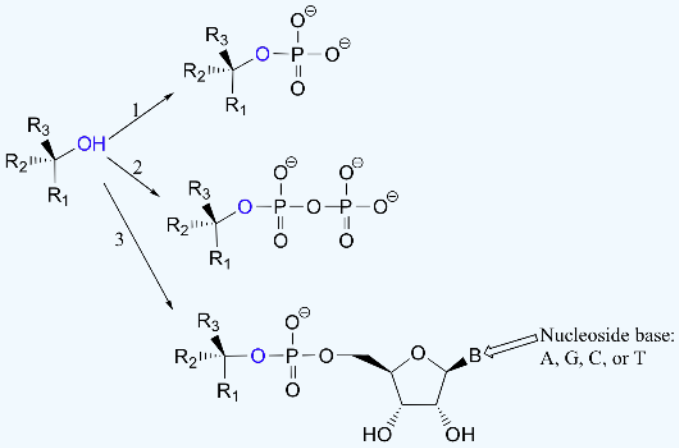
- discuss the importance of leaving groups in biological substitution reactions

Leaving Groups in Biochemical Reactions

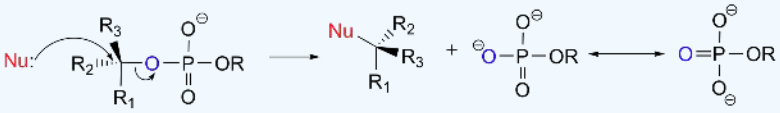
In biological reactions, we do not often see halides serving as leaving groups (in fact, outside of some marine organisms, halogens are fairly unusual in biological molecules). More common leaving groups in biochemical reactions are phosphates, water, alcohols, and thiols. In many cases, the leaving 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.



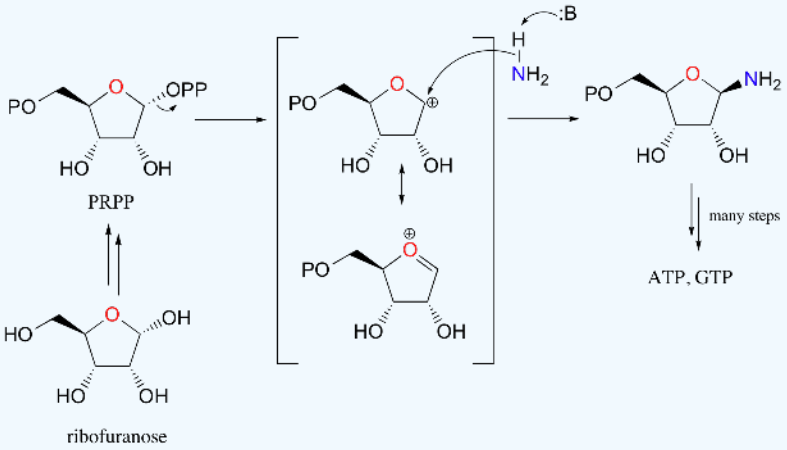
More often, however, the hydroxyl group of an alcohol is first converted enzymatically to a phosphate ester in order to create a better leaving group. This phosphate ester can take the form of a simple monophosphate (arrow 1 in the figure below), a diphosphate (arrow 2), or a nucleotide monophosphate (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):

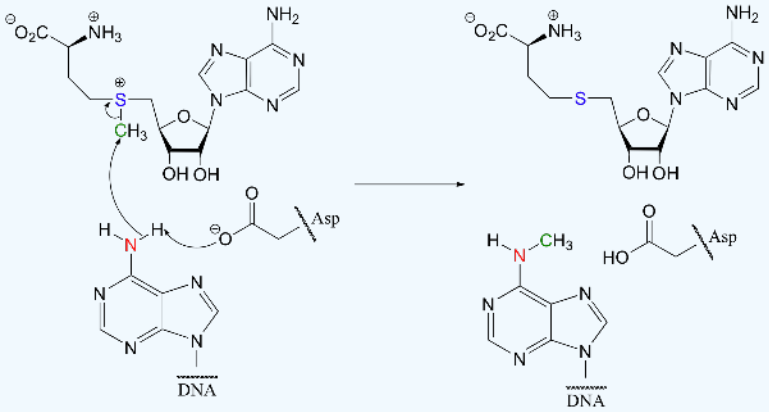


Here, the OH group on ribofuranose is converted to a diphosphate, a much better leaving group. Ammonia is the nucleophile in the second step of this S_N1-like reaction.

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.

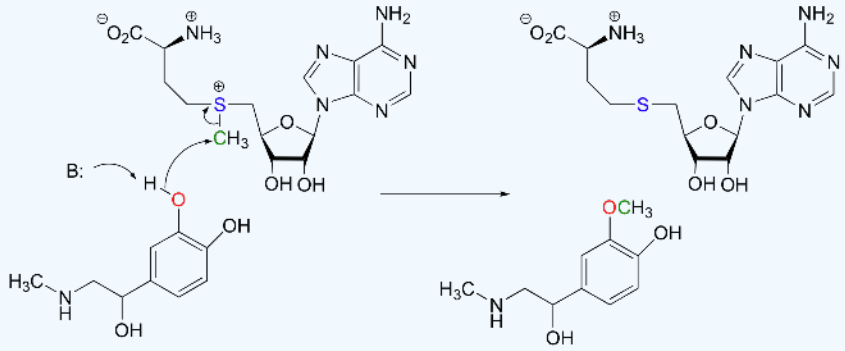
SAM Methyltransferases

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).

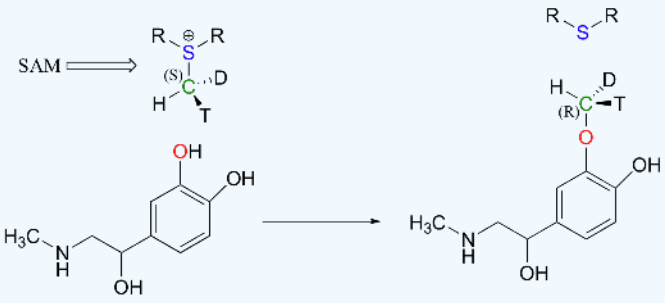
Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



https://chem.libretexts.org/@go/page/182919

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).

Example	

Contributors

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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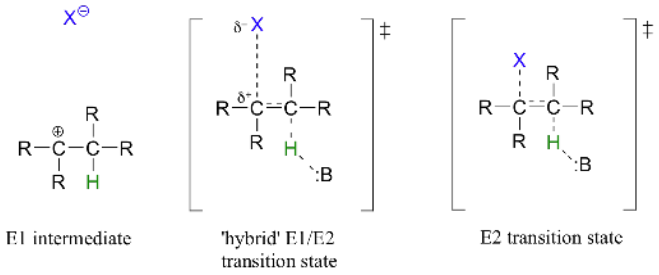
6.21: Biological Elimination Reactions

Learning Objective

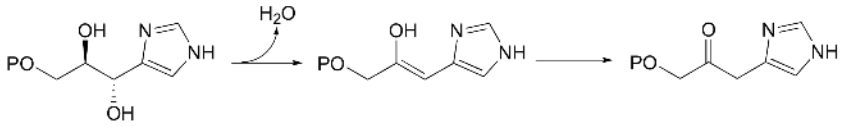
- discuss enzymatic elimination reactions of histidine

Enzymatic E1 and E2 reactions

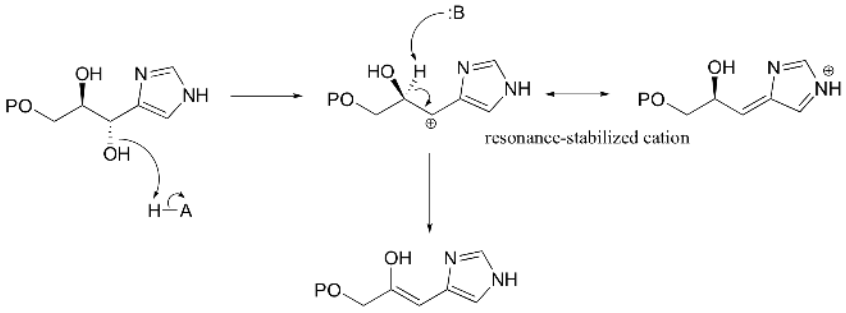
While most biochemical b-elimination reactions are of the E1cb type, some enzymatic E2 and E1 reactions are known. Like the enzymatic S_N2 and S_N1 substitution mechanisms discussed in chapters 8 and 9, the E2 and E1 models represent two possible mechanistic extremes, and actual enzymatic elimination 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'.



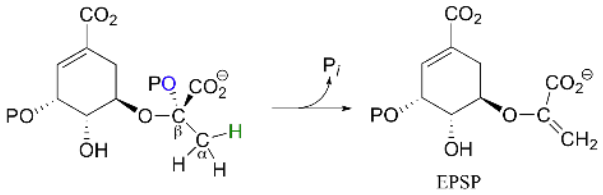
A reaction in the histidine biosynthetic pathway provides a good example of a biological E1-like elimination step (we're looking specifically here at the first, enol-forming step in the reaction below - the second step is simply a tautomerization from the enol to the ketone product.



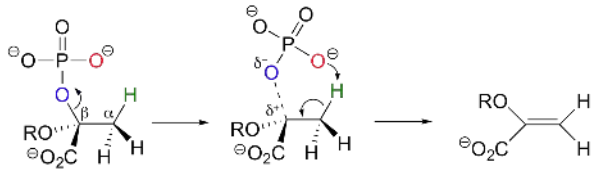
Notice in this mechanism that an E1cb elimination is not possible - there is no electron-withdrawing group (like a carbonyl) to stabilize the carbanion intermediate that would form if the proton were abstracted first. There is, however, an electron-*donating* group (the lone pair on a nitrogen) that can stabilize a positively-charged intermediate that forms when the water leaves.



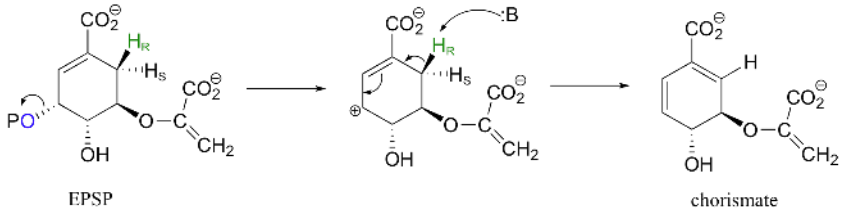
Another good example of a biological E1-like reaction is the elimination of phosphate in the formation of 5-enolpyruvylshikimate-3-phosphate (EPSP), an intermediate in the synthesis of aromatic amino acids.



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):

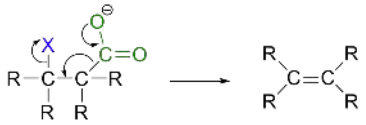


The very next step in the aromatic acid biosynthesis pathway is also an elimination, this time a 1,6-conjugated elimination rather than a simple beta-elimination.

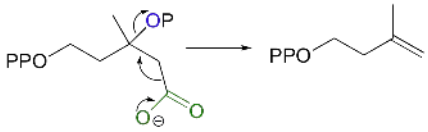


An E1-like mechanism (as illustrated above) has been proposed for this step, but other evidence suggests that a free-radical mechanism may be involved.

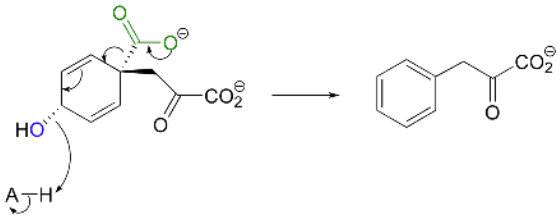
While most E1 and E2 reactions involve proton abstraction, eliminations can also incorporate a decarboxylation step.



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.



Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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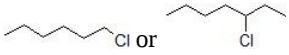
6.22: Additional Exercises

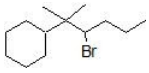
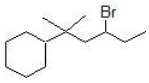
SN2

7-1 Predict which compound in each pair would undergo the SN2 reaction faster.

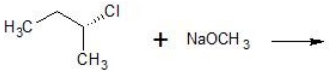
a)  or

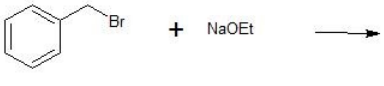
b) or

c) or

d)  or 

7-2 Predict the products of these nucleophilic substitution reactions, including stereochemistry when appropriate.

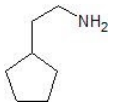
a) 

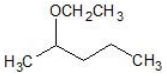
b) 

c) $CH_3CH_2C(CH_3)_2Cl + NaCN \rightarrow$

d) (S)-2-bromopentane + sodium hydroxide $\rightarrow$

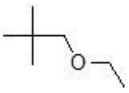
7-3 Show how each compound might be synthesized using S_N2 reaction.

a) 

b) 

c)

7-4 Show 2 ways to synthesize the ether below using S_N2 reaction



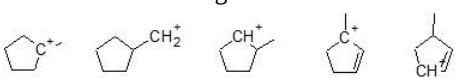
7-5 Of the two ways of synthesizing the compound in previous question (**7-4**), which one would be the most efficient? Why? Show the mechanism of the reaction as part of your explanation.

7-6 Arrange the compounds below in increasing order of nucleophilicity.

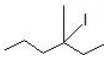
H_2O; NH_2^-; CH_3O^-; $CH_3CH_2O^-$

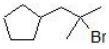
SN1

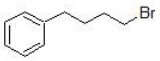
7-7 List the following carbocations in order of increasing stability.

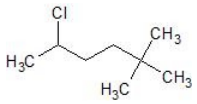


7-8 Give the solvolysis product expected when the compound is heated in methanol.

a) 

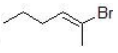
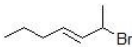
b) 

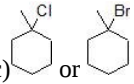
c) 

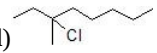
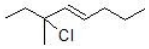
d) 

7-9 Predict with compound in each pair will undergo an SN1 reaction more quickly.

a) or

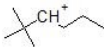
b)  or 

c) 

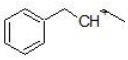
d)  or 

7-10 Show how the following carbocations would rearrange to become more stable. Draw the mechanism of the rearrangement.

a)

b) 

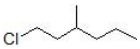
c)

d) 

SN2 vs SN1

7-11 Predict whether each compound below would be more likely to undergo a S_N2 or S_N1 reaction.

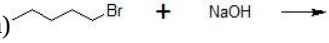
a)

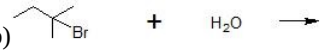
b) 

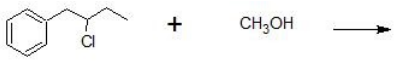
c)

d)

7-12 Predict the product of the following reactions.

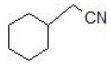
a) 

b) 

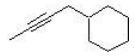
c) 

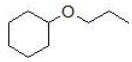
d)

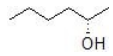
7-13 Show how each compound may be synthesized using nucleophilic substitution reactions.

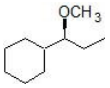
a) 

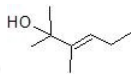
b)

c) 

d) 

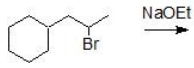
e) 

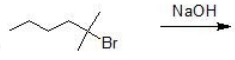
f) 

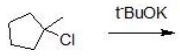
g) 

E2 vs E1

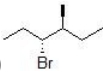
7-14 Predict the major products of the following reactions.

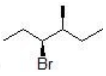
a) 

b) 

c) 

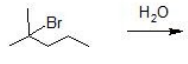
7-15 Draw the expected major product when each of the following compounds is treated with hydroxide to give an E2 reaction.

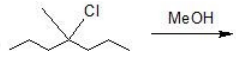
a) 

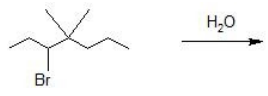
b) 

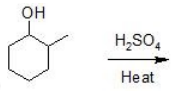
c)

7-16 Predict all the elimination products of the following reactions and label the major product.

a) 

b) 

c) 

d) 

Substitution vs Elimination

7-17 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^-

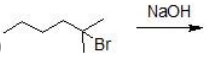
d) OH^-

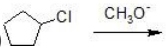
e) H_2O

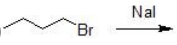
f) HS^-

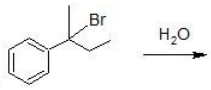
g) MeOH

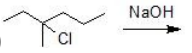
7-18 Identify which mechanism the following reactions would undergo.

a) 

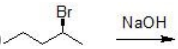
b) 

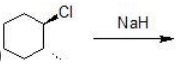
c) 

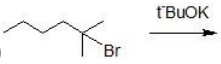
d) 

e) 

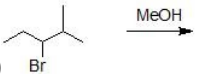
7-19 Identify all the products of the following reactions and specify the major product.

a) 

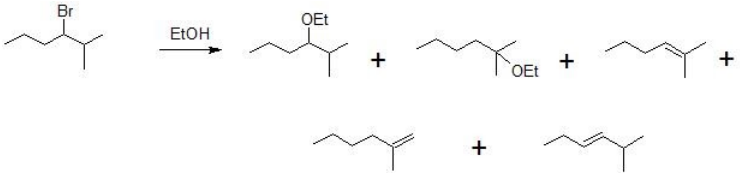
b) 

c) 

d)

e) 

7-20 The following reaction yields five different products. Give the mechanisms for how each is formed.



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6.23: Solutions to Additional Exercises

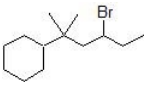
SN2

7-1

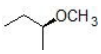
a)

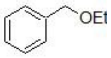
b)

c)

d) 

7-2

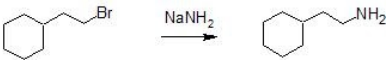
a) 

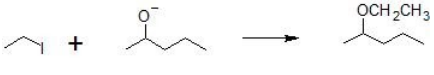
b) 

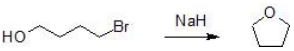
c) No reaction

d)

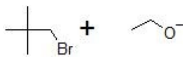
7-3

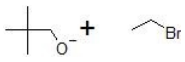
a) 

b) 

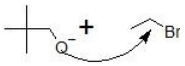
c) 

7-4

First method: 

Second method: 

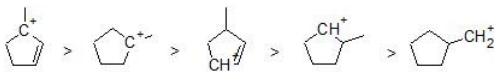
7-5 The second method is more efficient since the alkyl halide is not sterically hindered



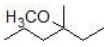
7-6 $H_2O < NH_2^- < CH_3CH_2O^- < CH_3O^-$

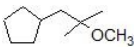
SN1

7-7

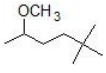


7-8

a) 

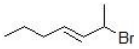
b) 

c) No reaction

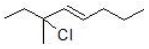
d) 

7-9

a)

b) 

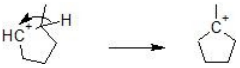
c)

d) 

7-10

a)

b)

c) 

d)

SN2 vs SN1

7-11

a) S_N2

b) S_N2

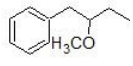
c) S_N1

d) S_N1

7-12

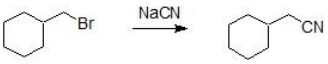
a)

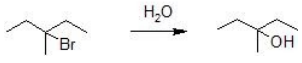
b)

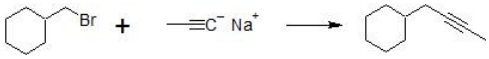
c) 

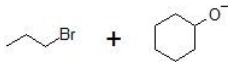
d)

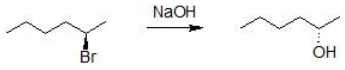
7-13

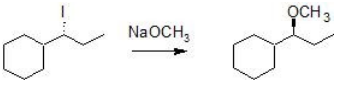
a) 

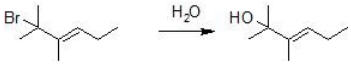
b) 

c) 

d) 

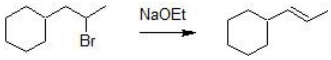
e) 

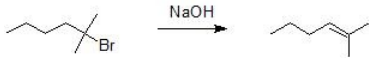
f) 

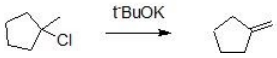
g) 

E2 vs E1

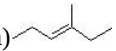
7-14

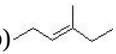
a) 

b) 

c) 

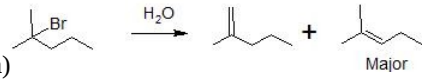
7-15

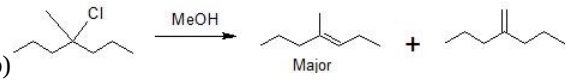
a) 

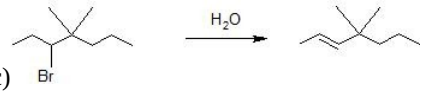
b) 

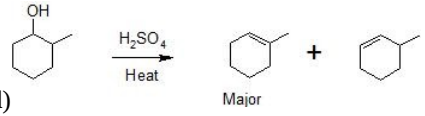
c)

7-16

a) 

b) 

c) 

d) 

Substitution vs Elimination

7-17

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

7-18

a) E2, S_N1

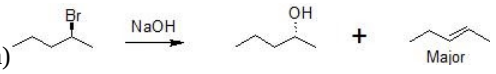
b) S_N2, E2

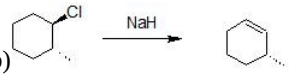
c) S_N2

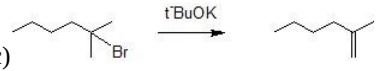
d) S_N1, E1

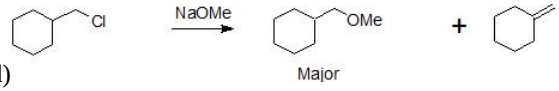
e) E2, S_N1

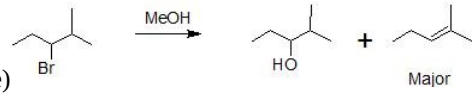
7-19

a) 

b) 

c) 

d) 

e) 

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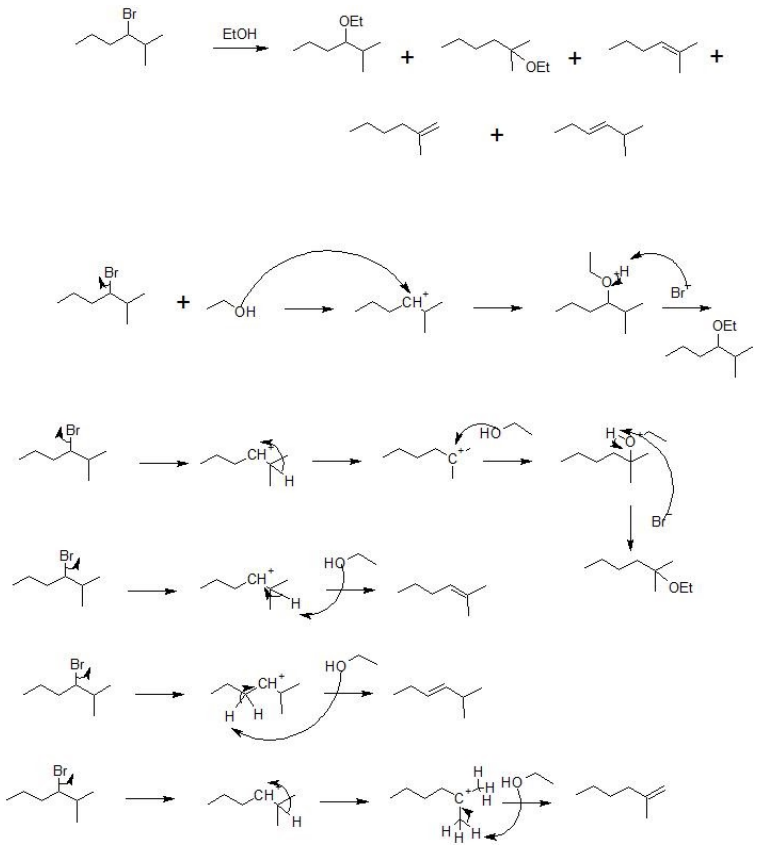

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CHAPTER OVERVIEW

7: Structure and Synthesis of Alkenes

Learning Objectives:

After reading the chapter and completing the exercises and homework, a student can be able to:

- describe the electronic structure of alkenes using Molecular Orbital (MO) Theory and Orbital Hybridization - refer to section 8.1
- memorize the common names for vinylic and allylic groups including isoprene and styrene refer to section 8.2
- predict the relative physical properties of alkenes - refer to section 8.2
- recognize and classify the stereochemistry of alkenes using the cis/trans and E/Z systems - refer to section 8.3
- calculate the Degrees of Unsaturation (DU) and apply it to alkene structure - refer to section 8.4
- give the IUPAC names for alkenes given their structure & vice versa including E/Z isomers - refer to section 8.5 and chapter 3
- use heats of hydrogenation to compare the stabilities of alkenes - refer to section 8.6
- interpret and draw reaction energy diagrams for dehydrohalogenation of R-X's and alcohol dehydration reactions - refer to sections 8.7 and 8.8 respectively and chapter 7
- propose mechanisms for a dehydrohalogenation or dehydration reactions - refer to sections 8.7 and 8.8 respectively and chapter 7
- predict the products and specify the reagents for alkene synthesis from dehydrohalogenation of R-X's and alcohol dehydration reactions - refer to sections 8.7 and 8.8 respectively
- predict and explain the stereochemistry of E2 eliminations to form alkenes, especially from cyclohexanes - refer to sections 8.7 and 8.8 and chapter 7
- discuss the uses and sources of alkenes including catalytic cracking - refer to section 8.9

7.1: Alkene Structure

7.2: Physical Properties and Important Common Names

7.3: The Alkene Double Bond and Stereoisomerism

7.4: Degrees of Unsaturation

7.05: The E

Z System (when cis

7.5: The E/Z System (when cis/trans does not work)

7.6: Stability of Alkenes

7.7: Alkene Synthesis by Elimination of Alkyl Halides

7.8: Alkene Synthesis by Dehydration of Alcohols

7.9: Uses

7.10: Additional Exercises

7.11: Solutions to Additional Exercises

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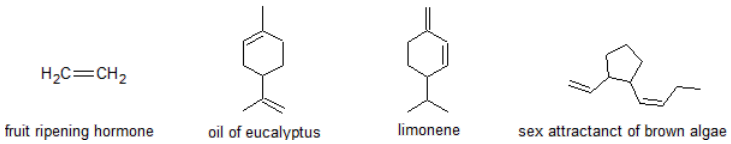
7.1: Alkene Structure

Learning Objective

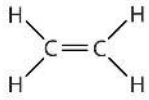
- describe the electronic structure of alkenes using Molecular Orbital (MO) Theory and Orbital Hybridization

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.



Alkenes

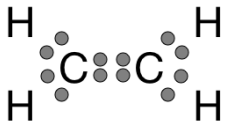
Nomenclature of alkenes is covered in chapter 3. Condensed structural formulas for the first eight alkenes are listed in Table **7.1.1** along with some relevant physical propoerties. Thus, CH_2=CH_2 stands for



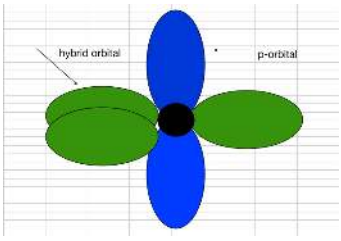
The double bond is shared by the two carbon atoms and does not involve the hydrogen atoms, although the condensed formula does not make this point obvious. Note that the molecular formula for ethene is C_2H_4, whereas that for ethane is C_2H_6.

Structure of Ethene - the simplest alkene

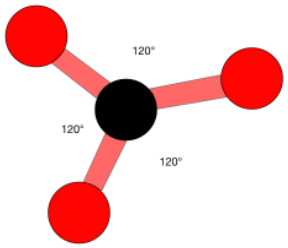
Ethene is not a very complicated molecule. It is made up of four $1s^1$ hydrogen atoms and two $2s^2$ $2p_x^1$ $2p_y^2$ carbon atoms. These carbon atoms already have four electrons, but they each want to get four more so that they have a full eight in the valence shell. Having eight valence electrons around carbon gives the atom itself 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, it has all of the electrons that it wants, so it is no longer reactive.



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 that's exactly what it is, it is made from one s orbital and two p orbitals.



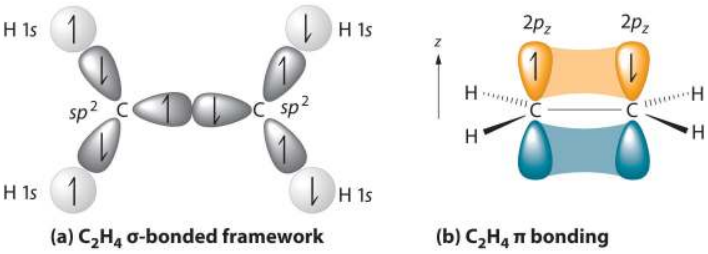
When atoms are an sp^2 hybrid they have a trigonal planar structure. These structures are very similar to a 'peace' sign, there is a central atom with three atoms around it, all on one plane. Trigonal planar molecules have an ideal bond angle of 120° on each side.



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. Free rotation the p-orbitals cause them to be 90° from each other breaking the π bond because there would be no overlap. Since the π 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 two carbon atoms of a double bond and the four atoms attached to them lie in a plane, with bond angles of approximately 120° as shownn in the figure below



(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.)

The first two alkenes in Table **7.1.1**, ethene and propene, are most often called by their common names—ethylene and propylene, respectively (Figure **7.1.1**). 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.

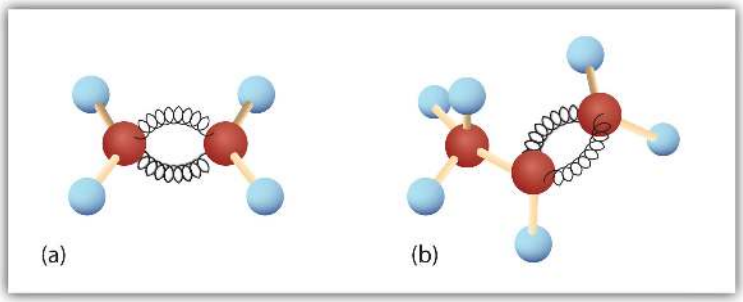


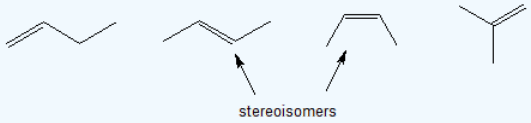
Figure **7.1.1**: *Ethene and Propene. The ball-and-spring models of ethene/ethylene (a) and propene/propylene (b) show their respective shapes, especially bond angles.*

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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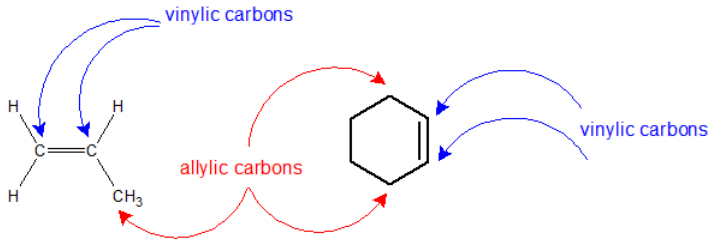
7.2: Physical Properties and Important Common Names

Learning Objectives

- memorize the common names for vinylic and allylic groups including isoprene and styrene
- predict the relative physical properties of alkenes

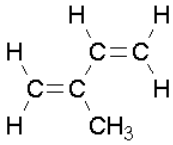
Common names

The carbon atoms sharing the double bond can be referred to as the "vinyl carbons". The carbon atoms adjacent to the vinyl carbon atoms are called "allylic carbons". These carbon atoms have unique reactivity because of the potential for interaction with the pi bond.



Overall, common names remove the -ane suffix and add -ylene. There are a couple of unique ones like ethenyl's common name is vinyl and 2-propenyl's common name is allyl that need to be memorized.

- vinyl substituent $H_2C=CH-$
- allyl substituent $H_2C=CH-CH_2-$
- allene molecule $H_2C=C=CH_2$
- isoprene is shown below



Physical Properties of Selected Alkenes

Some representative alkenes—their names, structures, and physical properties—are given in the table below.

Physical Properties of Some Selected Alkenes

IUPAC Name	Molecular Formula	Condensed Structural Formula	Melting Point (°C)	Boiling Point (°C)
ethene	C_2H_4	$CH_2=CH_2$	–169	–104
propene	C_3H_6	$CH_2=CHCH_3$	–185	–47
1-butene	C_4H_8	$CH_2=CHCH_2CH_3$	–185	–6
1-pentene	C_5H_{10}	$CH_2=CH(CH_2)_2CH_3$	–138	30
1-hexene	C_6H_{12}	$CH_2=CH(CH_2)_3CH_3$	–140	63
1-heptene	C_7H_{14}	$CH_2=CH(CH_2)_4CH_3$	–119	94
1-octene	C_8H_{16}	$CH_2=CH(CH_2)_5CH_3$	–102	121

Polarity and Physical Properties

Alkenes are non-polar hydrocarbons. The dominant intermolecular forces shared by alkenes are the London dispersion forces. These interactions are weak and temporary, so they are easily disrupted.

Physical States: The physical states reflect the weak attractive forces between molecules. Ethene, propene, and butene exist as colorless gases. Alkenes with 5 to 14 carbons are liquids, and alkenes with 15 carbons or more are solids.

Density: Alkenes are less dense than water with most densities in the range of 0.6 to 0.7 g/mL. Alkenes float on top of water.

Solubility: Alkenes are virtually insoluble in water, but dissolve in organic solvents. The reasons for this are exactly the same as for the alkanes.

Boiling Points: The boiling point of each alkene is very similar to that of the alkane with the same number of carbon atoms. Boiling points of alkenes depend on more molecular mass (chain length). The more intermolecular mass is added, the higher the boiling point. Intermolecular forces of alkenes gets stronger with increase in the size of the molecules. In each case, the alkene has a boiling point which is a small number of degrees lower than the corresponding alkane. The only attractions involved are Van der Waals dispersion forces, and these depend on the shape of the molecule and the number of electrons it contains.

Compound	**Boiling points (oC)**
Ethene	-104
Propene	-47
Trans-2-Butene	0.9
Cis-2-butene	3.7
Trans 1,2-dichlorobutene	155
Cis 1,2-dichlorobutene	152
1-Pentene	30
Trans-2-Pentene	36
Cis-2-Pentene	37
1-Heptene	115
3-Octene	122
3-Nonene	147
5-Decene	170

Melting Points: Melting points of alkenes depends on the packaging of the molecules so the stereochemistry of the carbon-carbon double bond has a strong influence on the relative melting points. Alkenes have similar melting points to that of alkanes, however, in cis isomers molecules are package in a U-bending shape, therefore, will display a lower melting points to that of the trans isomers. This effect is notable when comparing the melting points of fats and oils. The differences in the

melting points is strongly influenced by the long hydrocarbon tails. Oils have a greater number of cis double bonds and exist as liquids at room temperature. Whereas, fats are primarily saturated and exist as solids at room temperature.

Compound	Melting Points (0C)
Ethene	-169
Propene	-185
Butene	-138
1-Pentene	-165
Trans-2-Pentene	-135
Cis-2-Pentene	-180
1-Heptene	-119
3-Octene	-101.9
3-Nonene	-81.4
5-Decene	-66.3

Exercise

1. Draw the bond-line structures for the following compounds in order of increasing boiling point: 2-methyl-2-pentene; 2-hexene; isoprene; 2-heptene.

2. Which phase will contain the most 3-octene?

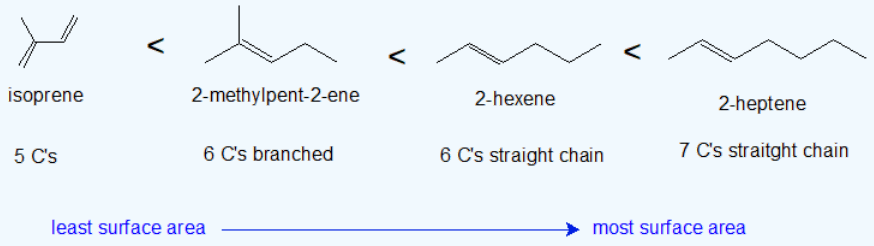
a) water or hexane

b) water or benzene

c) methanol or 1-octanol

Answer

1. relative boiling points



2. a) hexane (Hydrocarbons are hydrophobic and lipophilic.)

b) benzene (Hydrocarbons are hydrophobic and lipophilic.)

c) 1-octanol (Hydrocarbons seek the solvent with the most carbons and fewest polar groups.)

Contributors

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7.3: The Alkene Double Bond and Stereoisomerism

Learning Objective

- recognize and classify the stereochemistry of alkenes using the cis/trans system

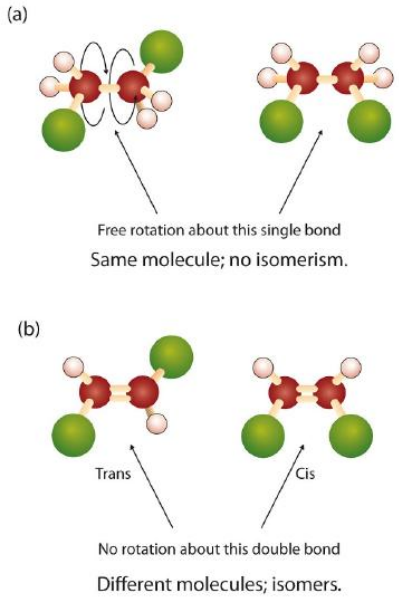
Steroisomerism in Alkenes

There is free rotation about the carbon-to-carbon single bonds (C–C) in alkanes. For example, in 1,2-dichloroethane, there is free rotation about the C–C bond. The two models shown represent exactly the same molecule; they are *not* isomers. You can draw structural formulas that look different, but if you bear in mind the possibility of this free rotation about single bonds, you should recognize that these two structures represent the same molecule:

In contrast, the structure of alkenes requires that the carbon atoms of a double bond and the two atoms bonded to each carbon atom all lie in a single plane, and that each doubly bonded carbon atom lies in the center of a triangle. This part of the molecule's structure is rigid; rotation about doubly bonded carbon atoms is *not* possible without rupturing the bond. In 1,2-dichloroethene, 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. The isomer in which the two chlorine (Cl) atoms lie on the same side of the molecule is called the cis isomer (Latin *cis*, meaning "on this side") and is named cis-1,2-dichloroethene. The isomer with the two Cl atoms on opposite sides of the molecule is the trans isomer (Latin *trans*, meaning "across") and is named *trans*-1,2-dichloroethene. 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.

cis-1,2-dichloroethene trans-1,2-dichloroethene

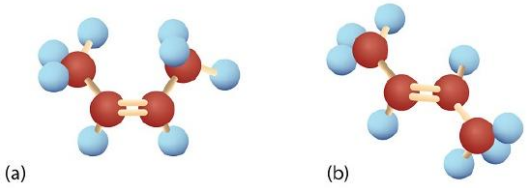
The diagram below summarizes the differences between alkanes and alkenes with respect to rotation where the carbons are red, hydrogens are off-white, and the chlorines are green.



In 1,2-dichloroethane (a), free rotation about the C–C bond allows the two structures to be interconverted by a twist of one end relative to the other. In 1,2-dichloroethene (b), restricted rotation about the double bond means that the relative positions of substituent groups above or below the double bond are significant.

Geometric Isomers have Different Physical Properties

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; the double bond results in cis-trans isomerism. *Cis*-2-butene has both methyl groups on the same side of the molecule. *Trans*-2-butene has the methyl groups on opposite sides of the molecule as shown in the diagram below.



Cis-2-butene and trans-2-butene are unique compounds with slightly different physical properties as shown below. For stereospecific reactions, these compounds produce different stereoisomeric products under the same reaction conditions. This phenonenom of reactivity will be explored more closely in the next chapter on alkene reactivity.

cis-2-butene
boiling point: 3.7°C
density: 0.641 g/mL

trans-2-butene
boiling point: 0.9°C
density: 0.626 g/mL

Example

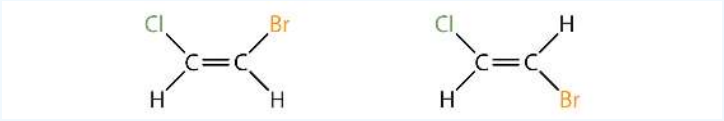
Which compounds can exist as cis-trans (geometric) isomers? Draw them.

1. CHCl=CHBr
2. $CH_2=CBrCH_3$
3. $(CH_3)_2C=CHCH_2CH_3$
4. $CH_3CH=CHCH_2CH_3$

Solutions Explained

All four structures have a double bond and thus meet rule 1 for cis-trans isomerism.

1. This compound meets rule 2; it has two nonidentical groups on *each* carbon atom (H and Cl on one and H and Br on the other). It exists as both cis and trans isomers:



2. This compound has two hydrogen atoms on one of its doubly bonded carbon atoms; it fails rule 2 and does not exist as cis and trans isomers.
3. This compound has two methyl (CH_3) groups on one of its doubly bonded carbon atoms. It fails rule 2 and does not exist as cis and trans isomers.
4. This compound meets rule 2; it has two nonidentical groups on *each* carbon atom and exists as both cis and trans isomers:

Exercise

Exercise

1. If the compound below can exist as cis-trans isomers, then draw both bond-line structures.

a. CH_2=$CHCH_2CH_2CH_3$
b. CH_3CH=$CHCH_2CH_3$
c. CH_3CH_2CH=$CHCH_2CH_3$
d. $CH_2C(CH_3)CH_2CH_3$
e. $CH_3C(CH_3)CHCH_3$

2. Write out the condensed structure for ethene.

3. Draw the Kekulé (Lewis) structure for ethene.

4. Draw the bond-line structure for ethene.

5. Why is it that the carbons in ethene cannot freely rotate around the carbon-carbon double bond?

Answer

1.

a. No cis/trans possible b/c one of the vinylic carbons is bonded to two hydrogen atoms.

b.

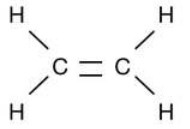
c.

d. No cis/trans possible b/c one of the vinylic carbons is bonded to two hydrogen atoms.

e. No cis/trans possible b/c one of the vinylic carbons is bonded to two methyl groups.

2. CH_2CH_2 The carbon-carbon double bond is not shown, but can be recognized by knowing the neutral bonding patterns of carbon.

3.



4." - " Note how easy it would be to misinterpret this small dash, therefore, the structure for ethene is typically shown with a condensed or Kekule structure.

5. The carbons cannot freely rotate about the carbon-carbon double bond because rotating p-orbitals would have to pass through a 90° point where there would no longer be any overlap, so the π bond would have to break for there to be free rotation.

References

1. Vollhardt, K. P.C. & Shore, N. (2007). *Organic Chemistry* (5th Ed.). New York: W. H. Freeman.

Outside Links

- Sigma Bond: http://en.Wikipedia.org/wiki/Sigma_bond
- Pi Bond: http://en.Wikipedia.org/wiki/Pi_bond
- Ethene (Ethylene): http://en.Wikipedia.org/wiki/Ethene

- Trigonal Planar Structure & Picture: http://en.Wikipedia.org/wiki/Trigonal_planar
- bcs.whfreeman.com/vollhardtsc...5e/default.asp

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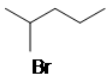
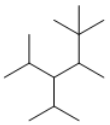
7.4: Degrees of Unsaturation

Learning Objectives

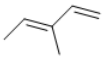
- calculate the Degrees of Unsaturation (DU) and apply it to alkene structure

Saturated and Unsaturated Molecules

In the lab, saturation may be thought of as the point when a solution cannot dissolve anymore of a substance added to it. In terms of degrees of unsaturation, a molecule only containing single bonds with no rings is considered saturated.

$CH_3CH_2CH_3$			1-methyoxypentane

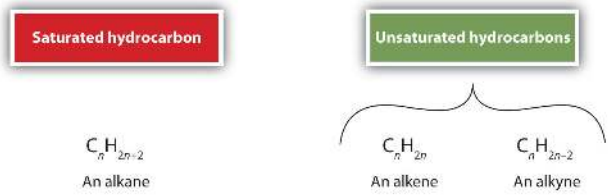
Unlike saturated molecules, unsaturated molecules contain double bond(s), triple bond(s) and/or ring(s).

$CH_3CH{=}CHCH_3$				3-chloro-5-octyne

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, these techniques require expensive instrumentation and are not always readily available. Fortunately, calculating the degrees of unsaturation provides useful information about the structure. The degree of unsaturation indicates the total number of pi bonds and rings within a molecule which makes it easier for one to figure out the molecular structure.

DU = Degrees of Unsaturation = (number of pi bonds) + (number of rings)

Alkenes ($R_2C{=}CR_2$) and alkynes (R–C≡C–R) are called unsaturated hydrocarbons because they have fewer hydrogen atoms than does an alkane with the same number of carbon atoms, as is indicated in the following general formulas:



Calculating The Degree of Unsaturation (DU)

If the molecular formula is given, plug in the numbers into this formula:

$$DoU = \frac{2C + 2 + N - X - H}{2} \tag{7.2.1}$$

- 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

The molecular formula of a hydrocarbon provides information about the possible structural types it may represent. A saturated molecule contains only single bonds and no rings. Another way of interpreting this is that a saturated molecule has the maximum number of hydrogen atoms possible to be an acyclic alkane. Thus, the number of hydrogens can be represented by 2C+2, which is the general molecular representation of an alkane. As an example, for the molecular formula C3H4 the number of actual hydrogens needed for the compound to be saturated is 8

[2C+2=(2x3)+2=8.]

The compound needs 4 more hydrogens in order to be fully saturated (expected number of hydrogens-observed number of hydrogens=8-4=4). Degrees of unsaturation is equal to 2, or half the number of hydrogens the molecule needs to be classified as saturated. Hence, the DoB formula divides by 2. The formula subtracts the number of X's because a halogen (X) replaces a hydrogen in a compound. For instance, in chloroethane, C2H5Cl, there is one less hydrogen compared to ethane, C2H6. For example, consider compounds having the formula C5H8. The formula of the five-carbon alkane pentane is C5H12 so the difference in hydrogen content is 4. This difference suggests such compounds may have a triple bond, two double bonds, a ring plus a double bond, or two rings. Some examples are shown here, and there are at least fourteen others!

For a compound to be saturated, there is one more hydrogen in a molecule when nitrogen is present. Therefore, we add the number of nitrogens (N). This can be seen with C_3H_9N compared to C_3H_8. Oxygen and sulfur are not included in the formula because saturation is unaffected by these elements. As seen in alcohols, the same number of hydrogens in ethanol, C_2H_5OH, matches the number of hydrogens in ethane, C_2H_6.

The following chart illustrates the possible combinations of the number of double bond(s), triple bond(s), and/or ring(s) for a given degree of unsaturation. Each row corresponds to a different combination.

- 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).

When the DU is 4 or greater, the presence of benzene rings is very likely.

DU	Possible combinations of rings/ bonds		
	# of rings	# of double bonds	# of triple bonds
1	1	0	0
	0	1	0
2	2	0	0
	0	2	0
	0	0	1
	1	1	0

Remember, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or rings. For instance, a degree of unsaturation of 3 can contain 3 rings, 2 rings+1 double bond, 1 ring+2 double bonds, 1 ring+1 triple bond, 1 double bond+1 triple bond, *or* 3 double bonds.

Example: Benzene

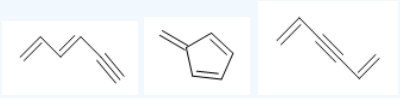
What is the Degree of Unsaturation for Benzene?

Solution

The molecular formula for benzene is C_6H_6. Thus,

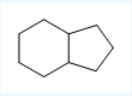
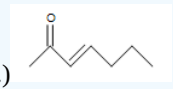
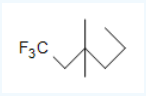
DU= 4, where C=6, N=0,X=0, and H=6. 1 DoB can equal 1 ring or 1 double bond. This corresponds to benzene containing 1 ring and 3 double bonds.

However, when given the molecular formula C_6H_6, benzene is only one of many possible structures (isomers). The following structures all have DU of 4 and have the same molecular formula as benzene. However, these compounds are very rare, unlike benzene. We will learn more about the reasons for benzen's high stability when we studey aromaticity in later chapters.



Exercises

1. Are the following molecules saturated or unsaturated:

1.  (b.)  (c.)  (d.) $C_{10}H_6N_4$

2. Using the molecules from (1) above, give the degrees of unsaturation for each.
3. Calculate the degrees of unsaturation, classify the compound as saturated or unsaturated, and list all the ring/pi bond combination possible for the following molecular formulas: (a.) C_9H_{20} (b.) C_7H_8 (c.) C_5H_7Cl (d.) $C_9H_9NO_4$
4. Calculate degrees of unsaturation (DoU) for the following, and propose a structure for each.

    a) C_5H_8

    b) C_4H_4

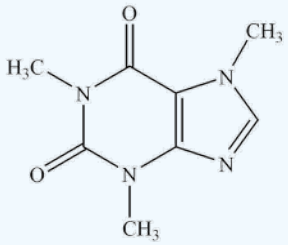
5. Calculate the degree of unsaturation (DoU) for the following molecules

    a) C_5H_5N

    b) $C_5H_5NO_2$

    c) C_5H_5Br

6. The following molecule is caffeine ($C_8H_{10}N_4O_2$), determine the degrees of unsaturation (DoU).



Answer

1.

(a.) **unsaturated** (E*ven though rings only contain single bonds, rings are considered unsaturated.)*

(b.) **unsaturated**

(c.) **saturated**

(d.) **unsaturated**

2. *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**

(b.) **2** *(one double bond and the double bond from the carbonyl)*

(c.) **0**

(d.) **10**

3.

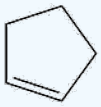
(a.) DU =**0 ; saturated** (Remember-a saturated molecule only contains single bonds)

(b.) DU = **4; unsaturated** *The molecule can contain any of these combinations of rings and pi bonds that add up to 4, such as* **(i) 4 double bonds (ii) 4 rings (iii) 2 double bonds+2 rings (iv) 1 double bond+3 rings (v) 3 double bonds+1 ring (vi) 1 triple bond+2 rings (vii) 2 triple bonds (viii) 1 triple bond+1 double bond+1 ring (ix) 1 triple bond+2 double bonds**

(c.) DU = **2; unsaturated (i) 1 triple bond (ii) 1 ring+1 double bond (iii) 2 rings (iv) 2 double bonds**

(d.) DU = **6; (i) 3 triple bonds (ii) 2 triple bonds+2 double bonds (iii) 2 triple bonds+1 double bond+1 ring (iv)...** *(As you can see, the degrees of unsaturation only gives the sum of double bonds, triple bonds and/or ring. Thus, the formula may give numerous possible structures for a given molecular formula.)*

4.



A)
2 DoU
1 ring, 1 double bond

B)
3 DoU
1 ring, 2 double bonds

5. a) 4 b) 4 c) 3

6. DU = 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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Z System (when cis

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7.5: The E/Z System (when cis/trans does not work)

Learning Objective

- recognize and classify the stereochemistry of alkenes using the cis/trans and E/Z systems
- give the IUPAC names for alkenes given their structure & vice versa including E/Z isomers

E/Z Nomenclature in Alkenes

The traditional system for naming the geometric isomers of an alkene, in which the same groups are arranged differently, is to name them as cis or trans. However, it is easy to find examples where the cis-trans system is not easily applied. IUPAC has a more complete system for naming alkene isomers. The R-S system for chirality is based on a set of "priority rules", which allow you to rank any groups. The rigorous IUPAC system for naming alkene isomers, called the E-Z system, is based on the same priority rules.

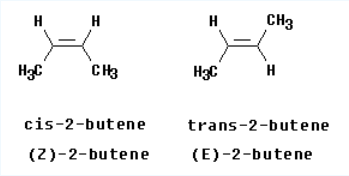
> The priority rules are often called the Cahn-Ingold-Prelog (CIP) rules, after the chemists who developed the system.

The general strategy of the E-Z system is to analyze the two groups at each end of the double bond. For each vinyl carbon, rank the two groups using the CIP priority rules. Determine whether the higher priority group at one end of the double bond and the higher priority group at the other end of the double bond are on the **same** side (Z, from German zusammen = together or "on Zee Zame Zide") or on **opposite** sides (E, from German entgegen = opposite) of the double bond.

Example 7.5.1

The figure below 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.

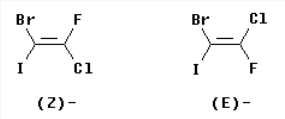


E/Z will work -- even when cis/trans fails

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 7.5.1

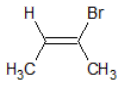
The following figure shows two isomers of an alkene with four different groups on the double bond, 1-bromo-2-chloro-2-fluoro-1-iodoethene.



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).

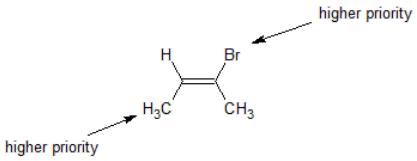
E/Z will work, but may not agree with cis/trans

There are also molecules for which the E/Z system will not agree with the cis/trans system. Let's use 2-bromo-2-butene to explore this option. Is this compound cis or trans? This molecule is clearly cis. The two methyl groups are on the same side. More rigorously, the "parent chain" is cis.



cis-2-bromo-2-butene

Is this compound 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.



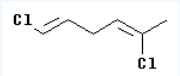
(2*E*)-2-bromobut-2-ene

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 7.5.3

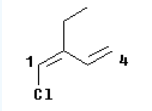


The configuration at the left hand double bond is E; at the right hand double bond it is Z. Thus this compound is (1E,4Z)-1,5-dichloro-1,4-hexadiene.

The double-bond rule in determining priorities

Example 7.5.4

Consider the compound below

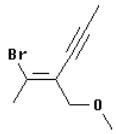


This is 1-chloro-2-ethyl-1,3-butadiene -- ignoring, for the moment, the geometric isomerism. There is no geometric isomerism at the second double bond, at 3-4, because it has 2 H at its far end.

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.

The "first point of difference" rule

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.



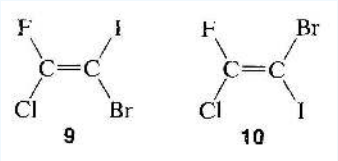
To illustrate this, consider the molecule at the left. Is the double bond here E or Z? At the left end of the double bond, Br > H. But the right end of the double bond requires a careful analysis.

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" feature of ChemSketch says it is (2E)-2-(1-bromoethylidene)pent-3-ynyl methyl ether.

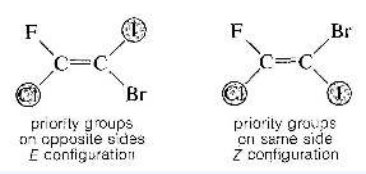
Example 7.5.1

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:

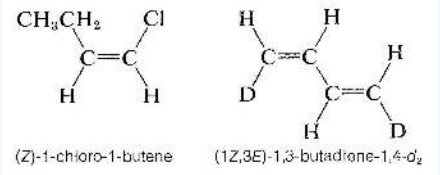


A system that is easy to use and which is based on the sequence rules already described for the R,S system works as follows:

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:



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:



Exercises

1. Order the following in increasing priority.

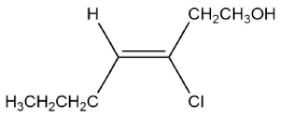
A) –H, –Cl, –OH

B) $–CH_3$, $–CH_2OH$, $–CH_2CH_3$

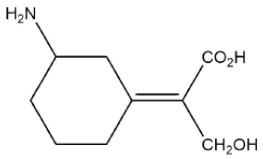
C) –C≡CH, $–CH=CH_2$, –CH=O

2. Label the following as *E* or *Z* conformations.

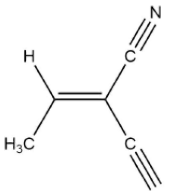
A)



B)



C)



Answer

1. A) –H < –OH < –Cl (highest priority)

B) $–CH_3$ < $–CH_2CH_3$ < $–CH_2OH$ (highest priority)

C) $–CH=CH_2$ < –C≡CH < –CH=O (highest priority)

2. A) *Z* B) *Z* C) *E*

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- Prof. Steven Farmer (Sonoma State University)

>Robert Bruner (http://bbruner.org)

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

7.5: The E/Z System (when cis/trans does not work) is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

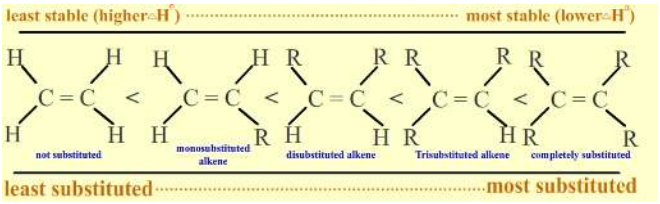
7.6: Stability of Alkenes

Learning Objective

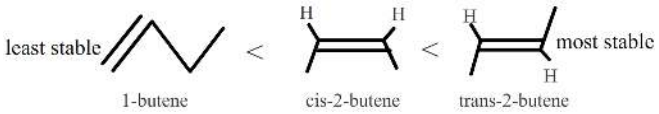
- use heats of hydrogenation to compare the stabilities of alkenes

Heats of Hydrogenation

The stability of an 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 ΔH^{o} 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:



In disubstituted alkenes, trans isomers are more stable than cis isomers due to steric hindrance. Also, internal alkenes are more stable than terminal ones. See the following isomers of butene:



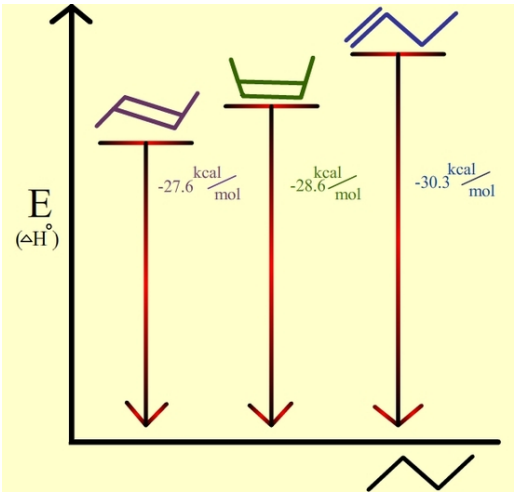
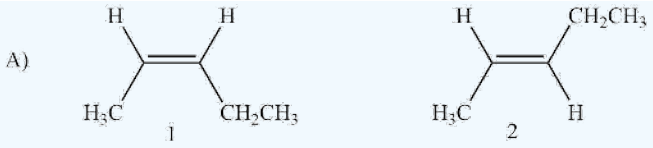


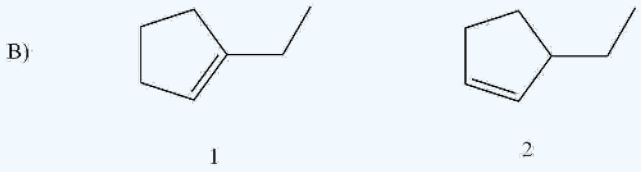
Figure ***7.6.3***: *Trans-2-butene is the most stable because it has the lowest heat of hydrogenation.*

In cycloalkenes smaller than cyclooctene, the cis isomers are more stable than the trans as a result of ring strain.

Exercises

1. When looking at their heats of hydrogenation, is the cis or the trans isomer generally more stable?
2. Arrange the following alkenes in order of increasing stability: 2,3-dimethyl-2-butene; trans-2-hexene; 2-methyl-2-pentene; cis-2-hexene
3. Which is the more stable alkene in each pair?





Answer

1. Trans alkenes are more stable as demonstrated by the lower heats of hydrogenation when compared to their cis-isomers.
2. (least substituted and cis) cis-2-hexene < trans-2-hexene < 2-methyl-2-pentene < 2,3-dimethyl-2-butene (most substituted)
3. A) 2 b/c trans with same substitution at C=C B) 1 b/c the C=C is more substituted

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1. Fox, Marye Anne, and James K. Whitesell. Organic Chemistry. 3rd ed. Sudbury, MA: Janes and Bartlett Publishers, 2004.
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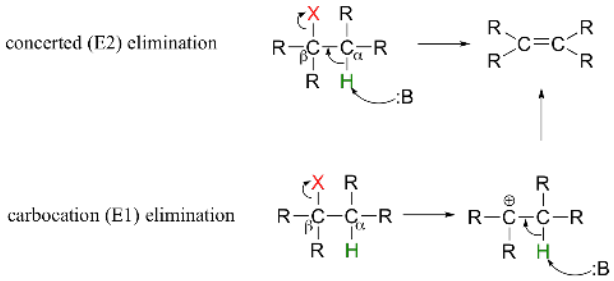
7.7: Alkene Synthesis by Elimination of Alkyl Halides

Learning Objective

- interpret and draw reaction energy diagrams for dehydrohalogenation of R-X's
- propose mechanisms for a dehydrohalogenation reactions -
- predict the products and specify the reagents for alkene synthesis from dehydrohalogenation of R-X's
- predict and explain the stereochemistry of E2 eliminations to form alkenes, especially from cyclohexanes

Alkene Synthesis by Elimination of Alkyl Halides is discussed in detail in chapter 7 sections 13 - 18. The major learning objectives are summarized briefly in this section.

Alkene Synthesis by Elimination of Alkyl Halides



When considering whether an elimination reaction is likely to occur via an E1 or E2 mechanism, we really need to consider three factors:

1. 1) **The base:** strong bases favor the E2 mechanism, whereas, E1 mechanisms only require a weak base.
2. 2) **The solvent**: good ionizing xolvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.
3. 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.

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	anti-coplanar bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Base]	rate = k[R-X]
stereochemisty	retained configuration	mixed configuration
solvent	not important	polar protic

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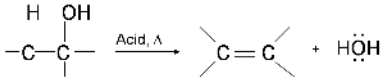
7.8: Alkene Synthesis by Dehydration of Alcohols

Learning Objective

- interpret and draw reaction energy diagrams for alcohol dehydration reactions
- propose mechanisms for dehydration reactions
- predict the products and specify the reagents for alkene synthesis from alcohol dehydration reactions
- predict and explain the stereochemistry of E2 eliminations to form alkenes, especially from cyclohexanes

Dehydration of Alcohols to Yield Alkenes

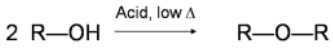
One way to synthesize alkenes is by dehydration of alcohols. Alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. This mechanism is analogous to the alkyl halide mechanism. The only difference is that hydroxide is a very poor leaving group so an extra step is required. The hydroxyl group is protonated so that water is now the leaving group. Therefore, 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 reaction temperature range 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 Alcohols

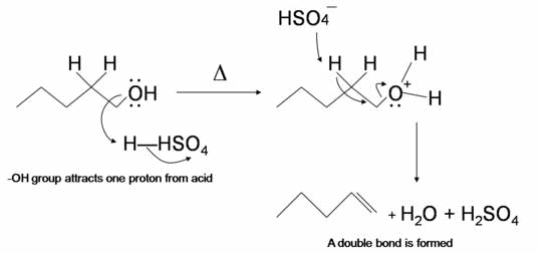
Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H^+ from the acid reagent to form an alkyloxonium ion. This ion acts as a very good leaving group for either the E1 or E2 mechanism. The deprotonated acid (the conjugate base) then reacts with one of the beta-hydrogens to form a double bond.

Primary Alcohols and the E2 Mechanism

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

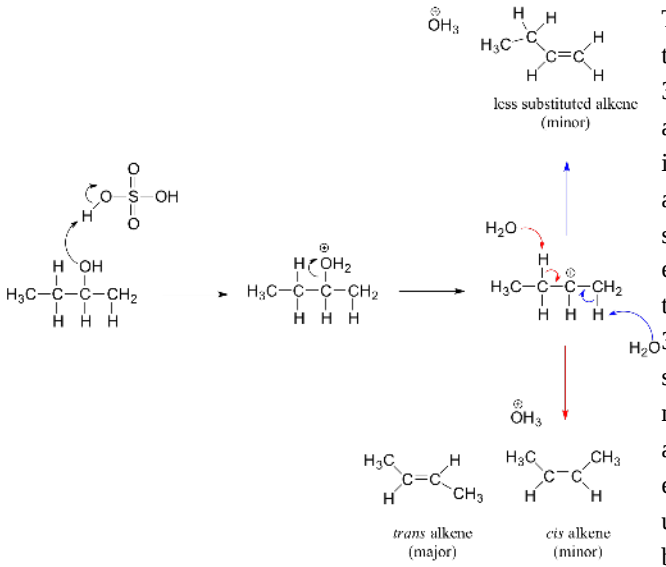
Primary alcohol dehydrates through the E2 mechanism. Oxygen donates two electrons to a proton from sulfuric acid H_2SO_4, forming an alkyloxonium ion. The resulting conjugate base (HSO_4^-) approaches in an anti-coplanar orientation relative to the leaving group and reacts with one adjacent hydrogen while the alkyloxonium ion simultaneously leaves in a concerted process, making a double bond.



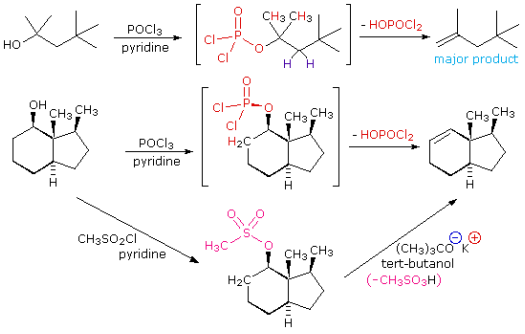
Secondary and Tertiary Alcohols and the E1 Mechanism

Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon, forming a double bond.

For example, in the mechanism below that the alkene formed depends on which 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. Recall the general rule that more substituted alkenes are more stable than less substituted alkenes, and *trans* alkenes are more stable than *cis* alkenes. Thereore, the *trans* diastereomer of the 2-butene product is most abundant.



The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol. The E2 elimination of 3º-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. This procedure is also effective with hindered 2º-alcohols, but for unhindered and 1º-alcohols an S_N2 chloride ion substitution of the chlorophosphate intermediate competes with elimination. Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3º-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2º-alcohol. The first uses the single step $POCl_3$ method, which works well in this case because S_N2 substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.

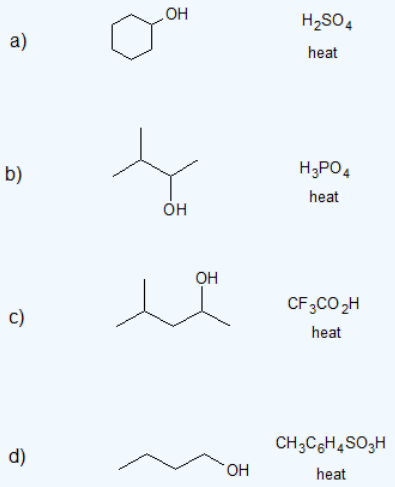


Carbocation Rearrangements and the E1 Mechanism

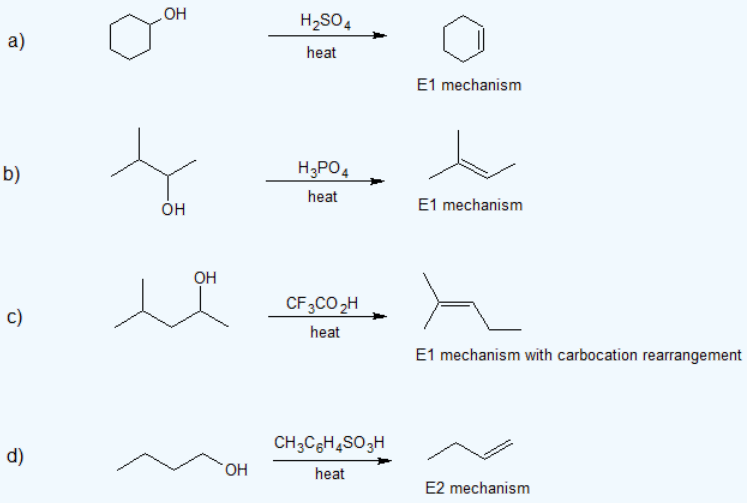
Carbocation stability is always a driving force in E1 mechanisms. It is important to evaluate the structure of all carbocation intermediates to look for the possibility of 1,2-hydride or 1,2-methyl shifts to form more stable carbocation intermediates. Carbocation rearrangements are discussed more completely in chapter 7.

Exercise

1. Draw the bond-line structure(s) for the product(s) formed and specify the mechanism (E1 or E2) for each reaction below.



Answer



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7.9: Uses

Learning Objectives

- discuss the uses and sources of alkenes including catalytic cracking

Uses of ethene and propene

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

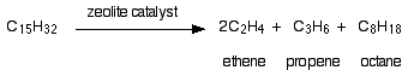
Catalytic Cracking to Form Ethylene

Cracking is the name given to breaking up large hydrocarbon molecules into smaller and more useful bits. This is achieved by using high pressures and temperatures without a catalyst, or lower temperatures and pressures in the presence of a catalyst. The source of the large hydrocarbon molecules is often the naphtha fraction or the gas oil fraction from the fractional distillation of crude oil (petroleum). These fractions are obtained from the distillation process as liquids, but are re-vaporized before cracking.

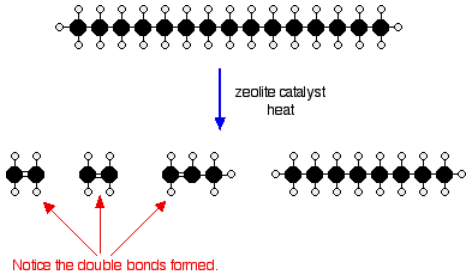
The hydrocarbons are mixed with a very fine catalyst powder. These days the catalysts are zeolites (complex aluminosilicates) - these are more efficient than the older mixtures of aluminium oxide and silicon dioxide. The whole mixture is then blown rather like a liquid through a reaction chamber at a temperature of about 500°C. Because the mixture behaves like a liquid, this is known as fluid catalytic cracking (or fluidized catalytic cracking). Although the mixture of gas and fine solid behaves as a liquid, this is

nevertheless an example of heterogeneous catalysis - the catalyst is in a different phase from the reactants. The catalyst is recovered afterwards, and the cracked mixture is separated by cooling and further fractional distillation.

There isnot any single unique reaction happening in the cracker. The hydrocarbon molecules are broken up in a fairly random way to produce mixtures of smaller hydrocarbons, some of which have carbon-carbon double bonds. One possible reaction involving the hydrocarbon $C_{15}H_{32}$ might be:



Or, showing more clearly what happens to the various atoms and bonds:



This is only one way in which this particular molecule might break up. The ethene and propene are important materials for making plastics or producing other organic chemicals. The octane is one of the molecules found in petrol (gasoline).

Ethene

Cracking is the name given to breaking up large hydrocarbon molecules into smaller and more useful bits. This is achieved by using high pressures and temperatures without a catalyst, or lower temperatures and pressures in the presence of a catalyst. The source of the large hydrocarbon molecules is often the naphtha fraction or the gas oil fraction from the fractional distillation of crude oil (petroleum). These fractions are obtained from the distillation process as liquids, but are re-vaporized before cracking.

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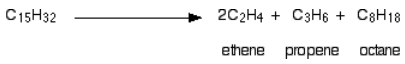
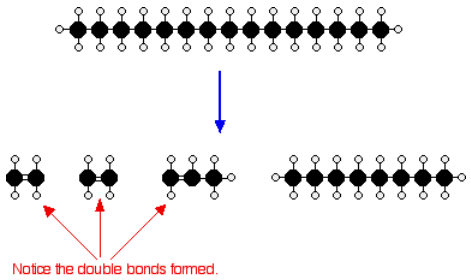
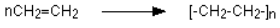


Or, showing more clearly what happens to the various atoms and bonds:



This is only one way in which this particular molecule might break up. The ethene and propene are important materials for making plastics or producing other organic chemicals. You will remember that during the polymeriation of ethene, thousands of ethene molecules join together to make poly(ethene) - commonly called polythene. The reaction is done at high pressures in the presence of a trace of oxygen as an initiator.



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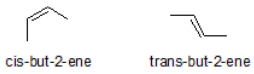
7.10: Additional Exercises

Physical Properties of Alkenes

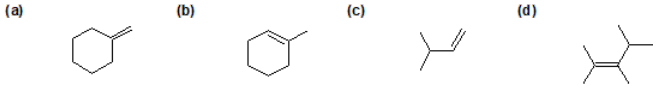
8-1 Explain why *cis*-2-butene is less stable than *trans*-2-butene.



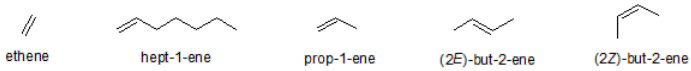
8-2 Order the following alkenes in increasing order of stability.

8-3 Why do more substituted alkenes experience more stability compared to less substituted alkenes?

8-4 Identify whether the following alkenes are mono-, di-, tri-, or tetra-substituted.



8-5 Place the following alkenes in order of increasing boiling points.



Elements of Unsaturation and the Orbital Description of Alkenes

8-6 Using the following equation, calculate the degrees of unsaturation for the following compounds.

$$\text{Degrees of Unsaturation} = \frac{2C + 2 + N - H - X}{2}$$

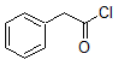
(a) C_6H_6

(b) C_3H_6O

(c) C_4H_6O

(d)

(e)



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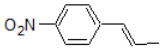

8-7 How many of each type of bonds (sigma/pi) make up a double bond?

Alkene Synthesis by Elimination of Alkyl Halides

8-8 Identify the major product(s) of the following reactions. Include stereochemistry.

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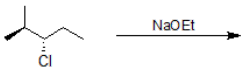
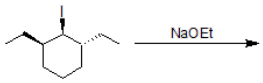
(a)

(b)

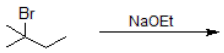


(c)

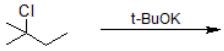


8-9 Identify the major products of the following reactions.

(a)



(b)



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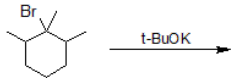
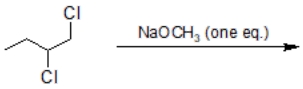


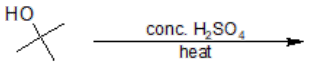
8-10 Give the product of the following reaction.



8-11 What is the IUPAC name of the product formed by the reaction in the previous problem (**8-10**)?

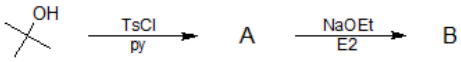
Alkene Synthesis by Dehydration of Alcohols

8-12 Identify the product of the following reaction.

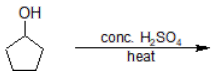


8-13 Draw the mechanism for the reaction in previous problem (**8-12**).

8-14 Draw the intermediate compounds for the following reaction.



8-15 Identify the product of the following reaction.



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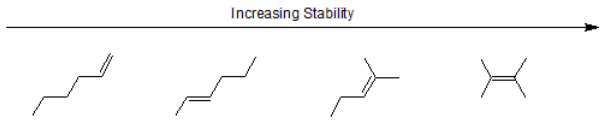
7.11: Solutions to Additional Exercises

Physical Properties of Alkenes

8-1 When in the *cis* configuration, the methyl groups experience steric strain as they are in close proximity to each other. They avoid steric interactions when in the *trans* configuration as they are able to stay as far apart as possible.

8-2



8-3 Alkyl groups are able to stabilize their neighboring carbon atoms by donating electron density, which allows for the delocalization of electron density and an increase in stability.

8-4

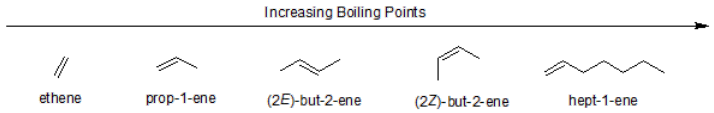
a) Disubstituted

b) Trisubstituted

c) Monosubstituted

d) Tetrasubstituted

8-5



Elements of Unsaturation and the Orbital Description of Alkenes

8-6

a) 4

b) 1

c) 2

d) 2

e) 5

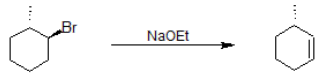
f) 6

8-7 One sigma and one pi bond together make a double bond.

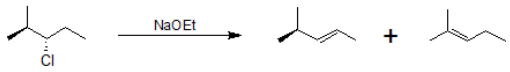
Alkene Synthesis by Elimination of Alkyl Halides

8-8

(a)



(b)



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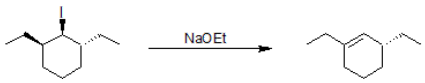
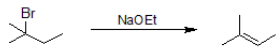
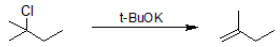


8-9

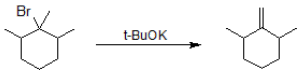
(a)



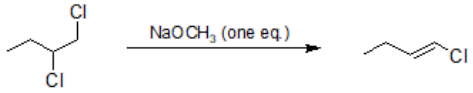
(b)



(c)



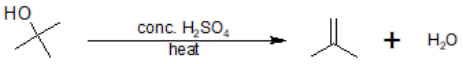
8-10



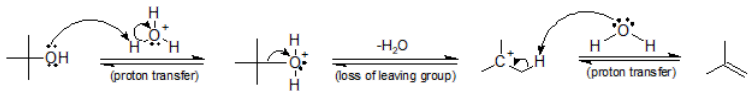
8-11 (1*E*)-1-chlorobut-1-ene

Alkene Synthesis by Dehydration of Alcohols

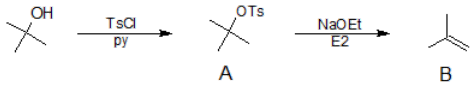
8-12



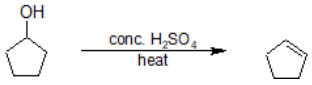
8-13



8-14



8-15



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CHAPTER OVERVIEW

8: Reactions of Alkenes

Learning Objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- draw the general Electrophilic Addition Reaction (EAR) mechanism for an alkene - refer to section 9.1
- predict the products/specify the reagents for EAR of hydrohalic acids (HX) with symmetrical alkenes - refer to section 9.2
- predict the products/specify the reagents for EAR of hydrohalic acids (HX) with asymmetrical alkenes using Markovnikov's Rule for Regioselectivity - refer to section 9.3
- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes - refer to sections 9.3 - 9.14
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation) - refer to sections 9.4, 9.5, and 9.6 respectively
- discern the stereochemical differences between the EAR of chiral and achiral alkenes - refer to sections 9.7 and 9.8
- predict the products/specify the reagents for halogenation and hydrohalogenation of alkenes - refer to sections 9.9 and 9.10 respectively
- recognize organic oxidation and reduction reactions - refer to sections 9.11 and 9.12
- predict the products/specify the reagents for hydrogenation (reduction) of alkenes - refer to section 9.11
- predict the products/specify the reagents for epoxidation of alkenes - refer to section 9.12
- predict the products/specify the reagents for dihydroxylation of alkenes - refer to sections 9.13 and 9.14
- predict the products/specify the reagents for oxidative cleavage of alkenes - refer to section 9.15
- predict the products of carbene additions to alkenes - refer to section 9.16
- predict the polymer/specify the monomer for radical, chain -growth polymers of alkenes - refer to section 9.17
- discuss an example biological addition reactions - refer to section 9.18

8.1: Electrophilic Addition Reactions (EARs)
8.2: Addition of Hydrogen Halides to Symmetrical Alkenes
8.3: Alkene Asymmetry and Markovnikov's Rule
8.4: Hydration: Acid Catalyzed Addition of Water
8.5: Hydration: Oxymercuration-Demercuration
8.6: Hydration: Hydroboration-Oxidation
8.7: Stereochemistry of Reactions - Hydration of Achiral Alkenes
8.8: Stereochemistry of Reactions - Hydration of Chiral Alkenes
8.9: Addition of Halogens
8.10: Formation of Halohydrins
8.11: Reduction of Alkenes - Catalytic Hydrogenation
8.12: Oxidation of Alkenes - Epoxidation
8.13: Dihydroxylation of Alkenes
8.14: Opening of Epoxides - Acidic versus Basic Conditions
8.15: Oxidative Cleavage of Alkenes
8.16: Addition of Carbenes to Alkenes - Cyclopropane Synthesis
8.17: Radical Chain-Growth Polymerization
8.18: 9.18 Biological Additions of Radicals to Alkenes
8.19: Additional Exercises
8.20: Solutions to Additional Exercises

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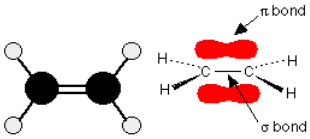
8.1: Electrophilic Addition Reactions (EARs)

Learning Objective

- draw the general Electrophilic Addition Reaction (EAR) mechanism for an alkene

Introduction

We are going to start by looking at ethene, because it is the simplest molecule containing a carbon-carbon double bond. What is true of C=C in ethene will be equally true of C=C in more complicated alkenes.



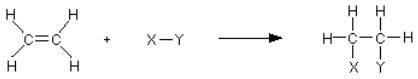
Ethene , C_2H_4, is often modeled as shown above. The double bond between the carbon atoms is, of course, two pairs of shared electrons. What the diagram doesn't show is that the two pairs aren't the same as each other. One of the pairs of electrons is held on the line between the two carbon nuclei as you would expect, but the other is held in a molecular orbital above and below the plane of the molecule. A molecular orbital is a region of space within the molecule where there is a high probability of finding a particular pair of electrons.

In this diagram, the line between the two carbon atoms represents a normal sigma bond - the pair of shared electrons lies in a molecular orbital on the line between the two nuclei where you would expect them to be. The other pair of electrons is found somewhere in the shaded part above and below the plane of the molecule. This bond is called a pi bond. The electrons in the pi bond are free to move around anywhere in this shaded region and can move freely from one half to the other. The pi electrons are not as fully under the control of the carbon nuclei as the electrons in the sigma bond. Because the pi bond electrons lie exposed above and below the rest of the molecule, they are relatively open to reaction with other compounds.

Electrophilic Addition Reactions (EARs)

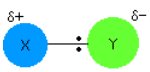
In a sense, the pi bond is an unnecessary bond. The structure would hold together perfectly well with a single bond rather than a double bond. The pi bond often breaks and the electrons in it are used to join other atoms (or groups of atoms) onto the alkene molecule. To continue with our example, ethene undergoes addition reactions. An addition reaction is a reaction in which two molecules join together to make a bigger one. Nothing is lost in the process. All the atoms in the original molecules are found in the bigger one. The pi bond is electron rich and takes the role of the nucleophile seeking out an electrophile with its full or partial positive charge.

Using a general molecule X-Y as the electrophile reacting with ethene, the atoms 'X' and 'Y' are added to the carbon chain across the vinylic carbons as shown below.

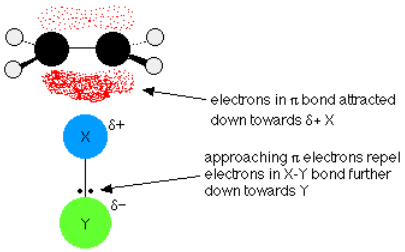


Understanding the Electrophilic Addition Mechanism

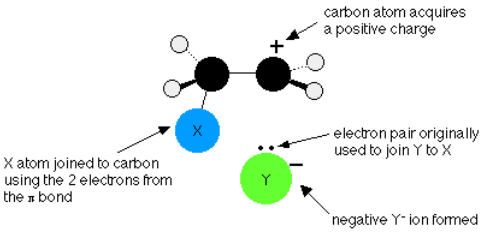
The mechanism for the reaction between ethene and a molecule X-Y begins by recognizing the electrophilic nature of X-Y. Trends in relative electronegativity help identify bonds to create partial positives within polar compounds. As shown below, we are going to assume that Y is more electronegative than X, so that the pair of electrons is pulled slightly towards the Y end of the bond. This polarity means that the X atom carries a slight positive charge (partial positive).



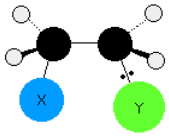
The slightly positive X atom is an electrophile and attracts the exposed pi electrons in the ethene. Now imagine what happens as they approach each other. The electrons in the half of the pi bond nearest the XY are attracted to the partial positive charge as shown below.



The two electrons in the pi bond move closer towards the X until a covalent bond is made. Simultaneously, the electrons in the X-Y bond are pushed entirely onto the Y to form the anion Y^- ion and a carbocation as shown below.

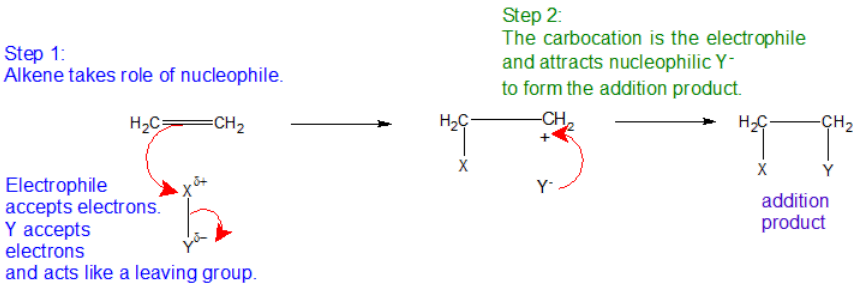


In the final step, the lone pair on Y^- is attracted to the positively charged carbocation and they react to form a second covalent bond and the product below.



EAR Mechanism

The movements of the electrons for the EAR mechanism are shown with curved arrows.



Regiochemistry and Regioselective Reactions

Regiochemistry is the orientation of the electrophile relative to the pi bond of the alkene. Electrophilic addition reactions of alkenes can be regioselective depending on the symmetry and structure of the alkene. The details will be discussed in a later sections of this chapter.

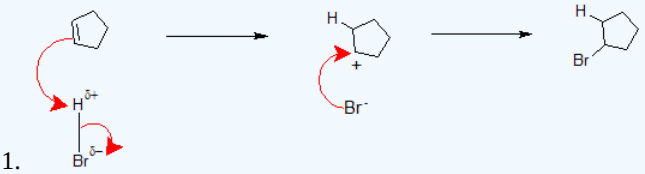
Stereoselective Reactions

Different stereoisomeric reactants produce different stereoisomeric products. Electrophilic addition reactions of alkenes can be stereoselective depending on the symmetry and structure of the alkene. The details will be discussed in a later sections of this chapter.

Exercise 8.1.1

1. In the next section, we will apply the Electrophilic Addition mechanism to actual compounds. Draw the complete mechanism when hydrogen bromide gas is bubbled through a solution of cyclopentene.

Answer

1. 

Contributors

- Jim Clark (Chemguide.co.uk)

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8.2: Addition of Hydrogen Halides to Symmetrical Alkenes

Learning Objective

- predict the products/specify the reagents for EAR of hydrohalic acids (HX) with symmetrical alkenes

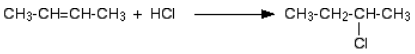
This section looks at the reaction of symmetrical alkenes (like ethene, but-2-ene or cyclohexene) with hydrogen halides such as hydrogen chloride and hydrogen bromide. Since these alkenes have identical groups attached to each end of the carbon-carbon double bond, regioselectivity does not apply.

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:

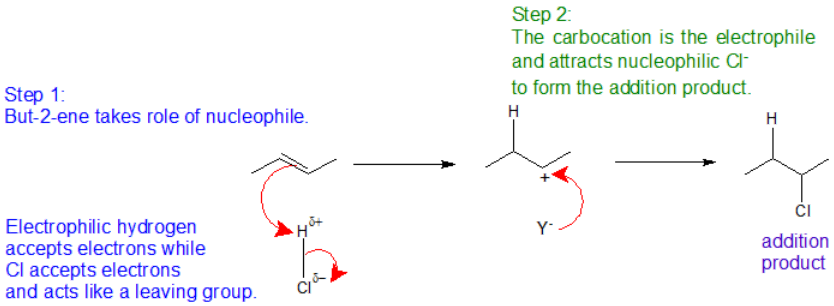


What happens if you add the hydrogen to the carbon atom at the right-hand end of the double bond, and the chlorine to the left-hand end? You would still have the same product. The chlorine would be on a carbon atom next to the end of the chain - you would simply have drawn the molecule flipped over in 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 a electrophile (proton) and a nucleophile (halide). First, the electrophile will attack the double bond and take up a set of 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 Chloride to But-2-ene



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

Variation of rates when you change the halogen

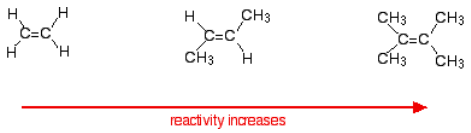
Reaction rates increase in the order HF < HCl < HBr < HI. Hydrogen fluoride reacts much more slowly than the other three, and is normally ignored in talking about these reactions.

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:



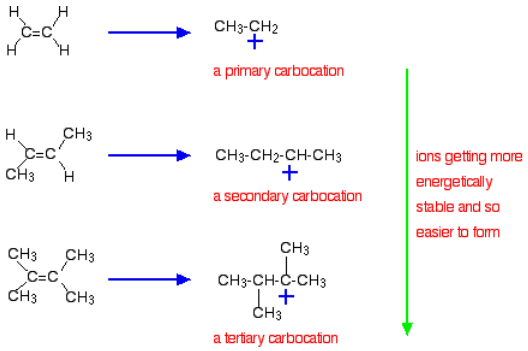
There are two ways of looking at the reasons for this - both of which need you to know about the mechanism for the reactions.

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.

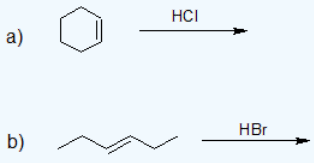
The more important reason, though, lies in the stability of the intermediate ion formed during the reaction. The three examples given above produce these carbocations (carbonium ions) at the half-way stage of the reaction:



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.

Exercise

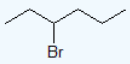
1. Draw the bond-line structures for the products of the following reactions.



Answer

1.

a)

b) 

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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8.3: Alkene Asymmetry and Markovnikov's Rule

Learning Objective

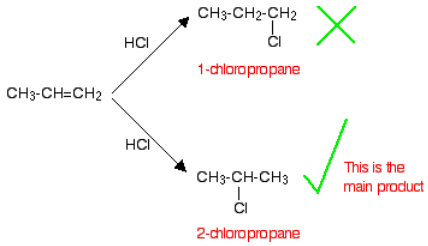
- predict the products/specify the reagents for EAR of hydrohalic acids (HX) with asymmetrical alkenes using Markovnikov's Rule for Regioselectivity
- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes

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 of the hydrogen and the halogen across the double bond.

Markovnikov's Rule

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 according to Markovnikov's Rule.



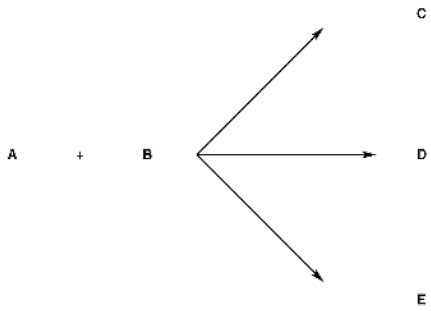
> Markovnikov's Rule: When HX is added to an unsymmetrical alkene, the hydrogen becomes attached to the carbon with the most hydrogens attached to it already.

Applying Markovnikov's Rule to the reaction above, the hydrogen bonds with 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.

Regioselectivity - a closer look

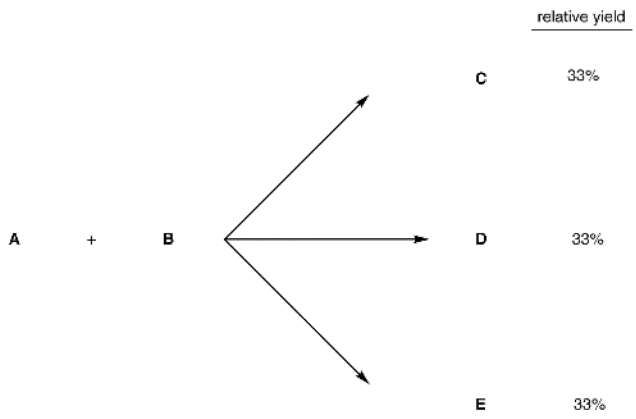
If more than one reaction could occur between a set of reactants under the same conditions giving products that are constitutional isomers and if one product forms in greater amounts than the others, the overall reaction is said to be regioselective.

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**.



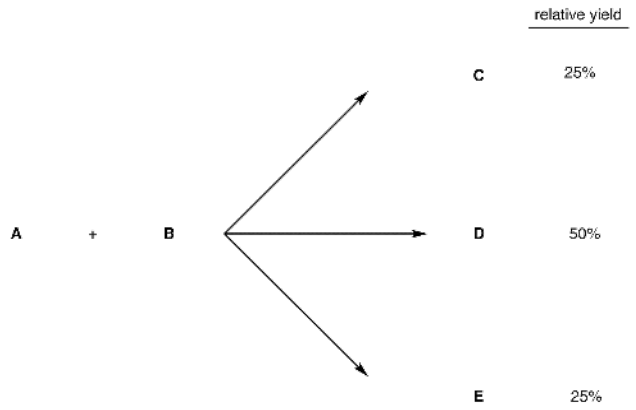
There are two possibilities:

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.)



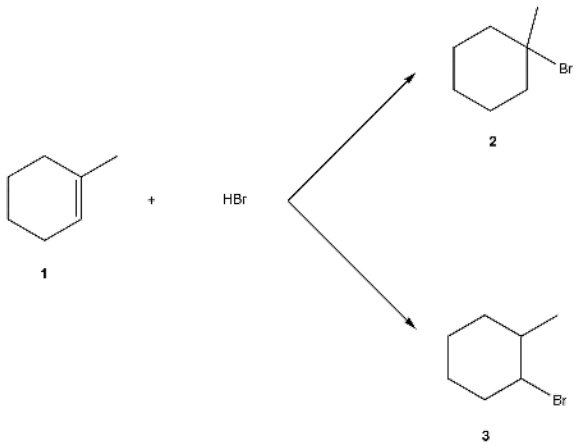
If this is what is observed, the overall reaction between **A** and **B** is not regioselective.

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.

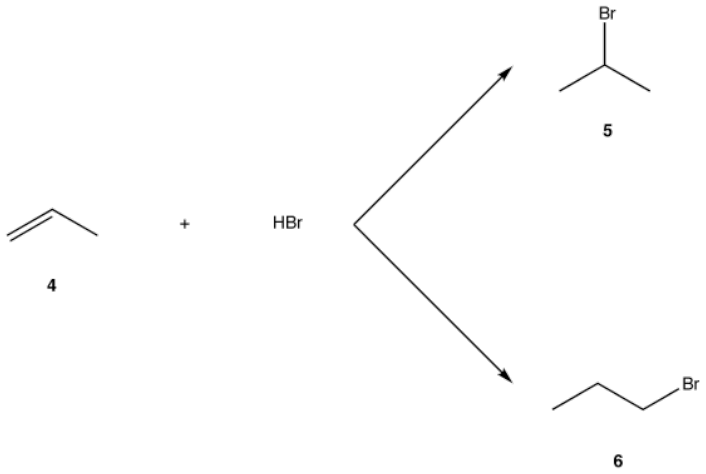
eg:



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:

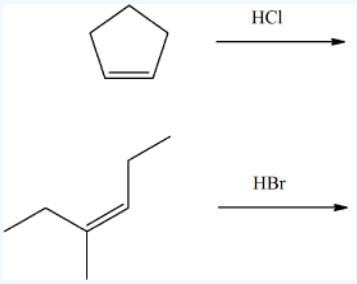


The only observed product is **5**. (Relative yields of **5** and **6** are 100% and 0%, respectively.) Thus the overall reaction between **4** and HBr is regiospecific toward **5**.

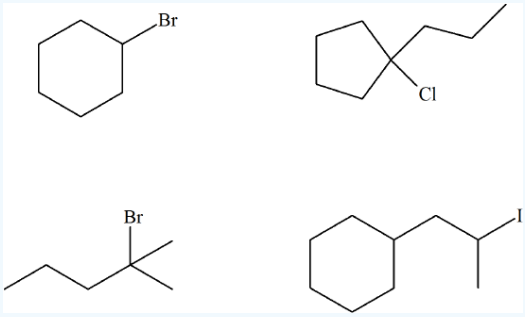
Regiospecificity is merely the limiting case of regioselectivity. All regiospecific reactions are regioselective, but not all regioselective reactions are regiospecific.

Exercises

1. Predict the product(s) for the following reactions:

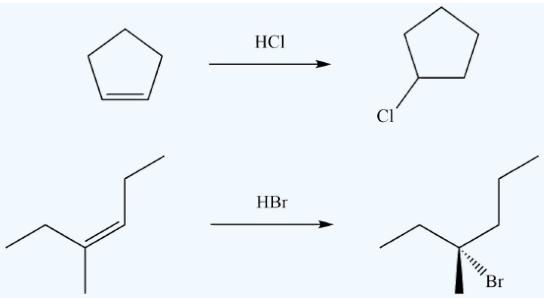


2. In each case, suggest an alkene that would give the product shown.

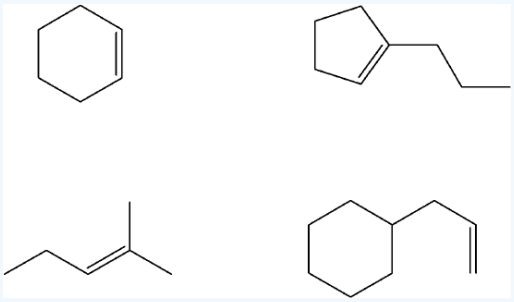


Answers

1.



2.



Contributors and Attributions

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8.4: Hydration: Acid Catalyzed Addition of Water

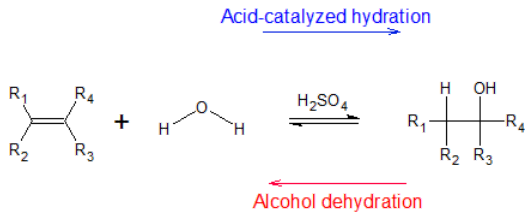
Learning Objective

- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation)

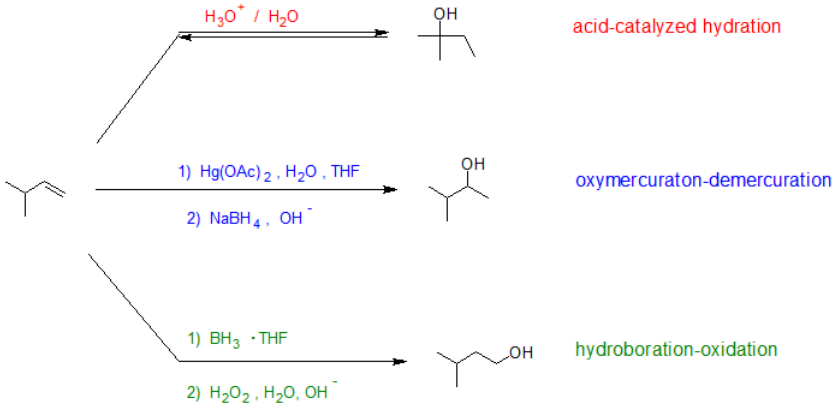
What Is Electrophilic Hydration?

Electrophilic hydration is the addition of hydrogen and a hydroxyl group across the two carbons of a double bond. Electrophilic hydration is the reverse of dehydration of alcohols and so begins the circular nature of organic chemistry. Alcohols can be dehydrated to form alkenes and alkenes can undergo electrophilic addition reactions to form alcohols. Electrophilic hydrogen is essentially a proton: a hydrogen atom stripped of its electrons. Electrophilic hydrogen is commonly used to help break double bonds or restore catalysts.

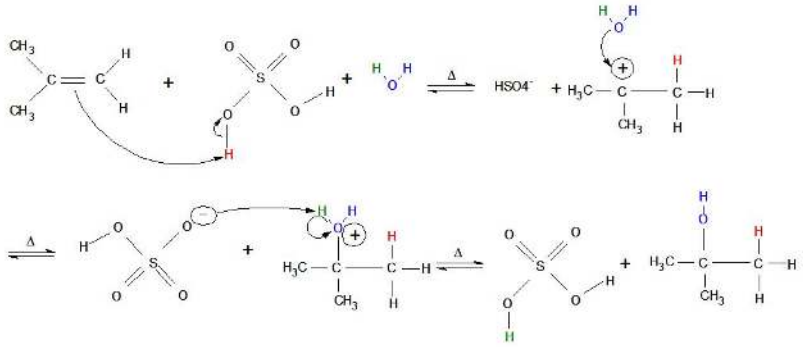
Electrophilic hydration of alkenes has practical applications in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



In later sections, we will learn that mercury (II) sulfate and borane are also electrophiles that can react with alkenes to form hydration products. Each reaction pathway has its own regio- and stereochemical considerations. In the example below, we see that the same alkene produces different hydration products depending on the hydration pathway.



Mechanism for Acid-catalyzed Hydration of Alkenes



Temperatures for Types of Alcohol Synthesis

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.*

- Primary Alcohol: Less than 170ºC
- Secondary Alcohol: Less than 100ºC
- Tertiary Alcohol: Less than 25ºC

But...Why Does Electrophilic Hydration Work?

- An alkene placed in an aqueous non-nucleophilic strong acid immediately "reaches out" with its double bond and attacks one of the acid's hydrogen atoms (meanwhile, the bond between oxygen and hydrogen performs heterolytic cleavage toward the oxygen—in other words, both electrons from the oxygen/hydrogen single bond move onto the oxygen atom).
- A carbocation is formed on the original alkene (now alkane) in the more-substituted position, where the oxygen end of water attacks with its 4 non-bonded valence electrons (oxygen has 6 total valence electrons because it is found in Group 6 on the periodic table and the second row down: two electrons in a 2s-orbital and four in 2p-orbitals. Oxygen donates one valence electron to each bond it forms, leaving four 4 non-bonded valence electrons).
- After the blue oxygen atom forms its third bond with the more-substituted carbon, it develops a positive charge (3 bonds and 2 valence electrons give the blue oxygen atom a formal charge of +1).
- The bond between the green hydrogen and the blue oxygen undergoes heterolytic cleavage, and both the electrons from the bond move onto the blue oxygen. The now negatively-charged strong acid picks up the green electrophilic hydrogen.
- Now that the reaction is complete, the non-nucleophilic strong acid is regenerated as a catalyst and an alcohol forms on the most substituted carbon of the current alkane. At lower temperatures, more alcohol product can be formed.

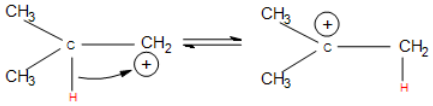
What is Regiochemistry and How Does It Apply?

Regiochemistry deals with where the substituent bonds on the product. **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 bonds onto the product. 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

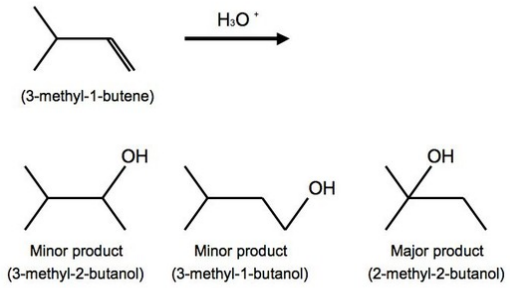
In the mechanism for a 3º alcohol shown above, the red H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3º carbon, causing it to be highly stabilized by *hyperconjugation*—electrons 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** connected to the double bond. Carbocations are also stabilized by resonance, but resonance is not a large factor in this case because any carbon-carbon double bonds are used to initiate the reaction, and other double bonded molecules can cause a completely different reaction. If the carbocation does originally form on the less substituted part of the alkene, carbocation rearrangements occur to form more substituted products.

Carbocation Rearrangements - a review

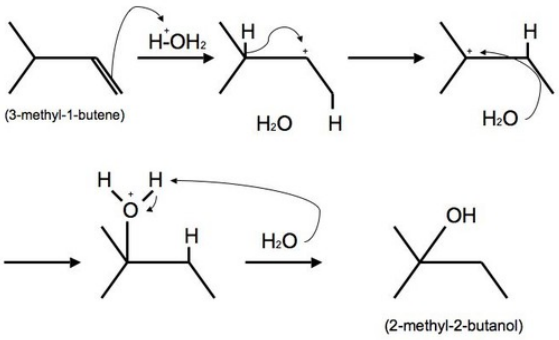
- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



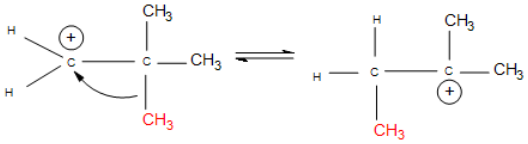
In a more complex case, when alkenes undergo hydration, we also observe hydride shift. Below is the reaction of 3-methyl-1-butene with H_3O^+ that furnishes to make 2-methyl-2-butanol:



Once again, we see multiple products. In this case, however, we see two minor products and one major product. We observe the major product because the -OH substitutent is attached to the more substituted carbon. When the reactant undergoes hydration, the proton attaches to carbon #2. The carbocation is therefore on carbon #2. Hydride shift now occurs when the hydrogen on the adjacent carbon formally switch places with the carbocation. The carbocation is now ready to be attacked by H_2O to furnish an alkyloxonium ion because of stability and hyperconjugation. The final step can be observed by another water molecule attacking the proton on the alkyloxonium ion to furnish an alcohol. We see this mechanism below:



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift.

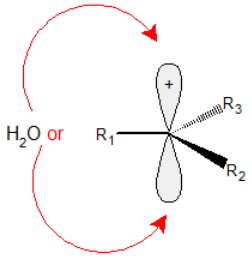


The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3º alcohol shown above, water is the nucleophile. When the green H is removed from the water molecule, the alcohol attached to the most substituted carbon. Hence, **electrophilic hydration follows Markovnikov's rule.**

Stereochemistry of Acid-catalyzed Hydration

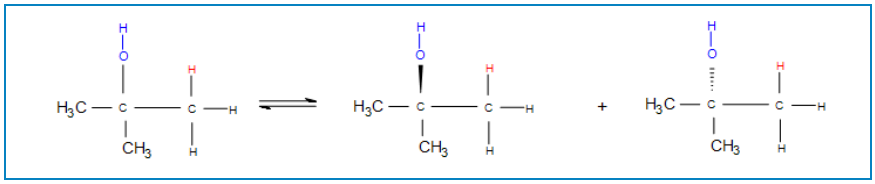
Stereochemistry deals with how the substituent bonds on the product directionally. Dashes and wedges denote stereochemistry by showing whether the molecule or atom is going into or out of the plane of the board. Whenever the bond is a simple single straight line, the molecule that is bonded is equally 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**.

There is no stereochemical control in acid-catalyzed hydration reactions. The carbocation intermediate has the trigonal planar geometry of sp^2 hybridization which allows the subsequent reaction with water from either orientation.



There is no stereochemical control with a carbocation intermedate.

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 could look like either of the following products:



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.

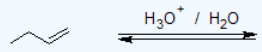
Is There a Better Way to Add Water to Synthesize an Alcohol From an Alkene?

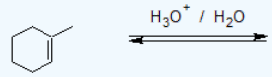
A more efficient pathway does exist: see Oxymercuration - Demercuration: A Special Electrophilic Addition. Oxymercuration does not allow for rearrangements, but it does require the use of mercury, which is highly toxic. Detractions for using electrophilic hydration to make alcohols include:

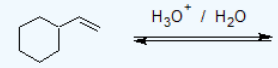
- Allowing for carbocation rearrangements
- Poor yields due to the reactants and products being in equilibrium
- Allowing for product mixtures (such as an (R)-enantiomer and an (S)-enantiomer)
- Using sulfuric or phosphoric acid

Exercise

1. Draw the bond-line structure for the major product of each reaction.

a) 

b) 

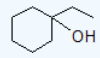
c) 

Answer

1.

a)

b)

c) 

1,2-hydride shift

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- Jim Clark (Chemguide.co.uk)
- Prof. Steven Farmer (Sonoma State University)

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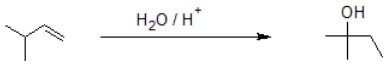
8.5: Hydration: Oxymercuration-Demercuration

Learning Objective

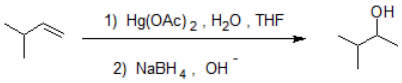
- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation)

Introduction

Acid-catalyzed hydration of alkenes is limited by carbocation stability. Carbocation rearrangement can occur to form a more stable ion as shown in the example below.



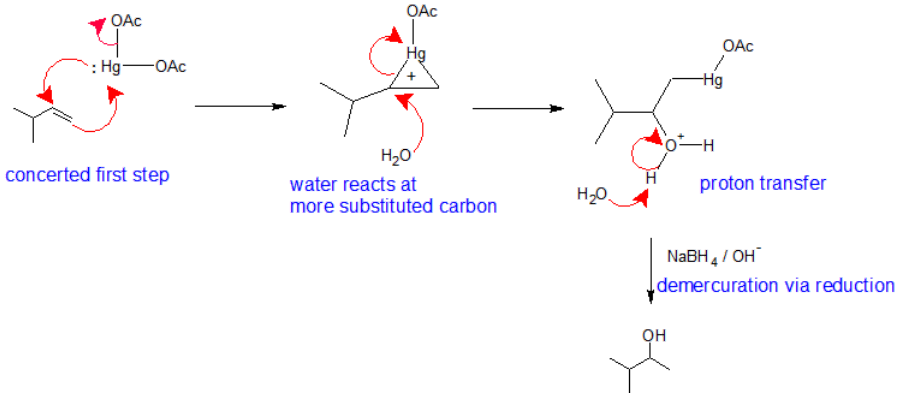
Alkene hydration using the oxymercuration-demercuration reaction pathway reliably produces the Markovnikov product without carbocation rearrangment as shown in the example below.



Oxymercuration-Demercuration is a two step pathway used to produce alcohols.

Oxymercuration-Demercuration Mechanism

This mechanism is similar to the previous electrophilic addition reactions. The major difference is that a mercurium ion bridge stabilizes the carbocation intermediate so that it cannot rearrange. Metals are electropositive. Mercury carries a partial positive charge in the acetate complex and is the electrophile. During the first step of this mechanism, the pi electrons form a bond to mercury while the lone pair on the mercury simultaneously bonds to the other vinyl carbon creating a mercurium ion bridge. The mercurium ion forms in conjunction with the loss of an acetate ion. The mercurium ion stabilizes the carbocation so that it does not rearrange. In the second step of this mechanism, a water molecule reacts with the most substituted carbon to open the mercurium ion bridge. The third step of this mechanism is a proton transfer to a solvent water molecule to neutralize the addition product. The fourth step of the reaction pathway is the reduction of the organomercury intermediate with sodium borohydride under basic conditions. The mechanism of the fourth step is beyond the scope of first year organic chemistry.



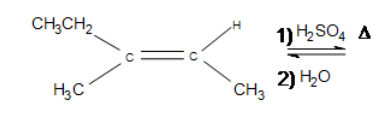
Notice that overall, the oxymercuration - demercuration mechanism follows Markovnikov's Regioselectivity with the OH group attached to the most substituted carbon and the H attached to the least substituted carbon. The reaction is useful, because strong acids are not required and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

Exercise

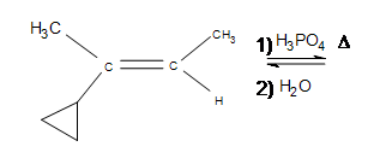
1. Show how to prepare 3-methyl2-pentanol from 3-methyl-1-pentene.

Note: Questions 2-5 have not shown the water present in the sulfuric acid solution and have indicated a second neutralization step. Some authors simply write H^+/H_2O as a single step.

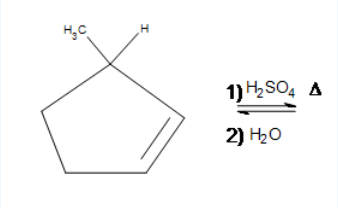
2. Draw the bond-line structure for the product.



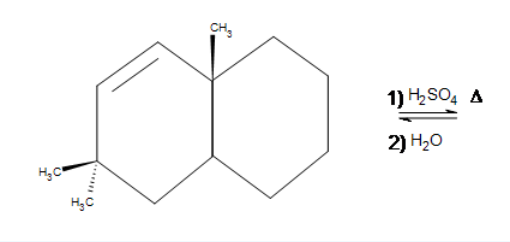
3. Draw the bond-line structure for the product. How does the cyclopropane group affect the reaction?



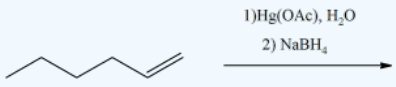
4. Draw the bond-line structure for the product. (Hint: What is different about this problem?)

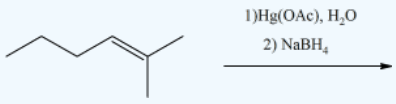


5. Draw the bond-line structure for the product(s). Indicate any shifts as well as the major product:

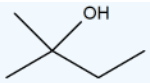


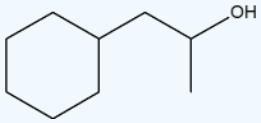
6. In each case, predict the product(s) of these reactants of oxymercuration.





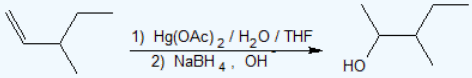
7. Propose the alkene that was the reactant for each of these products of oxymercuration.



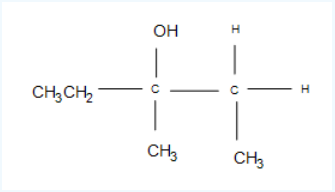


Answer

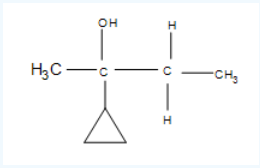
1.



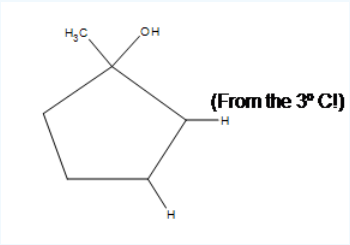
2. This reaction is electrophilic hydration.



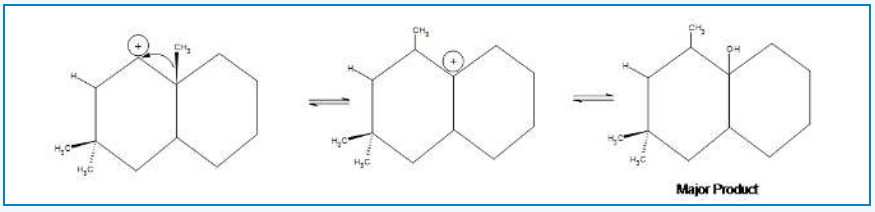
3. The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3º carbon will remain as such).



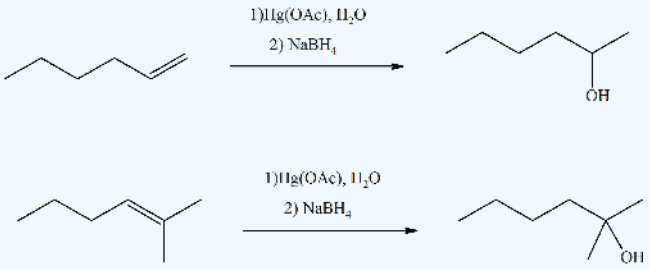
4. A hydride shift actually occurs from the top of the 1-methylcyclopentane to where the carbocation had formed.



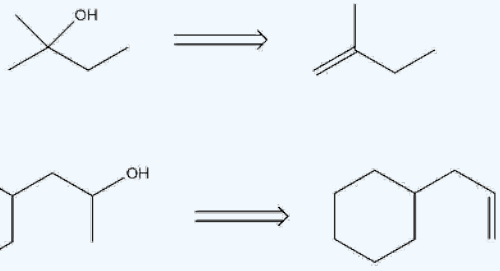
5. In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups 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.



6.



7.



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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.

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8.6: Hydration: Hydroboration-Oxidation

Learning Objectives

- apply the principles of regioselectivity and stereoselectivity to the addition reactions of alkenes
- predict the products, specify the reagents, and discern most efficient reaction for hydration of alkenes (acid catalyzed hydration; or oxymercuration/demercuration; or hydroboration/oxidation)

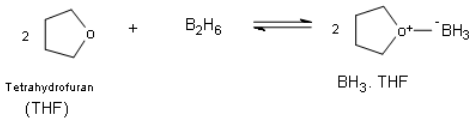
Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an anti-Markovnikov manner, where the hydrogen (from $\mathbf{BH_3}$ or $\mathbf{BHR_2}$) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene double bond. Furthermore, the borane acts as the electrophile 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.

The Borane Complex

It is very important to understand the structure and properties of the borane molecule. Borane exists naturally as a very toxic gas and it exists as dimer of the general formula $\mathbf{B_2H_6}$ (diborane).

$$\mathbf{BH_3 \longrightarrow B_2H_6}$$

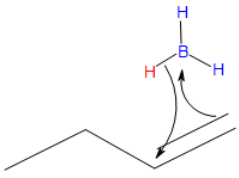
Since diborane dimer ignites spontaneously in air, it commercially distributed in ether or tetrahydrofuran (THF) solutions. In these solutions, the borane can exist as a Lewis acid-base complex which allows boron to have an octet of electrons.



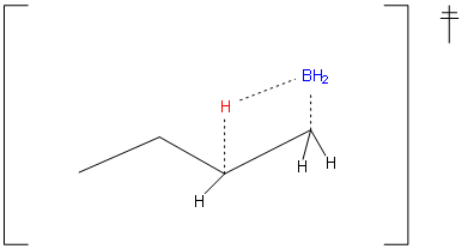
The Mechanism

Step #1: Hydroboration of the alkene

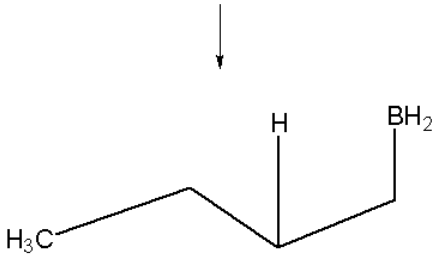
The addition of the borane to the alkene is initiated and proceeds as a concerted reaction because bond breaking and bond formation occur at the same time. The vacant 2p orbital of the boron takes the role of electrophile and accepts the pi electrons from the nucleophilic alkene. The boron adds to the 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). With a concerted mechanism, there is no carbocation formation.



Transition state



* Note that a carbocation is not formed. Therefore, no rearrangement takes place.

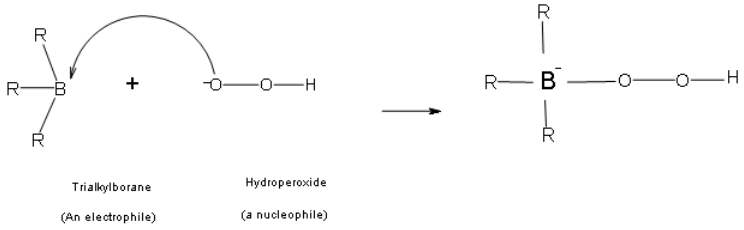


It is important to note that reaction continues two more times until all three hydrogens on the borane have reacted with alkenes to create the trialkylborane intermediate R3B.

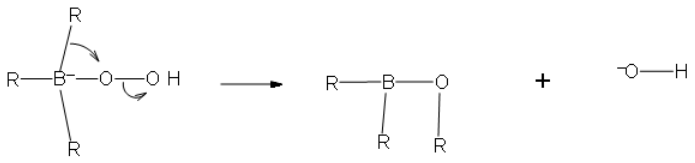
Step #2: Oxidation of the Trialkylborane by Hydrogen Peroxide

The hydrogen peroxide (**HOOH**) is the nucleophile in this reaction because it is the electron donor to the newly formed trialkylborane that resulted from the previous hydroboration.

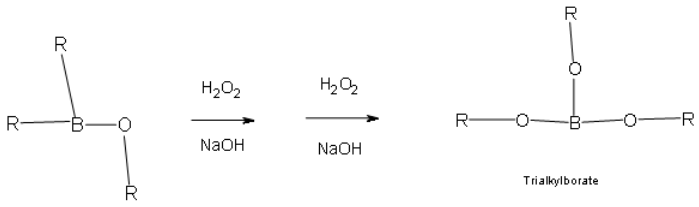
$$\mathbf{HOOH + OH^- \longrightarrow HOO^- + HOH} \tag{8.6.1}$$



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 loss of a hydroxide ion.



Two more of these reactions with hydroperoxide will occur in order give a trialkylborate



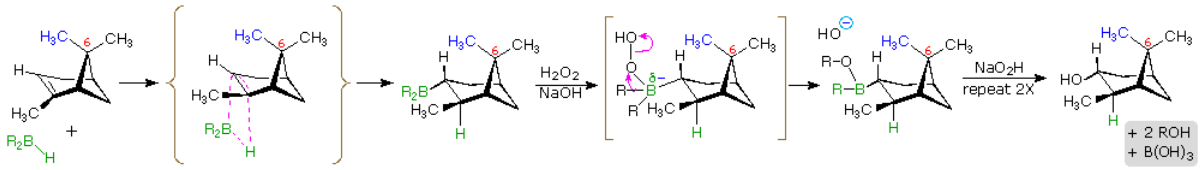
In the final step of the oxidation process, the trialkylborate reacts with aqueous **NaOH** to give the alcohol and sodium borate (\ce{Na3BO3}\).

$$\mathbf{(RO_3)B + 3\,NaOH \longrightarrow 3\,OH + Na_3BO_3} \qquad \mathbf{(8.6.2)}$$

If you need additional visuals to aid you in understanding the mechanism, click on the outside links provided at the end of this section.

Stereochemistry of the Hydroboration Step

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.



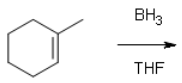
Since the hydroboration procedure is most commonly used to hydrate alkenes in an anti-Markovnikov fashion, we also need to know the stereoselectivity of the second oxidation reaction, which substitutes a hydroxyl group for the boron atom. Independent study has shown this reaction takes place with retention 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 blue 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.

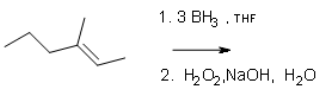
Exercises

1. Draw the bond-line structure of the product(s) for these following reactions?

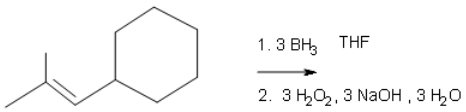
a)



b)

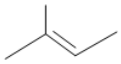


c)



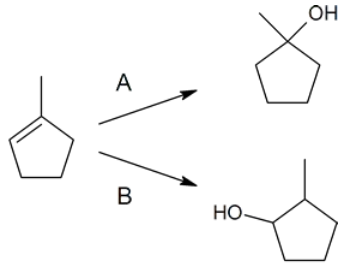
2. Draw the structural formulas for the alcohols that result from hydroboration-oxidation of the alkenes shown.

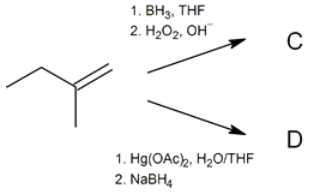
a)



b) (E)-3-methyl-2-pentene

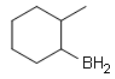
3. Write out the reagents or products (A–D) shown in the following reaction schemes.

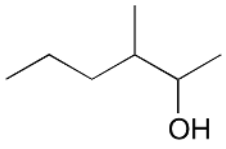


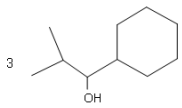


Answer

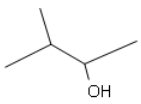
1.

a) 

b) 

c) 

2.

a) 

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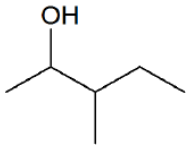
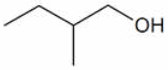


3.

A: 1. $Hg(OAc)_2$, H_2O/THF; 2. $NaBH_4$

B: 1. BH_3, THF; 2. H_2O_2, OH^-

C: 

D:

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- Jim Clark (Chemguide.co.uk)
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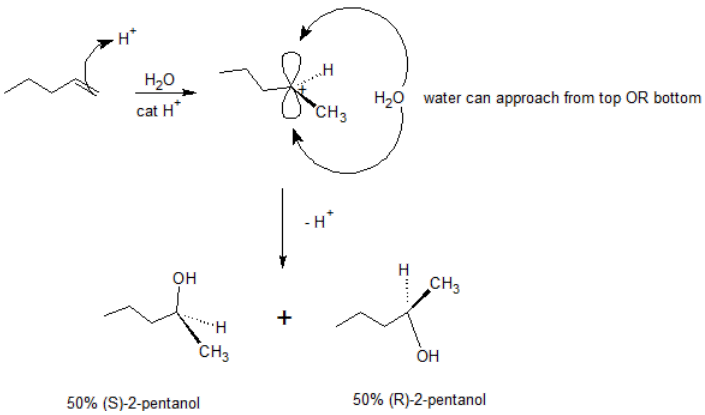
8.7: Stereochemistry of Reactions - Hydration of Achiral Alkenes

Learning Objective

- discern the stereochemical differences between the EAR of chiral and achiral alkenes

Stereochemistry and the Subtle Details

Organic reactions in the laboratory or in living systems can produce chiral centres. Consider reaction of 1-pentene 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-pentene results in a planar carbocation intermediate. A molecule of water is then equally likely to react from the top or the bottom of this cation to produce either (S)-2-pentanol or (R)-2-pentanol, respectively, as shown in the mechanism below.



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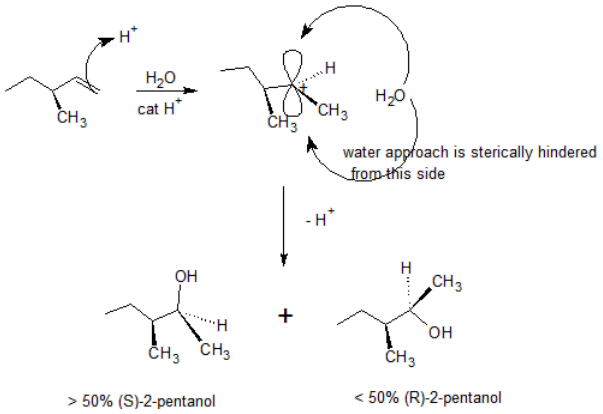
8.8: Stereochemistry of Reactions - Hydration of Chiral Alkenes

Learning Objective

- discern the stereochemical differences between the EAR of chiral and achiral alkenes

Stereochemistry - the Subtle Details

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 as shown in the mechanism below.



Exercise

1. Predict the products of the following reaction showing stereochemistry.

Answer

1. The products are diastereomers of one another.

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8.9: Addition of Halogens

Learning Objective

- predict the products/specify the reagents for halogenation of alkenes

Introduction

As the halogen molecule, for example Br_2, approaches the double bond of an alkene, electrons in the double bond repel electrons in the bromine molecule causing polarization of the halogen bond. This interaction induces a dipole moment in the halogen molecule bond allowing one of the halogens to gain a partial positive charge and take the role of electrophile. The nucleophilic pi electrons form a bond to the electrophilic halogen while the halogen molecular bond heterolytically breaks to release bromide as a leaving group. The halogen addition is not regioselective but stereoselective. Stereochemistry of this addition is analogous to the oxymercuration mechanism. In this reaction, a bromonium (halogenium) ion froms as the intermediate. The bromonium ion formation stabilizes the positive charge and prevents carbocation rearrangement. In the second step, the bromide released from the first step takes the role of thenucleophile and reacts with the cyclic bromonium ion with back side orientation. Therefore, the stereochemistry of the product is a **vicinial dihalides** through **anti-addition**.

$$\mathbf{R_2C{=}CR_2 + X_2 \rightarrow R_2CX{-}CR_2X} \tag{8.9.1}$$

Halogens that are commonly used in this type of the reaction are: Br_2 and Cl_2. In thermodynamical terms I_2 is too slow for this reaction because of the size of its atom, and F_2 is too vigorous and explosive. Solvents that are used for this type of electrophilic halogenation are inert (e.g., CCl_4) can be used in this reaction.

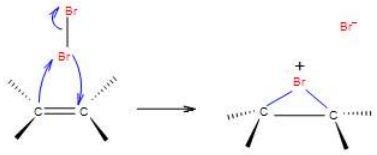
Because halogen with negative charge can attack any carbon from the opposite side of the cycle it creates a mixture of steric products.Optically inactive starting material produce optically inactive achiral products (meso) or a racemic mixture.

Electrophilic addition mechanism consists of two steps.

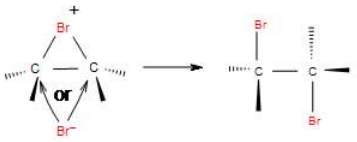
Before constructing the mechanism let us summarize conditions for this reaction. We will use Br_2 in our example for halogenation of ethylene. Halogens can act as electrophiles due to polarizability of their covalent bond. Addition of halogens is stereospecific and produces vicinial dihalides with anti-addition. Cis starting materials will give a mixture of enantiomers and trans starting materials produce a meso compound.

Nucleophile	pi electrons of alkene double bond
Electrophile	halogen (Cl_2 or Br_2)
Regiochemistry	none
Stereochemistry	anti-additon

Step 1: The addition the Br-Br bond polarizes, heterolytic cleavage occurs and Br with the positive charge forms a intermediate cycle with the double bond.

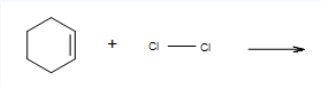


Step 2: The bromide anion reacts with either carbon of the bridged bromonium ion from the back side of the ring. The ring opens up and the two halogens are in the **anti-position** relative to each other.



Exercise

1. What is the mechanism of adding Cl_2 to the cyclohexene?

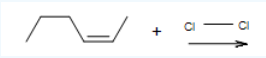


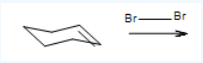
2. A reaction of Br_2 molecule in an inert solvent with alkene follows?

a) syn addition

b) anti addition

c) Morkovnikov rule

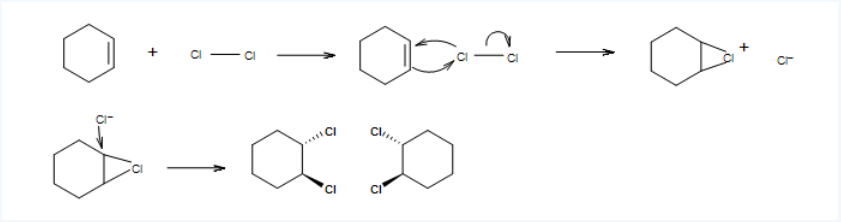
3. 

4. 

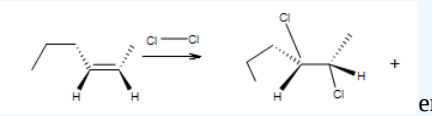
5. Predict the product of the product of 1,2-dimethylcyclopentene reacting with Br_2 with proper stereochemistry.

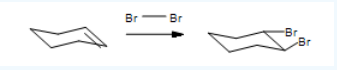
6. Predict the products for 1,2-dimethylcyclpentene reacting with HCl, give the proper stereochemistry. What is the relationship between the two products?

Answer

1. 

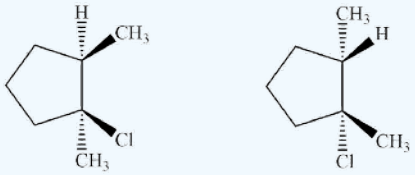
2. b

3.  enantiomer

4. 

5.

6.



These compounds are enantiomers.

References

1. Vollhard,K.Peter C., and Neil E.Schore.Organic Chemistry:Structure and Function.New Yourk: W.H.Freeman and Company 2007
2. Chemestry-A Europian Journal 9 (2003) :1036-1044

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8.10: Formation of Halohydrins

Learning Objective

- predict the products/specify the reagents for hydrohalogenation of alkenes

Introduction

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 accept the alkene pi-electrons. The resulting positively charged intermediates attract nucleophiles to give addition products.The electrophilic character of the halogens is well known. Fluorine adds uncontrollably with alkenes, and the addition of iodine is unfavorable, so these are not useful preparative methods. Chlorine (Cl_2) and bromine (Br_2) react selectively with the double bond of alkenes, so we will focus on these reactions.

The addition of chlorine and bromine to alkenes, as shown below, produces vicinal dihalo-compounds. In this reaction, we can assume that the solvent was something that is not nucleophilic, such as tetrahydrofuran (THF).

$R_2C{=}CR_2 + X_2 \longrightarrow R_2CX\text{-}CR_2X$

If this same reaction is performed in a nucleophilic solvent like water or an alcohol, then the solvent becomes the nucleophile in the second step and reacts with the bromonium (or chloronium) ion to form a halohydrin as shown below.

$$R_2C{=}CR_2 + X_2 + H_2O \longrightarrow R_2COH\text{-}CR_2X$$

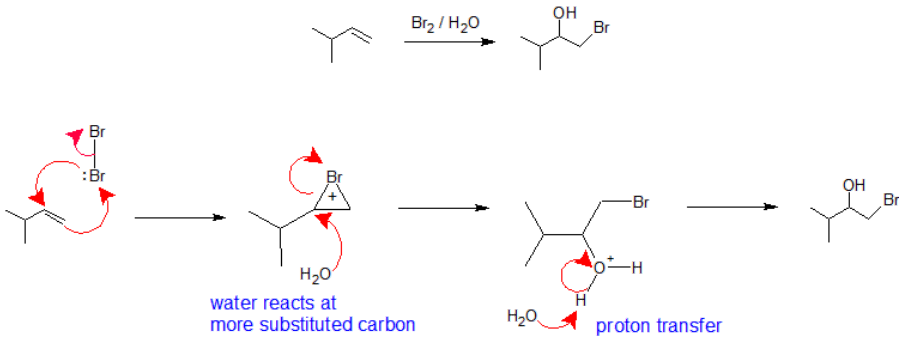
There are also other halogen-containing reagents that add to double bonds, such as hypohalous acids, HOX, and sulfenyl chlorides, RSCl. These reagents are unsymmetrical, so their addition to unsymmetrical double bonds may in principle take place in two ways. In practice, these addition reactions are regioselective, with one of the two possible constitutionally isomeric products being favored. The electrophilic moiety in both of these reagents is the halogen.

$(CH_3)_2C{=}CH_2 + HOBr \longrightarrow (CH_3)_2COH\text{-}CH_2Br$

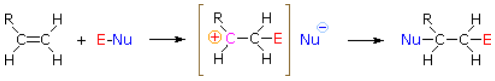
$(CH_3)_2C{=}CH_2 + C_6H_5SCl \longrightarrow (CH_3)_2CCl\text{-}CH_2SC_6H_5$

Mechanisms explain the Regioselectivity

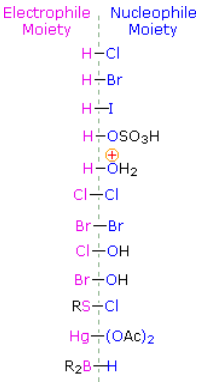
X_2/H_2O or X_2/ROH: The regioselectivity of halohydrin formation from an alkene reaction with a halogen in a nucleophilic solvent is analogous to the oxymercuration-demercuration pathway. The halogen molecule takes the role of electrophile accepting nucleophilic pi electrons from the alkene while simultaneously forming a bond with the other vinyl carbon to create a bromonium (or chloroium) ion. The bromonium (or chloronium) ion formation stabilizes the positive charge and prevents carbocation rearrangement. The solvent takes the role of the nucleophile because it is present is a much greater percentage than the leaving group and reacts with the most substituted carbon of the cyclic bromonium (or chloronium) ion to create regiochemistry. The stereochemistry of this reaction is anti-addition because the solvent approaches the bromonium ion with back side orientation to produce the addition product. However, since the interaction of the halogen with the alkene can occur from above or below, there is no stereochemical control in this reaction and a mixture of enantiomers will be produced when applicable. The final step of this mechanism is a proton transfer to a solvent water molecule to neutralize the addition product.



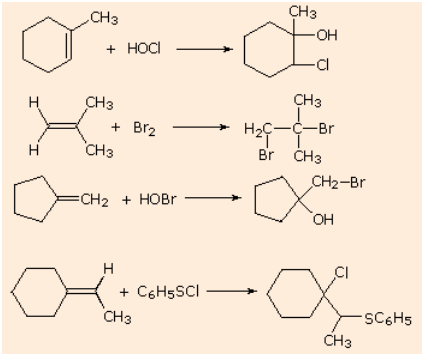
HOX or RSCl: The regioselectivity of the hypohalous acids and sulfenyl chloride reactions may be explained by the same mechanism we used to rationalize the Markovnikov rule. Bonding of an electrophilic species to the double bond of an alkene forms preferentially to produce the more stable (more highly substituted) carbocation. This intermediate should then combine rapidly with a nucleophilic species to produce the addition product.



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, a**s shown on the right**. In the case of hypochlorous and hypobromous acids (HOX), these weak Brønsted acids (pKa's ca. 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).

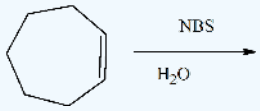


Below are some examples illustrating the addition of various electrophilic halogen reagents to alkene groups. Notice the specific regiochemistry of the products, as explained above.



Exercise

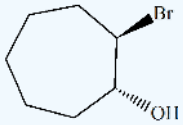
1. Predict the product of the following reaction:



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

1.



2. Since the bromine is the first addition to the alkene, this addition would be an anti-Markovnikov addition.

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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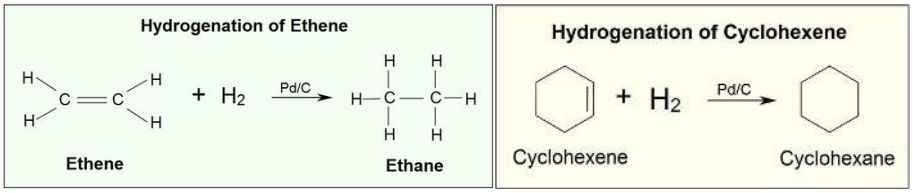
8.11: Reduction of Alkenes - Catalytic Hydrogenation

Learning Objective

- recognize organic oxidation and reduction reactions
- predict the products/specify the reagents for hydrogenation (reduction) of alkenes

Introduction

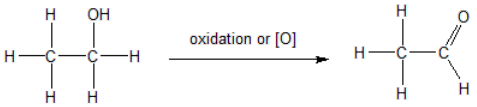
Addition of hydrogen to a carbon-carbon double bond to form an alkane is a reduction reaction that is also called catalytic hydrogenation. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the 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. Regioselectivity is not an issue because the same group (a hydrogen atom) is bonded to each of the vinyl 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 reactions below.



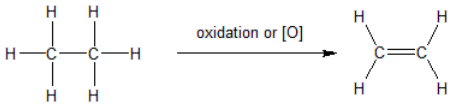
The O-chem View of Oxidation and Reduction

For inorganic chemistry, the flow of electrons is easily counted with the change in oxidation numbers of the metals and non-metals. The expressions "LEO says GER" for "Loss of Electrons is Oxidation and Gain of Electrons is Reduction" or "OIL RIG" for "Oxidation Is Loss and Reduction Is Gain" can be useful guides to recognizing oxidation and reduction reactions for inorganic chemistry. However for organic chemistry, most of the reactants and products are neutral so the electron flow is more difficult to track. For organic compounds, oxidation and reduction reactions can be recognized at least three different ways.

1) Oxidation is an increase in the number of carbon to oxygen bonds or a decrease in the number of carbon to hydrogen bonds.

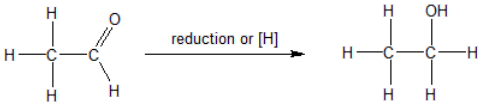


Oxidation can be recognized by the gain of carbon to oxygen bonds.

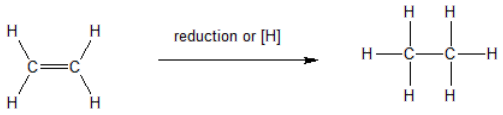


Oxidation can be recognized by the loss of carbon to hydrogen bonds.

2) Reduction is the opposite of oxidation so it is a decrease in the number of carbon to oxygen bonds or an increase in the number of carbon to hydrogen bonds.

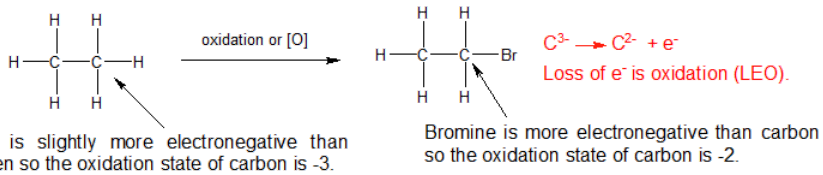


Reduction can be recognized by the loss of carbon to oxygen bonds.



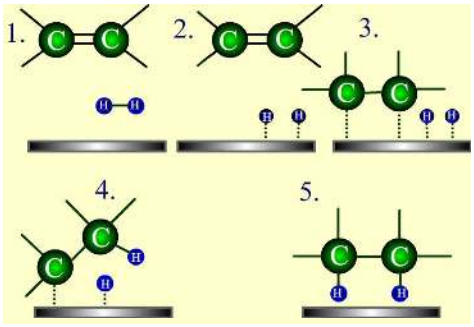
Reduction can be recognized by the gain of carbon to hydrogen bonds.

3) For reactions that do not involve a change in the bonding of carbon with oxygen and hydrogen, then we need to look at the differences in electronegativity. The shared electrons are assigned to the more electronegative element to determine the oxidation numbers.



The Catalyst

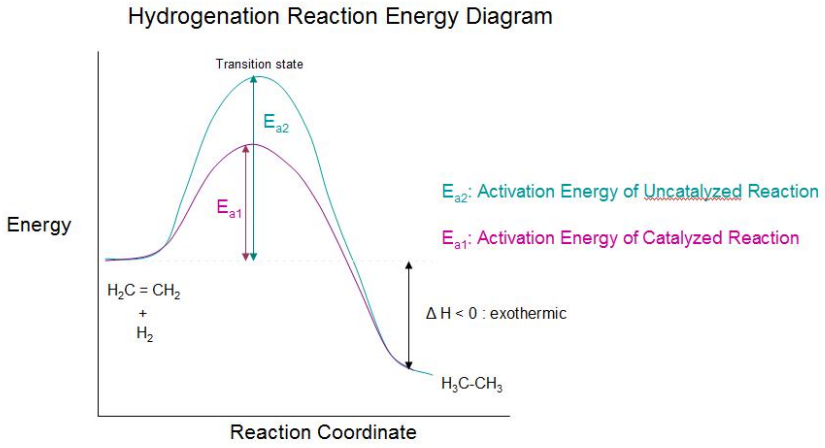
The reaction between hydrogen (H_2) gas and an alkene (a carbon-carbon double bond) requires an active metal catalyst. A catalyst increases the reaction rate by lowering the activation energy of the reaction. Although the catalyst is not consumed in the reaction, it is required to accelerate the reaction 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 as shown in step #3 of the diagram 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 as shown in steps #4 and #5 above. 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.

Alkene Stability and Catalytic Hydrogenation

As shown in the reaction energy diagram below, the hydrogenation of alkenes is exothermic, and heat is released corresponding to the ΔE (colored green).



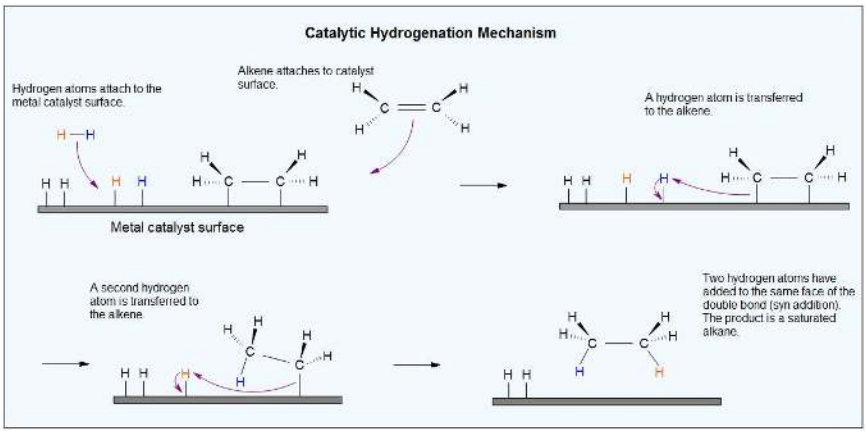
A catalyst lowers the activation energy needed for the reacting molecules to reach the transition state. The addition of a catalyst enables the hydrogenation reaction to occur, that otherwise, would not.

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 large heat of reaction indicates a high 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.

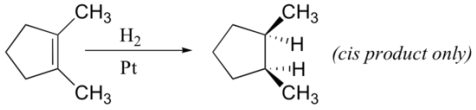
Alkene Isomer	$(CH_3)_2CHCH{=}CH_2$ 3-methyl-1-butene	$CH_2{=}C(CH_3)CH_2CH_3$ 2-methyl-1-butene	$(CH_3)_2C{=}CHCH_3$ 2-methyl-2-butene
Heat of Reaction (ΔH^o)	–30.3 kcal/mole	–28.5 kcal/mole	–26.9 kcal/mole

Stereochemistry of Catalytic Hydrogenation

From the mechanism shown below, we expect the addition of hydrogen to occur with syn-stereoselectivity since both reactants approach the same side of the catalyst's surface.



For example, 1,2-dimethylcyclopentene is reduced to 1,2-dimethylcyclopentane during catalytic hydrogenation.



(cis product only)

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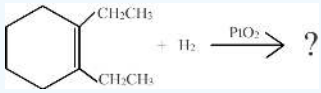
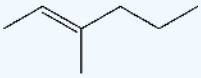
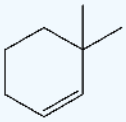
Exercises

1. Use the catalytic hydrogenation of ethene with platinum oxide to answer the following questions.
   a. 0.500 mol of ethene reacts with _____ mol of hydrogen.
   b. Ethene is being _____; while _____ is being oxidized.
   c. The oxidation number of carbon in ethene is _____; in ethane it is _____.
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?
3. Bromobutene reacts with hydrogen gas in the presence of a platinum catalyst. What is the name of the product?
4. Cyclohexene reacts with hydrogen gas in the presence of a palladium catalyst. What is the name of the product?
5. What is the stereochemistry of an alkene hydrogenation reaction?
6. When looking at their heats of hydrogenation, is the cis or the trans isomer generally more stable?
7. 2-chloro-4-ethyl-3methylcyclohexene reacts with hydrogen gas in the presence of a platinum catalyst. What is the name of the product?
8. 

9. Predict the products if the following alkenes were reacted with catalytic hydrogen.





Answer

1. a. 0.500 mole of hydrogen gas

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.

2. Amount of hydrogen consumed
$$\begin{aligned} &= n \text{ mol} \\ &= \frac{PV}{RT} \\ &= \frac{99.8 \text{ kPa} \times 0.162 \text{ L}}{8.31 \text{ kPa} \cdot \text{mol}^{-1} \cdot \text{K}^{-1} \times 298 \text{ K}} \\ &= 6.53 \times 10^{-3} \text{ mol } H_2 \end{aligned}$$

Amount of fat used
$$\begin{aligned} &= \frac{(1.000 \text{ g}) \times (1 \text{ mol})}{(914 \text{ g})} \\ &= 1.09 \times 10^{-3} \text{ mol fat} \end{aligned}$$

Ratio of moles of hydrogen consumed to moles of fat
$$\begin{aligned} &= 6.53 \times 10^{-3} : 1.09 \times 10^{-3} \\ &= 6 : 1 \end{aligned}$$

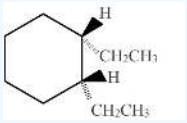
Thus, the fat contains six carbon-carbon double bonds per molecule.

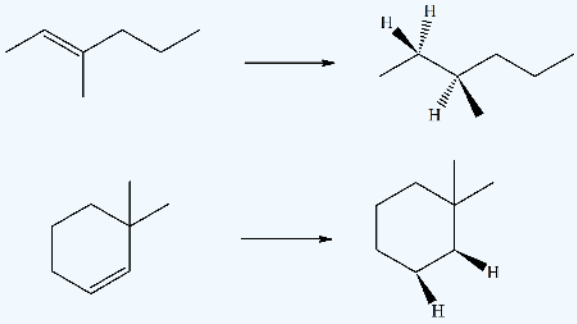
3. Bromobutane

4. Cyclohexane

5. Syn-addition

6. Trans

7. 2-chloro-4-ethyl-3methylcyclohexane
8. 

9. 

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8.12: Oxidation of Alkenes - Epoxidation

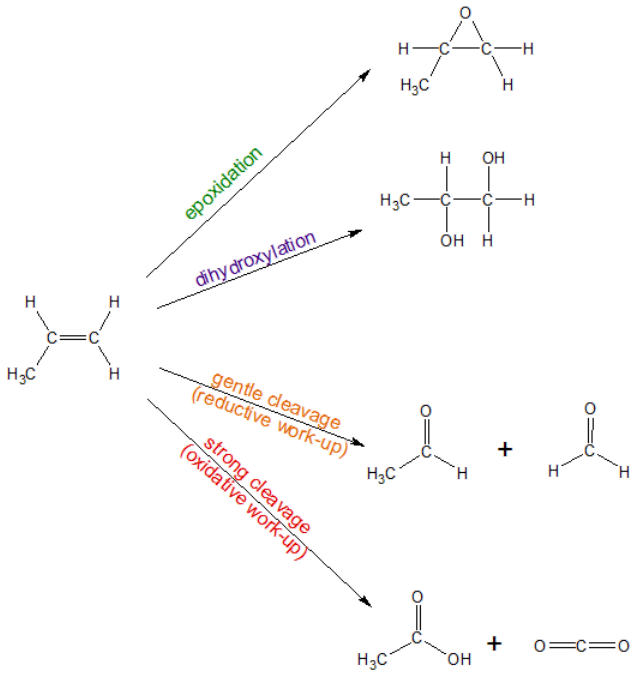
Learning Objective

- recognize organic oxidation and reduction reactions
- predict the products/specify the reagents for epoxidation of alkenes

Oxidation - a closer look

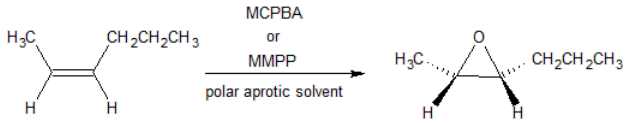
There are a variety of oxidative reagents that can react with alkenes. These reagents oxidize the alkene to different degrees and have different synthetic applications. It can be helpful to describe the relative oxidative strength of the reagents. Some reagents are so strong that the carbon chain will be cleaved at the alkene. This reactivity can also be a useful distinction. Before we explore the specific details of these different reaction pathways, let's look at the overall patterns of functional group reactivity.

The are four levels of oxidation for alkenes. The gentlest and least oxidative is epoxide (oxacyclopropane) formation in which the vinyl carbons share a single oxygen atom as a three membered ring. Moderate oxidation will convert the alkene into a vicinal diol in which each vinyl carbon is bonded to an independent oxygen atom. The stronger oxidative reactions cleave the carbon chain at the alkene. While the overall chemical process is an oxidation reaction, the work-up (second step) of the reaction can be performed under reductive or gentle conditions or a strong, oxidative cleavage reaction can occur with the strongest reagents. These four reaction pathways are summarized below.



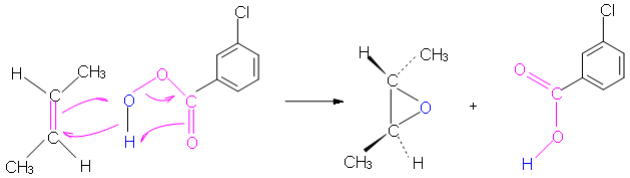
Epoxide (Oxacyclopropane) Synthesis by Peroxycarboxylic Acid

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 a peroxycarboxylic acid, such as MCPBA (m-chloroperoxybenzoic 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.



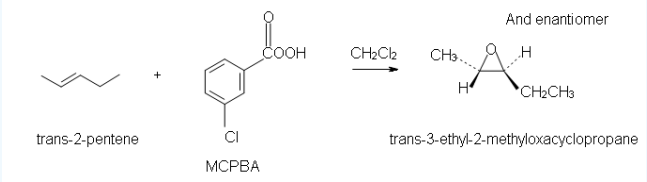
Mechanism

The mechanism is a concerted reaction between the alkene and peroxyacid. As seen with other concerted reactions, it is stereospecific: a cis-alkene will produce a cis-epoxide and a trans alkene will produce a trans-epoxide.



Peroxycarboxylic acids are generally unstable. An exception is MCPBA, 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.

Example 8.12.1

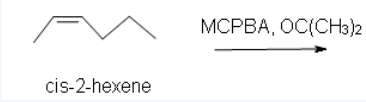


Since the transfer of oxygen is to the same side of the double bond, the resulting oxacyclopropane ring will have the same stereochemistry as the starting alkene. A good way to think of this is that the alkene is rotated so that some constituents are coming forward and some are behind. Then, the oxygen 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.

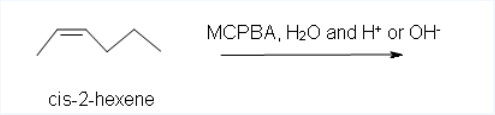
Exercise 8.12.1

1. Predict the product of the reaction of cis-2-hexene with MCPBA (meta-chloroperoxybenzoic acid)

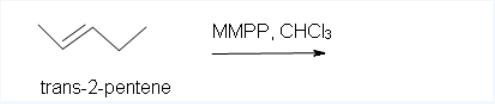
    a) in acetone solvent.



    b) in an aqueous medium with acid or base catalyst present.



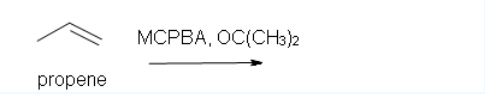
2. Predict the product of the reaction of trans-2-pentene with magnesium monoperoxyphthalate (MMPP) in a chloroform solvent.



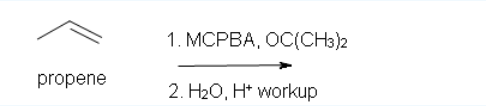
3. Predict the product of the reaction of trans-3-hexene with MCPBA in ether solvent.

4. Predict the reaction of propene with MCPBA.

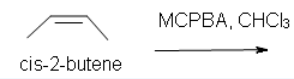
a) in acetone solvent



b) after aqueous work-up.

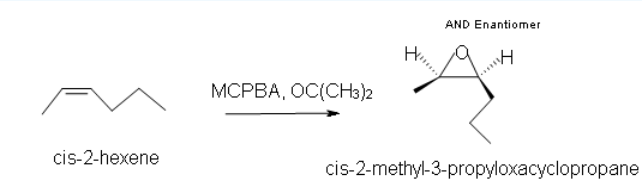


5. Predict the reaction of cis-2-butene in chloroform solvent.

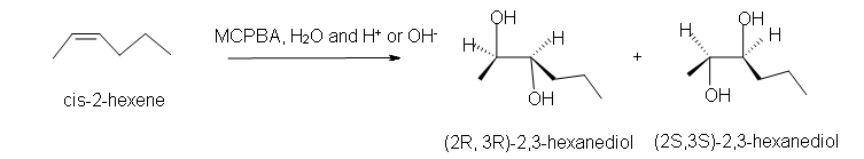


Answer

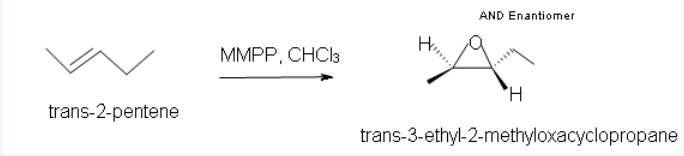
1. a) Cis-2-methyl-3-propyloxacyclopropane



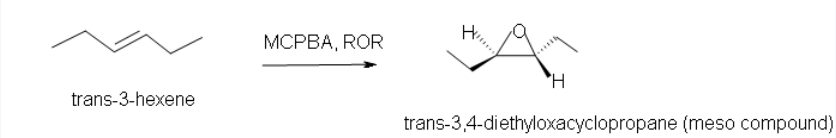
b) Racemic (2R,3R)-2,3-hexanediol and (2S,3S)-2,3-hexanediol



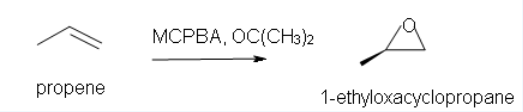
2. Trans-3-ethyl-2-methyloxacyclopropane.



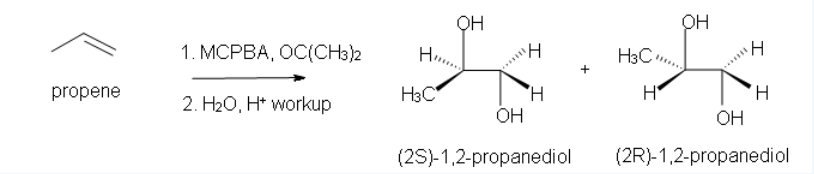
3. Trans-3,4-diethyloxacyclopropane.



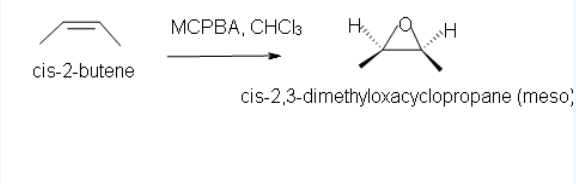
4. a) 1-ethyl-oxacyclopropane



b) Racemic (2S)-1,2-propandiol and (2R)-1,2-propanediol



5. Cis-2,3-dimethyloxacyclopropane



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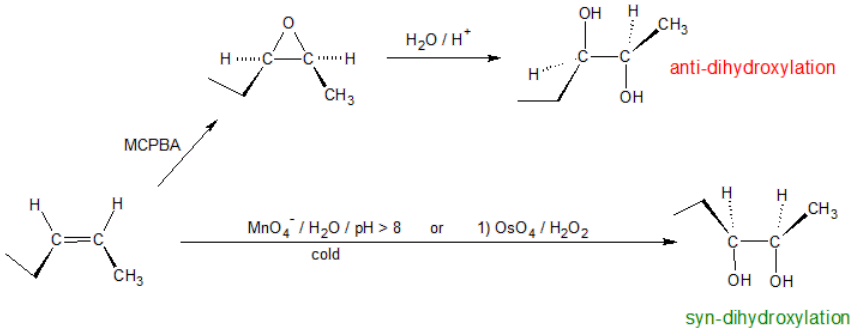
8.13: Dihydroxylation of Alkenes

Learning Objective

- predict the products/specify the reagents for dihydroxylation of alkenes

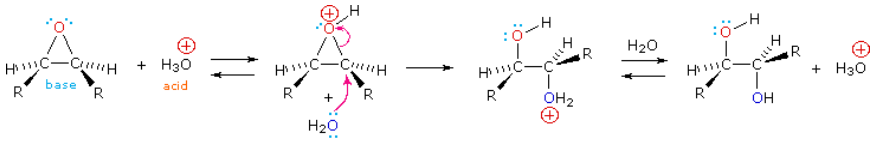
Dihydroxylation of alkenes

Alkenes can be dihydroxylated by two different stereochemical pathways: anti-dihydroxylation or syn-dihydroxylation. The opening of epoxides follows the anti-dihydroxylation mechanism, while potassium permanganate or osmium tetroxide produce the syn-dihydroxylated products. The osmium tertroxide reaction can also take place by a two-step process: 1) OsO_4 in pyridine followed by 2) H_2S or $NaHSO_3$. It is important to note that different professors will emphasize different reagent systems to accomplish the same chemical reaction. In these situations, it can be helpful to recognize the role of each reagent to discern patterns.



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. The mechanism for the ring opening of epoxides depends on the reaction conditions and is discussed in more detail in the next section of this chapter.

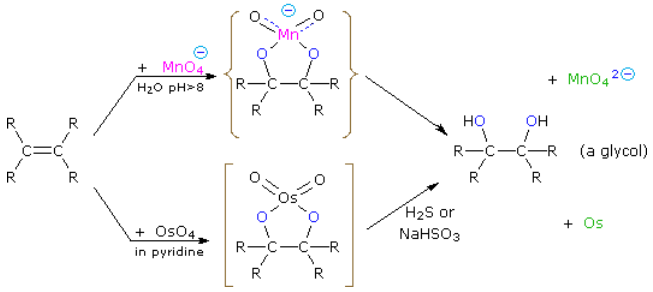


Syn Dihydroxylation

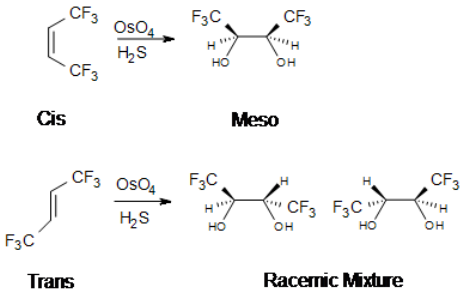
Osmium tetroxide oxidizes alkenes to give glycols through syn addition. A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.

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.



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:

$$Os_{(s)} + 2O_{2\ (g)} \rightarrow OS_4 \tag{8.13.1}$$

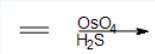
Since Osmium tetroxide is expensive and highly toxic, the reaction with alkenes has been modified. Catalytic amounts of OsO_4 and stoichiometric amounts of an oxidizing agent such as hydrogen peroxide are now used to eliminate some hazards. Also, an older reagent that was used instead of OsO_4 was potassium 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*.

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.

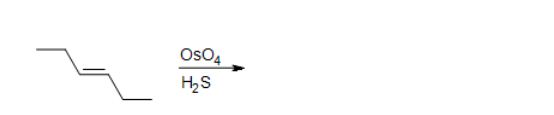
Exercise

1. Give the major product.

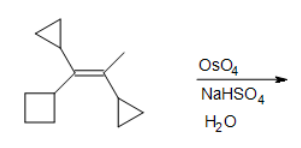


2. What is the product in the dihydroxylation of (Z)-3-hexene?

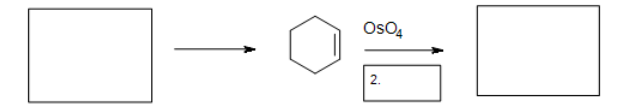
3. What is the product in the dihydroxylation of (E)-3-hexene?



4. Draw the intermediate of this reaction.

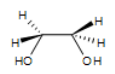


5. Fill in the missing reactants, reagents, and product.

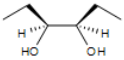


Answer

1. A syn-1,2-ethanediol is formed. There is no stereocenter in this particular reaction. The OH groups are on the same side.

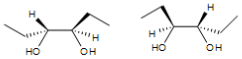


2. Meso-3,4-hexanediol is formed. There are 2 stereocenters in this reaction.



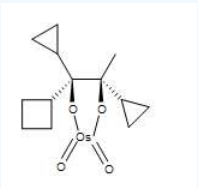
(3S, 4R)

3. A racemic mixture of 3,4-hexanediol is formed. There are 2 stereocenters in both products.

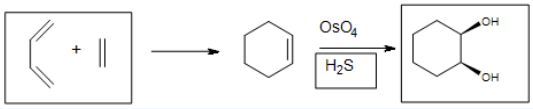


(3R, 4R) (3S, 4S)

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.

Contributors and Attributions

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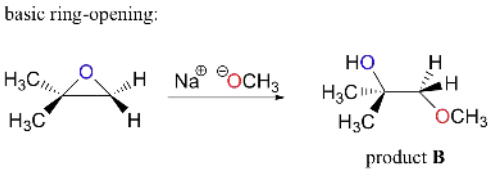
8.14: Opening of Epoxides - Acidic versus Basic Conditions

Learning Objective

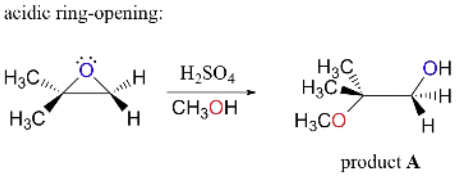
- predict the products/specify the reagents for dihydroxylation of alkenes

Epoxide ring-opening reactions - S_N1 vs. S_N2, regioselectivity, and stereoselectivity

The nonenzymatic ring-opening reactions of epoxides provides an oppourtunity to review the nucelophilic substitution mechansims. 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 solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon reacts with the nucleophile under steric considerations and produces product B in the example below.

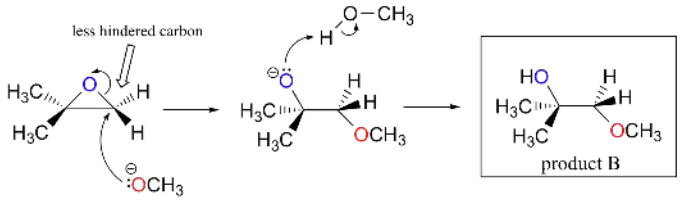


Conversely, when solvolysis occurs in acidic methanol, the reaction occurs by a mechanism with substantial S_N1 character, and the *more* substituted carbon reacts with the nucleophile under electrostatic considerations and produces product A in the example below.



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).

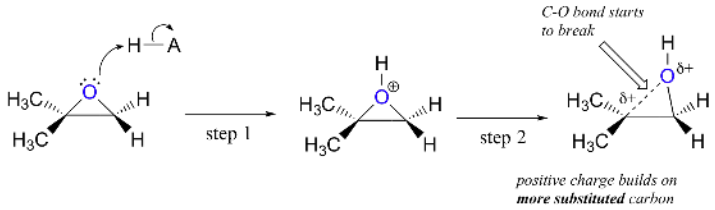
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



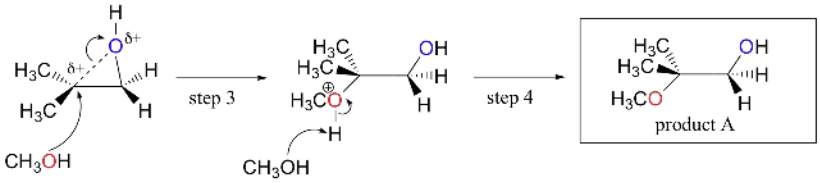
The nucleophile itself is potent: a deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? 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 reactions take place with backside orientation relative to the leaving group, resulting in inversion at the electrophilic carbon.

Probably 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) . Electrostatic considerations have greater importance with a protonated intermediate. As the carbon-oxygen bond begins to break (step 2), positive charge builds on the more substituted carbon with greater carbocation stability.



Unlike in an S_N1 reaction, the nucleophile reacts with the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

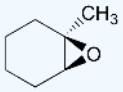


Reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, the regiochemical outcome is different from the base-catalyzed reaction. In the acid-catalyzed process, the nucleophile reacts with the more substituted carbon because it is this carbon that holds a greater degree of positive charge and electrostatics (carbocation stability) take a dominant role in determining the mechanism.

Example 8.14.1

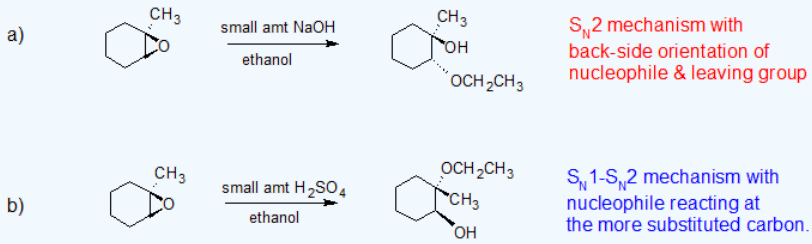
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

1. ethanol and a small amount of sodium hydroxide
2. ethanol and a small amount of sulfuric acid



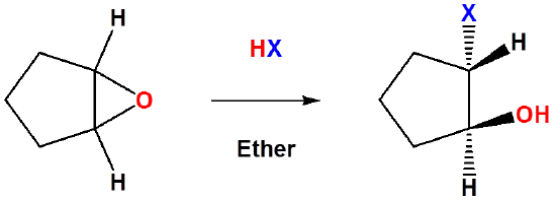
Hint: be sure to consider both regiochemistry ***and*** *stereochemistry!*

Solution



Addition of HX

Epoxides can also be opened by other 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 and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily attack the tertialy cabon in a S_N1 like reaction.



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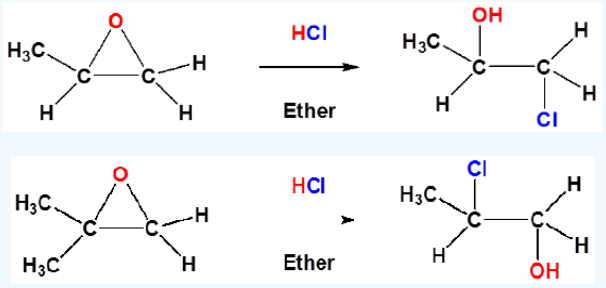
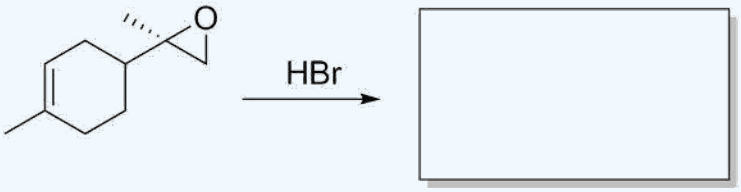
Example 8.14.1

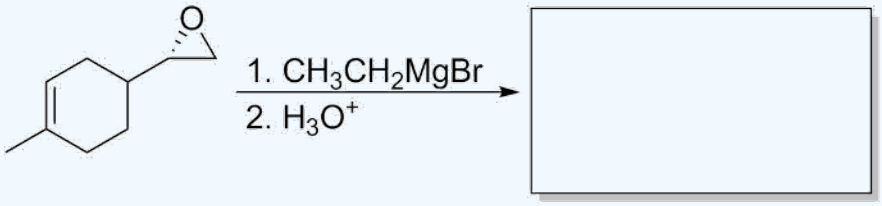


Exercise

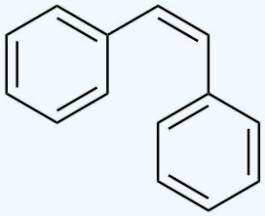
1. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



2. Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

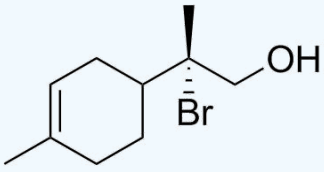


3. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



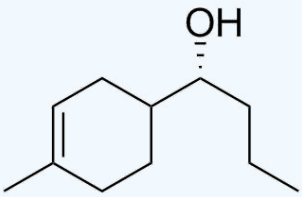
Answer

1.



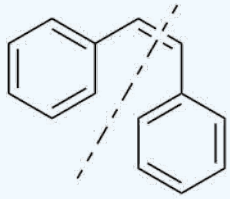
Note that the stereochemistry has been inverted

2,

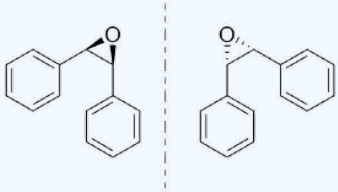


3.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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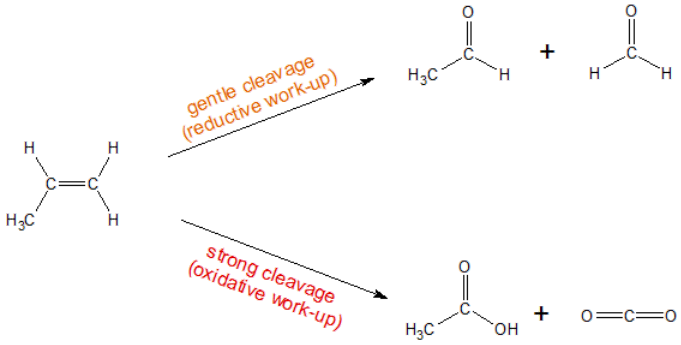
8.15: Oxidative Cleavage of Alkenes

Learning Objective

- predict the products/specify the reagents for oxidative cleavage of alkenes

Overview

Oxidative cleavage can occur by several different reaction pathways. The cleavage can be strong or gentle depending on the reaction conditions and/or the work-up of the initial reaction product. Both alkenes and alkynes can undergo cleavage reactions. This section will focus on alkenes.



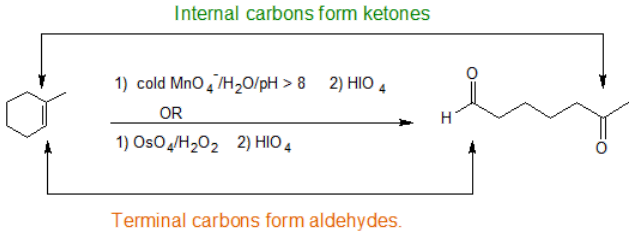
Gentle cleavage of alkenes occurs by two primary reaction pathways: ozolysis with a reductive work-up or syn-dihydroxylation followed by oxidation with perioidc acid. Gentle cleavage will leave terminal carbons partially oxidized to aldehydes. Strong cleavage of alkenes will fully oxidize terminal carbons to carboxylic acids. Internal carbons become ketones by either reaction pathway.

Why so many reactions?

At first glance, it may seem silly to have more than more reaction pathway for the same functional group conversion. As this course proceeds, it will become necessary to target reactions to a single functional group of an organic compound with multiple functional groups. A particular reaction pathway can be advantageous when the reactivity of the entire molecule is considered, not just a single functional group.

Gentle Cleavage: Syn-Dihydroxylation followed by Periodic Acid

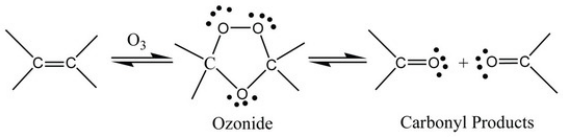
Alkenes can also be gently cleavage in a two-step reaction sequence in which the alkene first undergoes syn-dihydroxylation using cold, slightly basic $KMnO_4$ or OsO_4/H_2O_2 followed by oxidation with periodic acid (HIO_4). Both reaction sequences are shown below using 1-methylcyclohexene as an example.



Gentle Cleavage: Ozonolysis with a Reduction Work-up

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

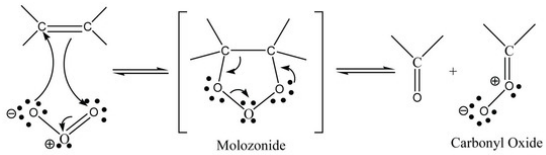
naturally and would break down repeated units used in rubber and other polymers. On an industrial scale, azelaic acid and pelargonic acids are produced from ozonolysis.



Ozonolysis Reaction Mechanism

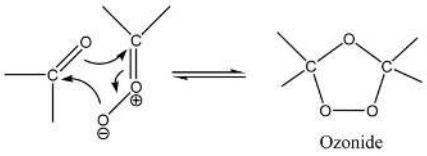
The gaseous ozone is first passed through the desired alkene solution in either methanol or dichloromethane. The first intermediate product is an ozonide molecule which is then further reduced to carbonyl products. This results in the breaking of the carbon-carbon double bond and is replaced by a carbon-oxygen double bond instead.

Step 1:



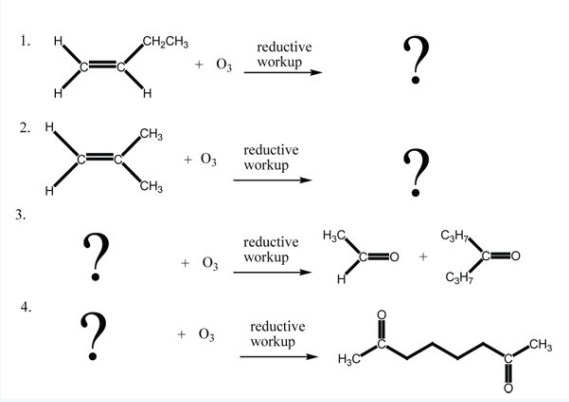
The first step in the mechanism of ozonolysis is the initial electrophilic addition of ozone to the carbon-carbon double bond to form the molozonide intermediate. Due to low stablility of molozonide, it continues reacting and breaks apart to form a carbonyl and a carbonyl oxide molecule.

Step 2:

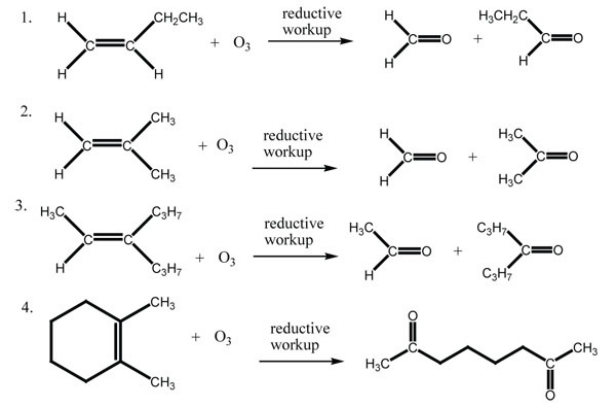


The electrons of the carbonyl and the carbonyl oxide form the stable ozonide intermediate which can then undergo an oxidative or reductive work-up to form the products of interest. A reductive workup converts the ozonide molecule into the desired carbonyl products with aldehyde on terminal carbons. An oxidative workup converts the ozonide molecule into the desired carbonyl products with carboxylic acids on terminal carbons. The two reaction workup conditions are summarized below.

Exercises

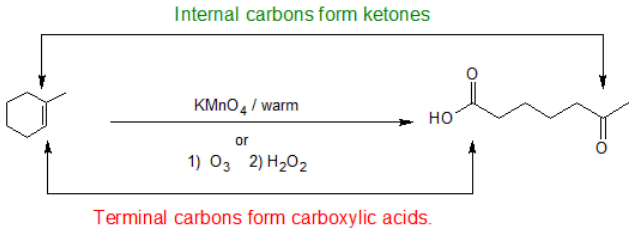


Answers



Strong Cleavage from Strong Oxidative Reactions

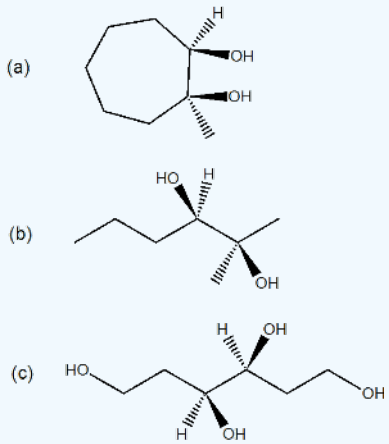
When the reaction conditions for potassium permanganate are warm, then the oxidation reaction is stronger and cleavage occurs at the alkene with any terminal carbons fully oxidizing to carboxylic acids. When the ozonolysis reaction is followed by an oxidative work-up, then any terminal carbons will oxidize fully to the carboxylic acid as shown in the example below. The example for 1-methylcyclohexene is shown below.



Exercise

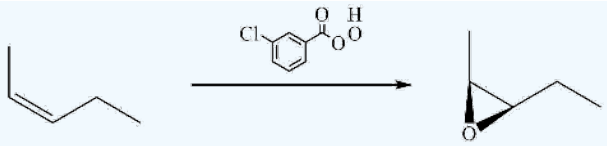
5. What would you expect the products to be from the reaction of *cis*-2-pentene with *m*-chloro-peroxybenzoic acid? Show the stereochemistry of the final product.

6. Give a reaction scheme with starting alkenes and required reagents to produce the following compounds.

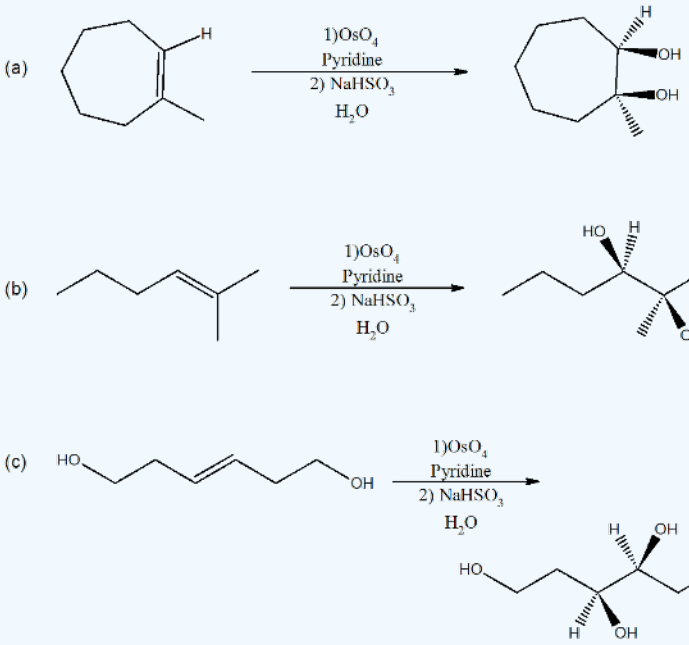


Answer

5.



6.



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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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John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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8.16: Addition of Carbenes to Alkenes - Cyclopropane Synthesis

Learning Objective

- predict the products of carbene additions to alkenes

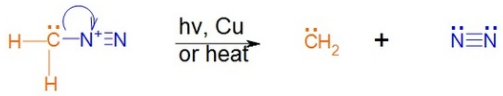
Introduction

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 (although, 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.

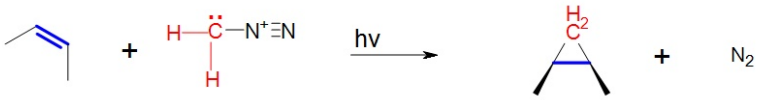
Preparation of methylene

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.

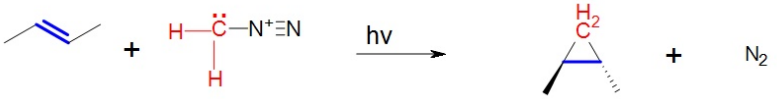


Carbene reaction with alkenes

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.



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. 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 carbenoid is formed in situ via the mixing of a Zn-Cu couple with CH_2I_2.Since this reacts thesame as a carbene, the same methods can be applied to determine the product. An example of this is given as problem 5.

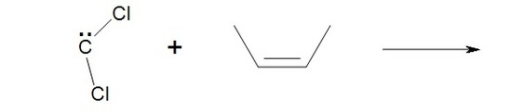
Exercise 8.16.1

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?

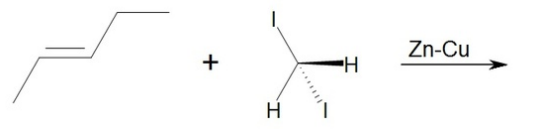
2. What would be the result of a Simmons-Smith reaction that used *trans*-3-pentene as a reagent?

3. What starting material could be used to form *cis*-1,2-diethylcyclopropane?

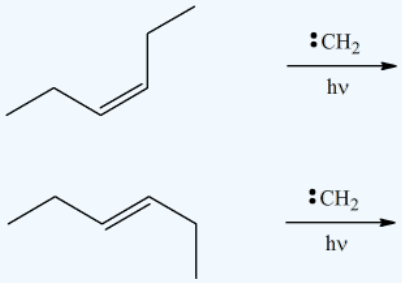
4. What would the following reaction yield?



5. Draw the product of this reaction. What type of reaction is this?

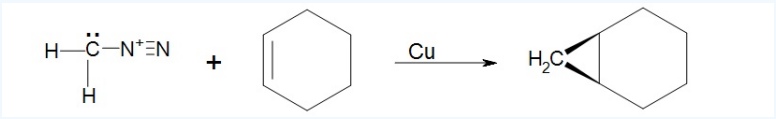


6. Predict the following products. Will they be the same product?



Answer

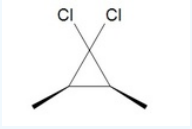
1. The product will be a bicyclic ring, Bicyclo[4.1.0]heptane.



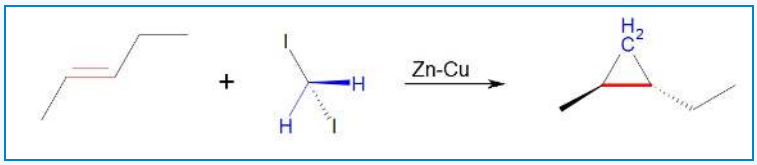
2. The stereochemistry will be retained making a cyclopropane with trans methyl and ethyl groups. *Trans*-1-ethyl-2-methylcyclopropane

3. 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.

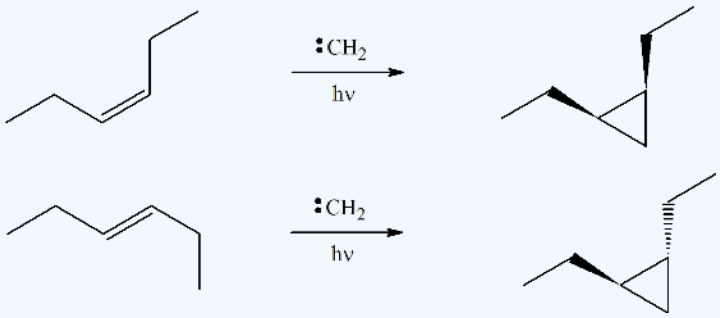
4. The halogenated carbene will react the same as methylene yielding, *cis*-1,1-dichloro-2,3dimethylcyclopropane.



5. 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.



6. No they will not be the same product, they will be isomers of each other.



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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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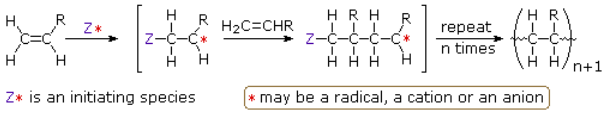
8.17: Radical Chain-Growth Polymerization

Learning Objective

- predict the polymer/specify the monomer for radical, chain -growth polymers of alkenes

Introduction

All the monomers from which addition polymers are made are alkenes or functionally substituted alkenes. 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.

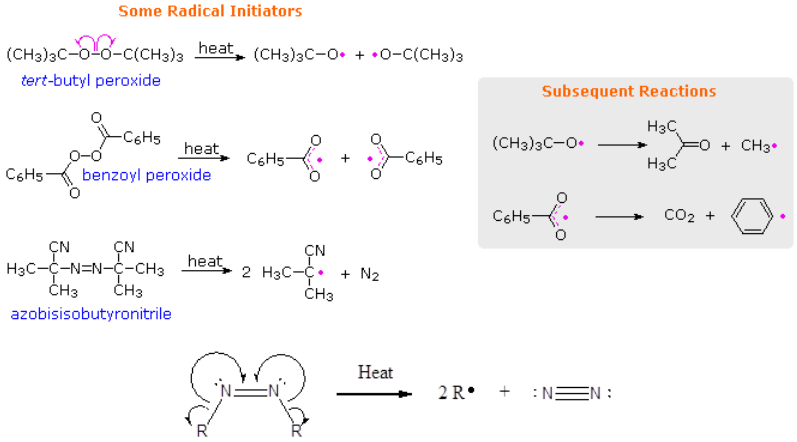


It is useful to distinguish four polymerization procedures fitting this general description.

• 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.

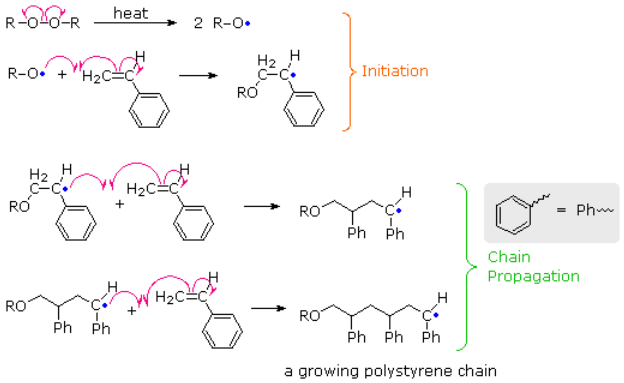
Radical Chain-Growth Polymerization

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.

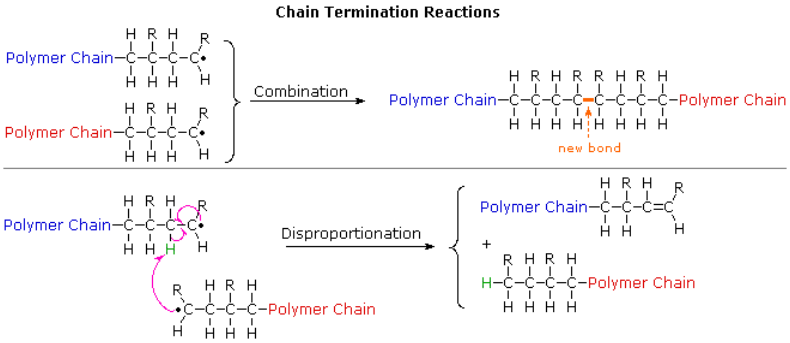


By using small amounts of initiators, a wide variety of monomers can be polymerized. One example of this radical polymerization is the conversion of styrene to polystyrene, shown in the following diagram. The first two equations illustrate the initiation process, and the last two equations are examples 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.

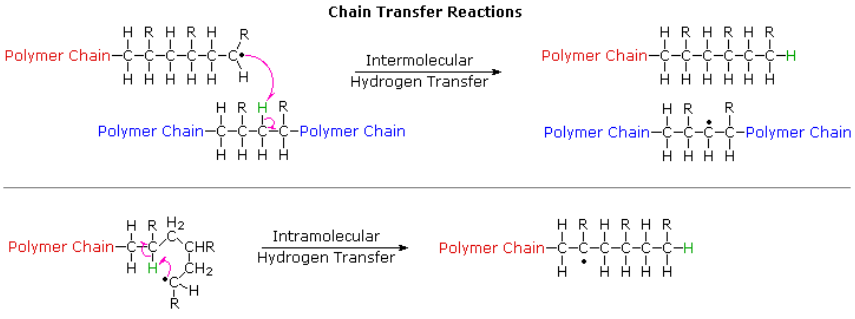


In principle, once started a radical polymerization might be expected to continue unchecked, producing a few extremely long chain polymers. In practice, larger numbers of moderately sized chains are formed, indicating that chain-terminating reactions must be taking place. The most common termination 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.



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

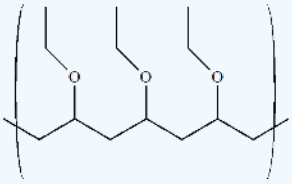


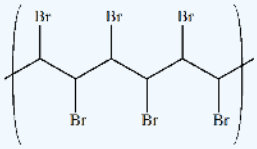
Chain transfer reactions are especially prevalent in the high pressure radical polymerization of ethylene, which is the method used to make LDPE (low density polyethylene). The 1º-radical at the end of a growing chain is converted to a more stable 2º-radical by

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.

Exercise

1. Propose the monomer units in the following polymers:





Answer

1.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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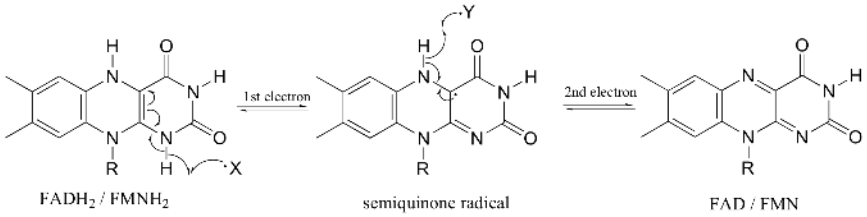
8.18: 9.18 Biological Additions of Radicals to Alkenes

Learning Objective

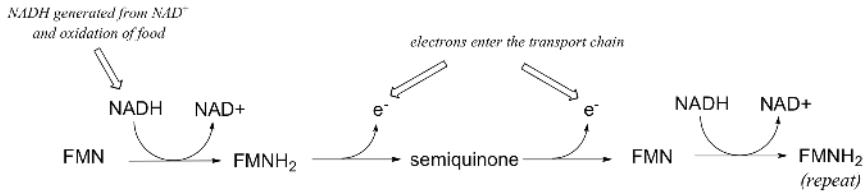
- discuss an example biological addition reactions

Radical mechanisms for flavin-dependent reactions

Flavin coenzymes, like their nicotinamide adenine dinucleotide 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.

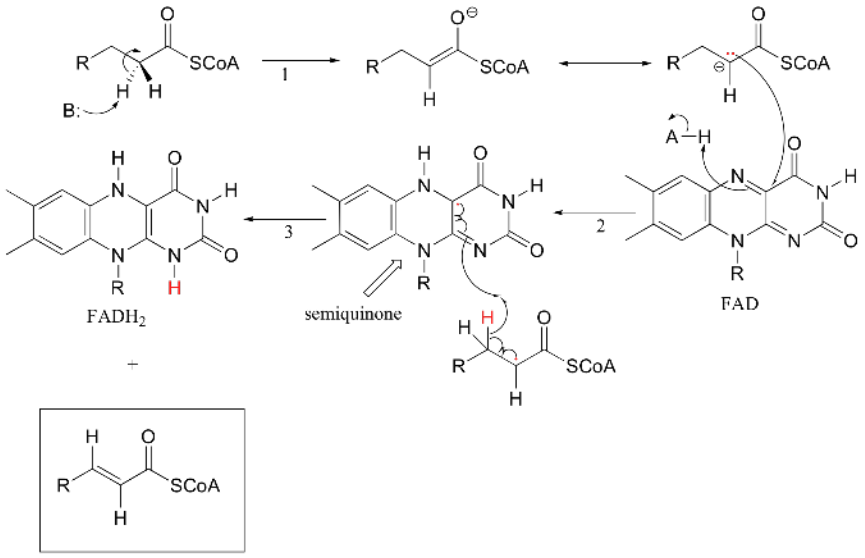


This single-electron transfer capability of flavins is critical to their metabolic role as the entry point of electrons into the electron transport phase of respiration. Electrons 'harvested' from the oxidation of fuel molecules are channeled, *one by one*, by $FMNH_2$ into the electron transport chain, 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.



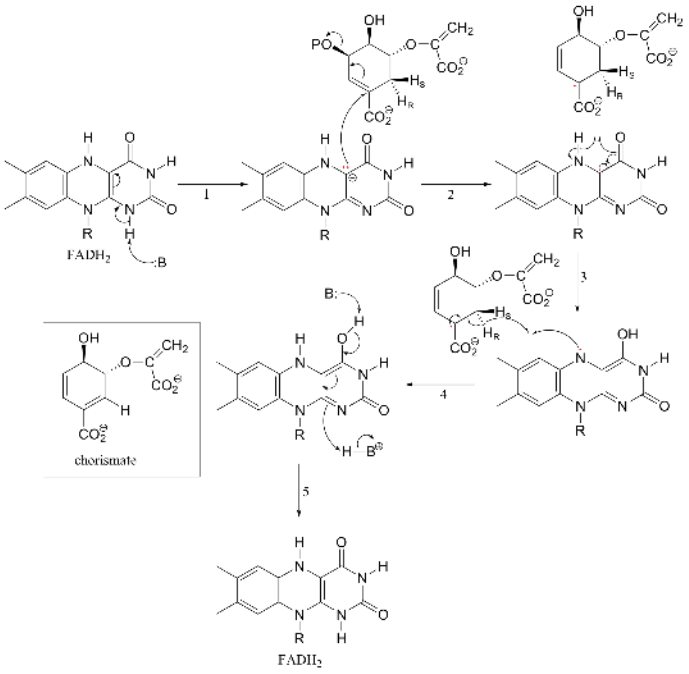
You will learn more details about this process in a biochemistry class.

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

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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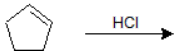
8.19: Additional Exercises

Addition of Hydrogen Halides to Alkenes

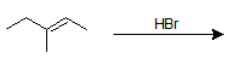
9-1 Give the IUPAC name for the product of the following reaction.



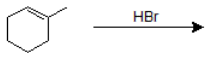
9-2 Draw the reaction mechanism of the previous problem (9-**1**)**.**

9-3 Identify the product of the following reactions.

(a)

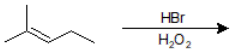


(b)



9-4 Identify the products of the following reactions.

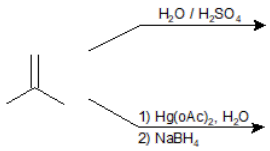
(a)



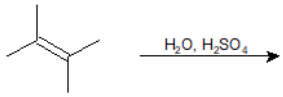
(b)

Addition of Water: Hydration of Alkenes

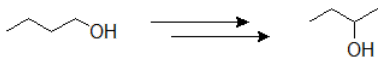
9-5 Identify the product of the following reactions.



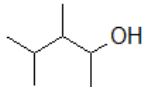
9-6 Identify the product of the following reaction.



9-7 Propose a plausible route of synthesis for the following product starting with 1-butanol.



9-8 Which of the following alkenes can be used to obtain 3,4-dimethylpentan-2-ol through a hydration reaction using dilute acid?



a) (2Z)-3,4-dimethylpent-2-ene

b) 3,4-dimethylpent-1-ene

c) 2,3,4-trimethylpent-2-ene

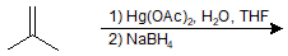
d) 2,4-dimethyl-3-methylidenepentane

Hydration by Oxymercuration-Demercuration

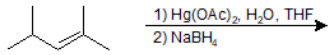
9-9 Explain why hydration of an alkene by Oxymercuration-Demercuration gives the Markovnikov product.

9-10 Identify the products of the following reactions.

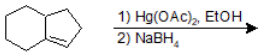
(a)



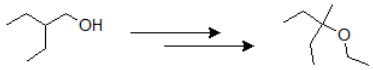
(b)



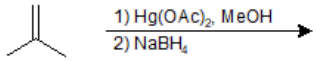
9-11 Identify the product of the following reaction.



9-12 Propose a possible route of synthesis for the following ether starting with 2-ethylbutan-1-ol.



9-13 Give the IUPAC name of the product of the following reaction.



a) 2-methylpropan-2-ol

b) 2,2-dimethylbutane

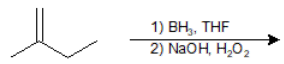
c) 2-methoxy-2-methylpropane

d) 1,1-dimethylcyclopropane

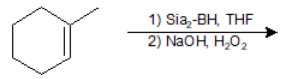
Hydroboration of Alkenes

9-14 Identify the products of the following reactions.

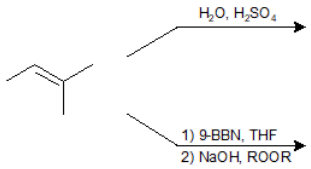
(a)



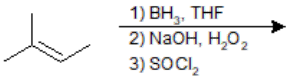
(b)



9-15 Identify the products of the following reactions.



9-16 Give the IUPAC name for the product of the following reaction.

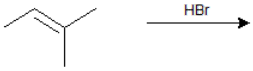


Addition of Halogens to Alkenes

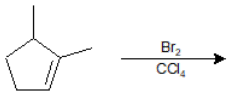
9-17 Identify the products of the following reactions.

(a)

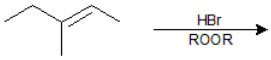
(b)



9-18 Identify the product of the following reaction.



9-19 What is the product of the following reaction?



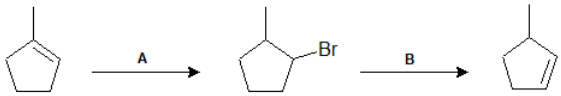
a) (2Z)-2-bromo-3-methylpent-2-ene

b) 2-bromo-3-methylpentane

c) 2,3-dibromo-3-methylpentane

d) (2E)-4-bromo-3-methylpent-2-ene

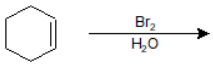
9-20 What reagents can be used in each step to obtain the following products?



9-21 Explain why you do not obtain a mixture of cis- and trans-brominated products when you react Br2/CCl4 with cyclopentene.

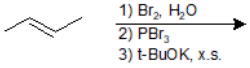
Formation of Halohydrins

9-22 Identify the product of the following reaction, making sure to include stereochemistry.

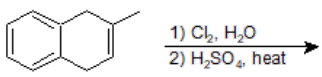


9-23 Draw the mechanism of the reaction in the previous problem (**9-22**).

9-24 Give the IUPAC name for the product of the following reaction.



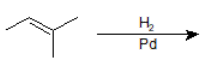
9-25 Identify the product of the following reaction.



Catalytic Hydrogenation of Alkenes

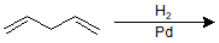
9-26 Identify the products of the following reactions.

(a)

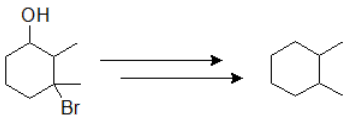


(b)

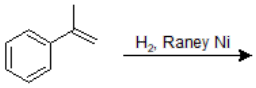
(c)



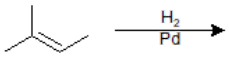
9-27 Suggest a possible route of synthesis, that includes a catalytic hydrogenation step, to obtain the following product.



9-28 Identify the product of the following reaction.

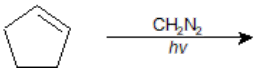


9-29 Identify the product of the following reaction, making sure to include stereochemistry.

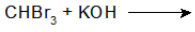


Addition of Carbenes to Alkenes

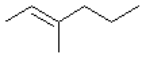
9-30 Identify the product of the following reaction.



9-31 Identify the product(s) of the following reaction.



9-32 Identify the product of the reaction when (*2E*)-3-methylhex-2-ene reacts with the carbene product from the previous problem (**9-31**), then reacts with Br_2 and *hv*.



(*2E*)-3-methylhex-2-ene

9-33 Propose a possible route of synthesis for the following reaction.

9-34 Identify the product of the following reaction.

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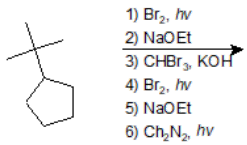
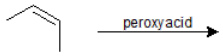


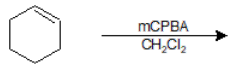
Epoxidation of Alkenes and Acid-Catalyzed Opening of Epoxides

9-35 Identify the product of the following reaction.

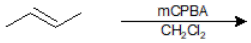


9-36 Identify the product of the following reactions, specifying stereochemistry where appropriate.

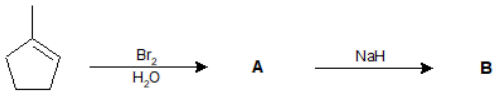
(a)



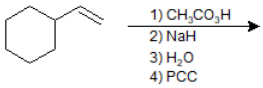
(b)



9-37 Identify the products of the following reaction, including stereochemistry.



9-38 What is the product of the following reaction?



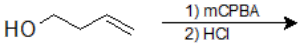
a) benzoic acid

b) 1-cyclohexylethan-1-ol

c) 1-cyclohexylethan-1-one

d) cyclohexanol

9-39 What is the product of the following reaction?



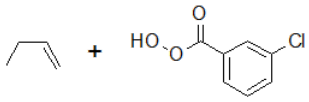
a) 4-chlorobutane-1,3-diol

b) 3-chlorobutan-1-ol

c) 2-chlorobutane-1,4-diol

d) 2,4-dichlorobutan-1-ol

9-40 Draw the arrows for the following epoxidation reaction to show the movement of electrons.



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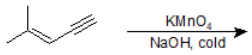
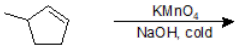
Syn Dihydroxylation of Alkenes

9-41 Identify the product of the following reaction, including stereochemistry.

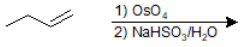
(a)



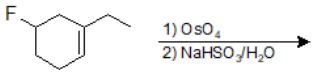
(b)



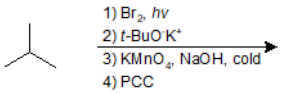
(c)



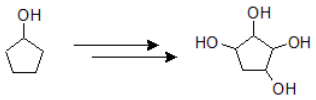
9-42 Give the IUPAC name for the product(s) of the following reaction. Include stereochemistry.



9-43 Identify the product of the following reaction.



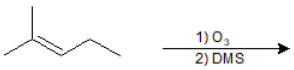
9-44 Suggest a possible route of synthesis for the following compound starting with cyclopentanol.



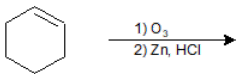
Oxidative Cleavage of Alkenes

9-45 Identify the products of the following reactions.

(a)

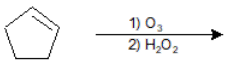


(b)

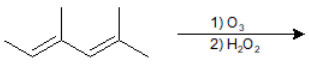


9-46 Identify the products of the following reactions.

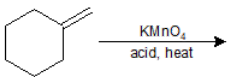
(a)



(b)



(c)



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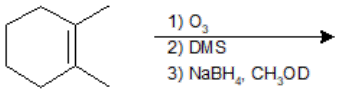
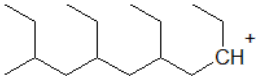
9-47 Identify the product of the following reaction.



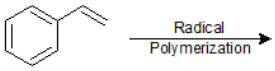
Polymerization of Alkenes

9-48 Identify the alkene monomer that composes the following polymer.



9-49 Draw the mechanism for the acid catalyzed formation of the polymer in the previous problem (**9-48**).

9-50 Draw the resulting polymer of the following reaction. Draw the chain four monomers in length.



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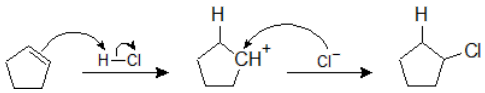
8.20: Solutions to Additional Exercises

Addition of Hydrogen Halides to Alkenes

9-1

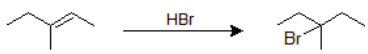
chlorocyclopentane

9-2

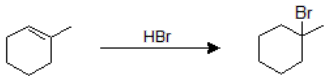


9-3

(a)

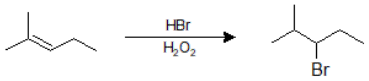


(b)



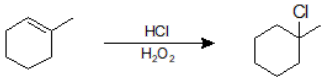
9-4

(a)



anti-Markovnikov

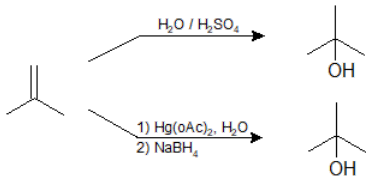
(b)



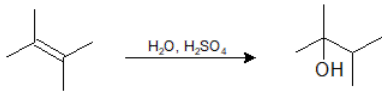
Markovnikov

Addition of Water: Hydration of Alkenes

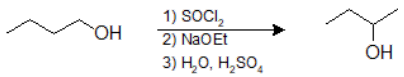
9-5



9-6



9-7



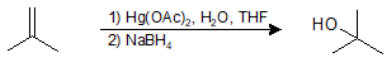
9-8 B.

Hydration by Oxymercuration-Demercuration

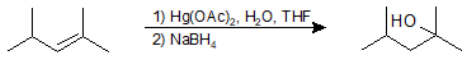
9-9 When an alkene is going through oxymercuration, it proceeds through a three-membered mercurinium ion intermediate. This does not allow for rearrangement as no carbocation is formed. In order to open the intermediate ring, the water molecule will attack the most substituted carbon, thus giving the Markovnikov regioselectivity in the final product.

9-10

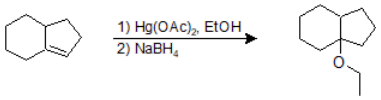
(a)



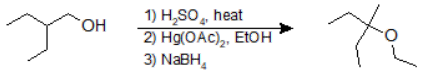
(b)



9-11



9-12

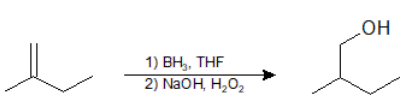


9-13 C.

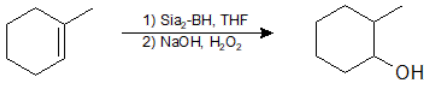
Hydroboration of Alkenes

9-14

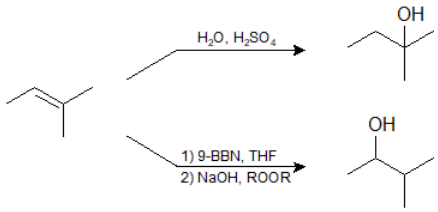
(a)



(b)



9-15

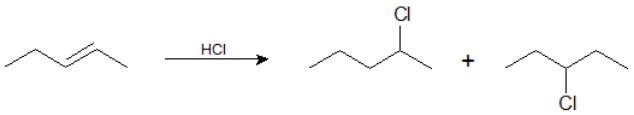


9-16 2-chloro-3-methylbutane

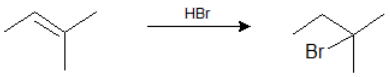
Addition of Halogens to Alkenes

9-17

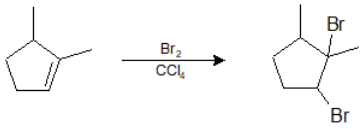
(a)



(b)



9-18



9-19 B.

9-20

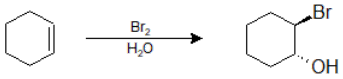
A: HBr, ROOR

B: $NaNH_2$

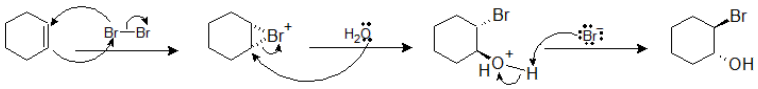
9-21 You do not obtain a mixture of cis- and trans-brominated products from this reaction (only trans products) due to the intermediate the reaction goes through. No carbocation is formed, which would allow the Br- to attack from two possible sides of the carbocation. Instead, a bromonium ion is formed and in order to add the second Br, it needs to attack one side of the bromonium ion intermediate, causing the product to always have a trans configuration.

Formation of Halohydrins

9-22

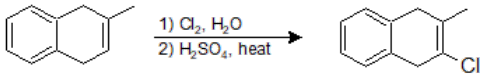


9-23



9-24 Buta-1,3-diene

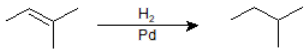
9-25



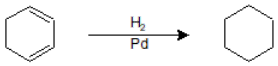
Catalytic Hydrogenation of Alkenes

9-26

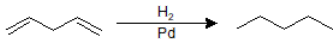
(a)



(b)



(c)



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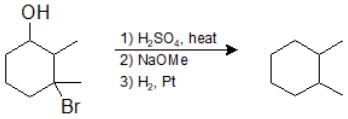

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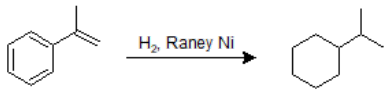

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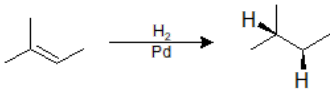

Addition of Carbenes to Alkenes

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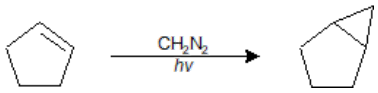

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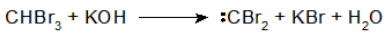

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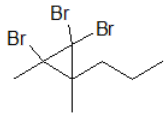
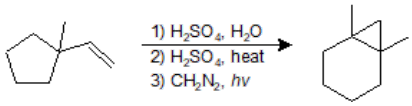


1,1,2-tribromo-2,3-dimethyl-3-propylcyclopropane

9-33



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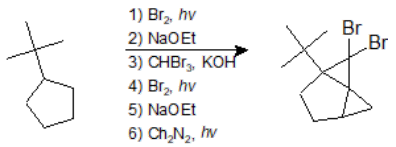

Epoxidation of Alkenes and Acid-Catalyzed Opening of Epoxides

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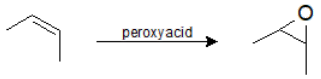

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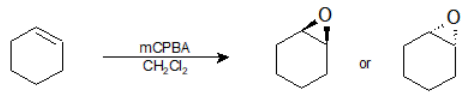

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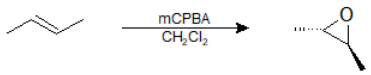

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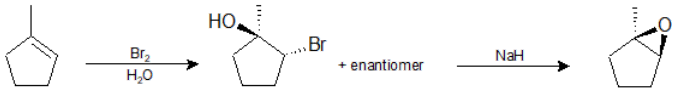

9-38 C.

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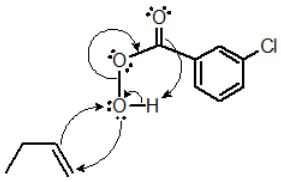

Syn Dihydroxylation of Alkenes

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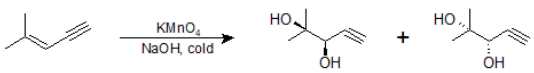

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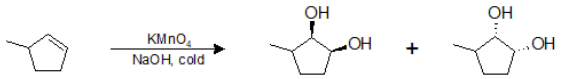

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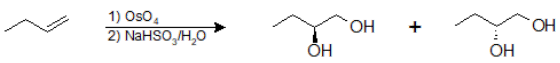

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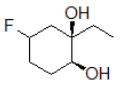
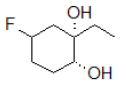
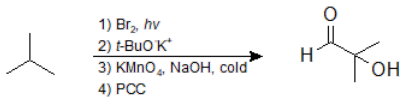


(1*R*,2*S*)-1-ethyl-5-fluorocyclohexane-1,2-diol



(1*S*,2*R*)-1-ethyl-5-fluorocyclohexane-1,2-diol

9-43



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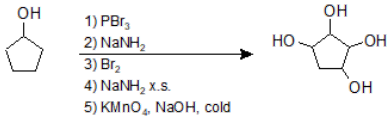

Oxidative Cleavage of Alkenes

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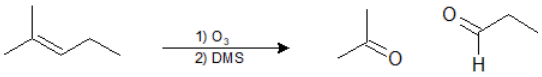
(a)



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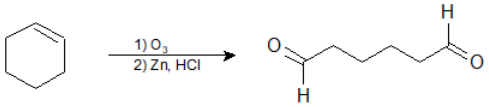

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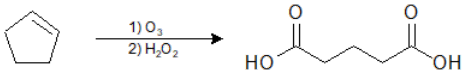

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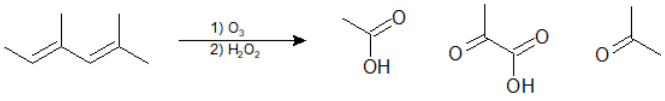

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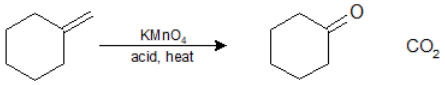

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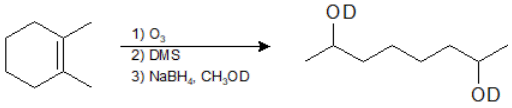

Polymerization of Alkenes

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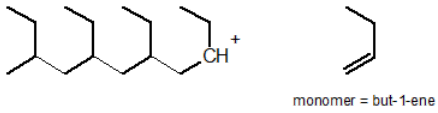
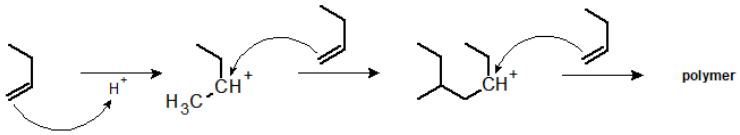


monomer = but-1-ene

9-49



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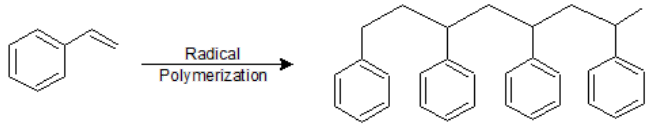

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CHAPTER OVERVIEW

9: Alkynes

learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- apply bonding theories to the structure of alkynes and distinguish between internal and terminal triple bonds - refer to section 10.1
- predict relative physical properties of alkynes, such as relative boiling points and solubilities - refer to section 10.1
- predict the products and specify the reagents for the synthesis of alkynes from the double elimination of dihaloalkanes refer to section 10.2
- predict the products and specify the reagents for the Electrophilic Addition Reactions (EARs) of alkynes with HX and X_2 - refer to section 10.3
- predict the products and specify the reagents for the Markovnikov-products of alkyne hydration - refer to section 10.4
- predict the products and specify the reagents for the anti-Markovnikov-products of alkyne hydration - refer to section 10.5
- predict the products and specify the reagents for the full or partial reduction of alkynes - refer to section 10.6
- predict the products and specify the reagents for the oxidation of alkynes - refer to section 10.7
- explain why alkynes are more acidic than alkanes and alkenes - refer to section 10.8
- predict the products and specify the reagents to generate nucleophilic acetylide ions and heavy metal acetylides - refer to section 10.8
- predict the products and specify the reagents to synthesize larger alkynes with acetylide ions - refer to section 10.9
- use retrosynthetic analysis to design a multi-step synthesis with correct regiochemistry and stereochemistry using the reactions studied to date - refer to section 10.10

Please note: IUPAC nomenclature and important common names of alkynes were explained in Chapter 3.

9.1: Structure and Physical Properties
9.2: 10.2 Synthesis of Alkynes - Elimination Reactions of Dihalides
9.3: Reactions of Alkynes - Addition of HX and X_2
9.4: Hydration of Alkynes for Markovnikov Products
9.5: Hydration of Alkynes for Anti-Markovnikov Products
9.6: 10.6 Reduction of Alkynes
9.7: Oxidation of Alkynes
9.8: Acidity of Terminal Alkynes
9.9: Synthesis of Larger Alkynes from Acetylides
9.10: An Introduction to Multiple Step Synthesis
9.11: Additional Exercises
9.12: Solutions to Additional Exercises

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9.1: Structure and Physical Properties

Learning Objective

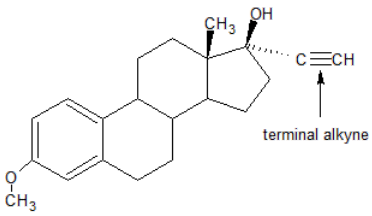
- apply bonding theories to the structure of alkynes and distinguish between internal and terminal triple bonds

Alkynes: Terminal vs Internal

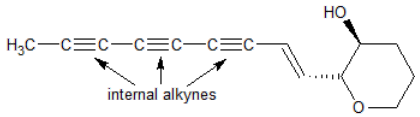
Alkynes are organic molecules with carbon-carbon triple bonds. They are unsaturated hydrocarbons with the empirical formula of C_nH_{2n-2}. The simplest alkyne is ethyne which has the common name acetylene. Acetylene is a common name to memorize.

ethyne or acetylene

It is important to distinguish between terminal and internal alkynes because they can undergo different patterns of reactivity.



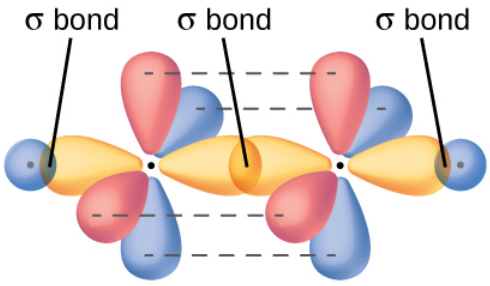
mestranol: component of oral contraceptives



ichthyothereol: used to poison arrowheads in the Amazon

Electronic Structure

The sp hybridization of the carbon-carbon triple bond results in the perpendicular orientation of the sigma bond and two pi bonds. The close proximity of the electrons in this geometry orientation creates molecules with less stability. The structure of the carbon-carbon triple bond strongly influences the chemical reactivity of alkynes and the acidity of terminal alkynes. Because of its linear configuration (the bond angle of a sp-hybridized carbon is 180º), a ten-membered carbon ring is the smallest that can accommodate this function without excessive strain.



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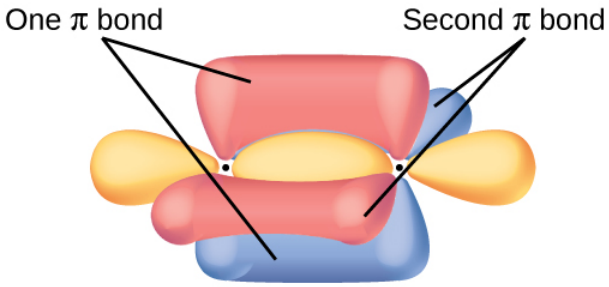

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Physical Properties

Alkynes are nonpolar, unsaturated hydrocarbons with physical properties similar to alkanes and alkenes. Alkynes dissolve in organic solvents, have slight solubility in polar solvents, and are insoluble in water. Compared to alkanes and alkenes, alkynes have slightly higher boiling points. For example, ethane has a boiling point of -88.6 C, while ethene is -103.7 C and ethyne has a higher boiling point of -84.0 ?C.

Exercise

1. Arrange ethane, ethene, and acetylene in order of decreasing carbon-carbon length.
2. How many pi bonds and sigma bonds are involved in the structure of ethyne?
3. What contribute to the weakness of the pi bonds in an alkyne?
4. Arrange the following hydrocarbons in order of decreasing boiling point: 1-heptyne, 1-hexyne, 2-methyl-1-hexyne.
5. Predict the solvent with greater 2-butyne solubility. a) water or 1-octanol? b) water or acetone? c) ethanol or hexane?

Answer

1. relative carbon-carbon bond length: ethane < ethene < acetylene
2. There are three sigma bonds and two pi bonds.
3. The sigma bond and two pi bonds are all perpendicular to each other in the triple bond creating electron repulsion between the three pairs of bonding electrons in the triple bond.
4. 1-heptyne (99.7C) > 2-methyl-1-hexyne (91C) > 1-hexyne (71C)
5. a) 1-octanol b) acetone c) hexane

Outside links

- www.ucc.ie/academic/chem/dolc...t/alkynes.html
- www.cliffsnotes.com/WileyCDA/...eId-22631.html

References

1. Bloch, D.R. Organic chemistry demystified, New York : McGraw-Hill, 2006.
2. Vollhardt. Schore, Organic Chemistry Structure and Function Fifth Edition, New York: W.H. Freeman and Company, 2007.

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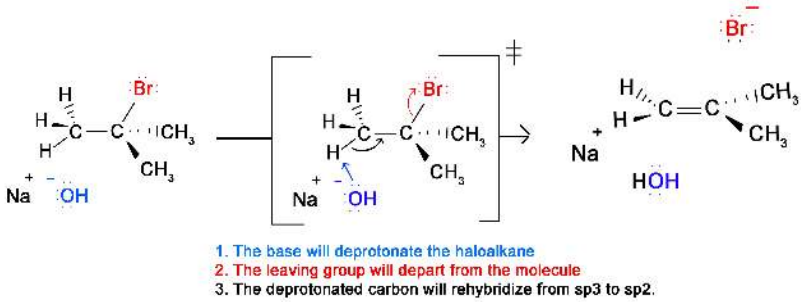
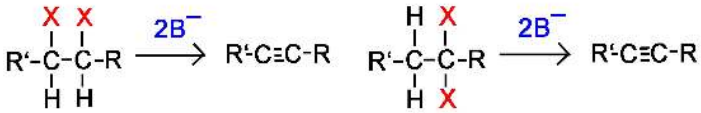
9.2: 10.2 Synthesis of Alkynes - Elimination Reactions of Dihalides

Introduction

To synthesize alkynes from dihaloalkanes we use dehydrohalogenation. The majority of these reactions take place using alkoxide bases (other strong bases can also be used) with high temperatures. This combination results in the majority of the product being from the E2 mechanism. Recall that the E2 mechanism is a concerted reaction (occurs in 1 step). However, in this 1 step there are 3 different changes in the molecule. This is the reaction between 2-bromo-2-methylpropane and sodium hydroxide.



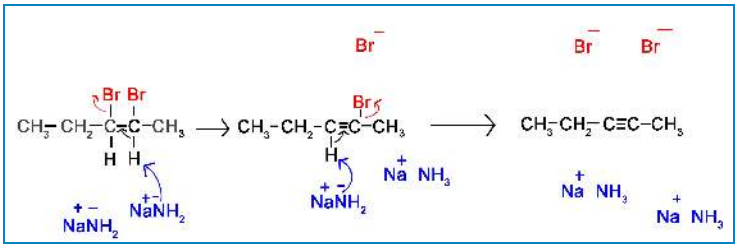
Now, if we apply this concept using 2 halides on vicinal or geminal carbons, the E2 reaction will take place twice resulting in the formation of 2 pi bonds and an alkyne as shown in the examples below where the strong base is symbolized B^-.



Double E2 of a Vicinal Dihalide Double E2 of a Geminal Dihalilde

It is important to note that the reaction of terminal haloalkanes requires 3 equivalents of base instead of 2 because of the relative acidity of alkynes that is discussed in a later section of this chapter.

The mechanism of a reaction between 2,3-dibromopentane with sodium amide in liquid ammonia is shown below where liquid ammonia is not part of the reaction, but is used as a solvent.

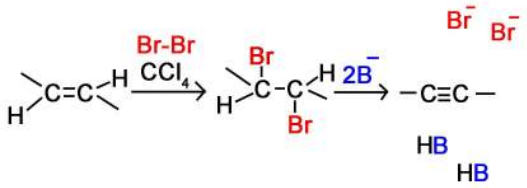


Notice the intermediate of the alkyne synthesis. It is stereospecifically in its anti form. Because the second proton and halogen are pulled off the molecule this is unimportant to the synthesis of alkynes.

Preparation of Alkynes from Alkenes

Lastly, we will briefly look at how to prepare alkynes from alkenes. This is a simple process using first halogenation of the alkene bond to form the dihaloalkane, and next, using the double elimination process form the 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 then reacted with a strong base and heated to produce an alkyne. The two-step reaction pathway is shown below.

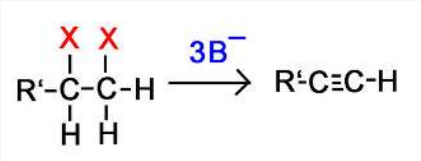


In The Lab

Due to the strong base and high temperatures needed for this reaction to take place, the triple bond may change positions. An example of this is when reactants that should form a terminal alkyne, form a 2-alkyne instead. The use of $NaNH_2$ in liquid NH_3 is used in order to prevent this from happening due to its lower reacting temperature. Even so, most chemists will prefer to use nucleophilic substitution instead of elimination when trying to form a terminal alkyne.

Exercise 9.2.1

Question 1: Why would we need 3 bases for every terminal dihaloalkane instead of 2 in order to form an alkyne?

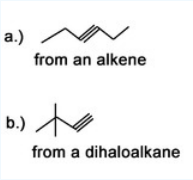


Question 2: What are the major products of the following reactions:

a.) 1,2-Dibromopentane with sodium amide in liquid ammonia

b.) 1-Pentene first with Br_2 and chloromethane, followed by sodium ethoxide ($Na^+ {}^-O\text{-}CH_2CH_3$)

Question 3: What would be good starting molecules for the synthesis of the following molecules:



Question 4: Use a 6 carbon diene to synthesize a 6 carbon molecule with 2 terminal alkynes.

Answer

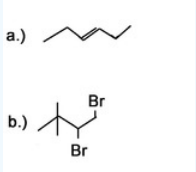
Answer 1: Remember that hydrogen atoms on terminal alkynes make the alkyne acidic. One of the base molecules will pull off the terminal hydrogen instead of one of the halides like we want.

Answer 2:

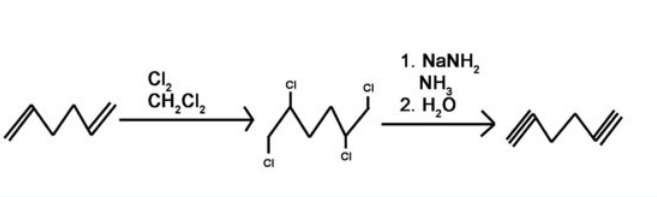
a.) 1-Pentyne

b.) 1-Pentyne

Answer 3:



Answer 4: 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.



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. <http://www.ochem4free.info/node/143>.

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9.3: Reactions of Alkynes - Addition of HX and X_2

Learning Objective

- predict the products and specify the reagents for the Electrophilic Addition Reactions (EARs) of alkynes with HX and X_2

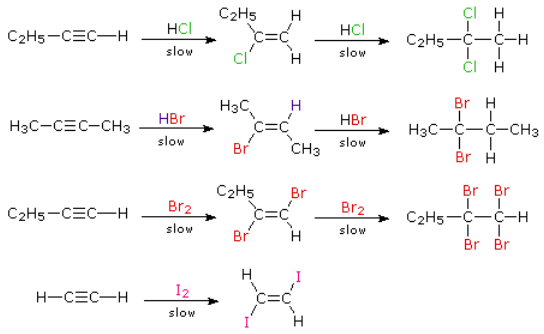
Addition by Electrophilic Reagents

Since the most common chemical transformation of a carbon-carbon double bond is an addition reaction, we might expect the same to be true for carbon-carbon triple bonds. Indeed, most of the alkene addition reactions also take place with alkynes with similar regio- and stereoselectivity.

When the addition reactions of electrophilic reagents, such as strong Brønsted acids and halogens, to alkynes are studied we find a curious paradox. The reactions 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 than addition to equivalently substituted alkenes. The reaction of one equivalent of bromine with 1-penten-4-yne, for example, gave 4,5-dibromo-1-pentyne as the chief product.

$$HC{\equiv}C\text{-}CH_2\text{-}CH{=}CH_2 + Br_2 \rightarrow HC{\equiv}C\text{-}CH_2\text{-}CHBrCH_2Br$$

Although these electrophilic additions to alkynes are sluggish, they do take place and generally display Markovnikov Rule regioselectivity and anti-stereoselectivity. One problem, of course, is that the products of these additions are themselves substituted alkenes and can therefore undergo further addition. Because of their high electronegativity, halogen substituents on a double bond act to reduce its nucleophilicity, and thereby decrease the rate of electrophilic addition reactions. Consequently, there is a delicate balance as to whether the product of an initial addition to an alkyne will suffer further addition to a saturated product. Although the initial alkene products can often be isolated and identified, they are commonly present in mixtures of products and may not be obtained in high yield. The following reactions illustrate many of these features. In the last example, 1,2-diodoethene does not suffer further addition inasmuch as vicinal-diiodoalkanes are relatively unstable.



As a rule, electrophilic addition reactions to alkenes and alkynes proceed by initial formation of a **pi-complex**, in which the electrophile accepts electrons from and becomes weakly bonded to the multiple bond. Such complexes are formed reversibly and may then reorganize to a reactive intermediate in a slower, rate-determining step. Reactions with alkynes are more sensitive to solvent changes and catalytic influences than are equivalent alkenes.

Why are the reactions of alkynes with electrophilic reagents more sluggish than the corresponding reactions of alkenes? After all, addition reactions to alkynes are generally 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 carbons exert a strong attraction for

these 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.

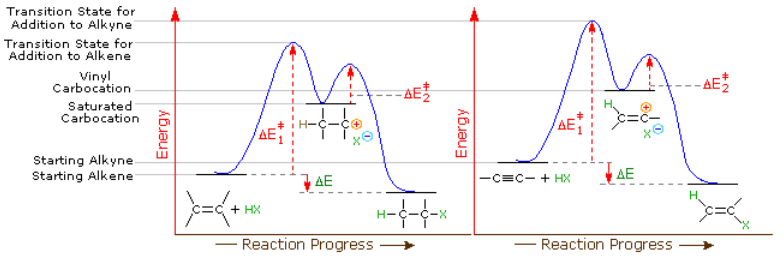
Acetylene	$HC{\equiv}CH + Energy \rightarrow [HC{\equiv}CH^{\bullet(+)} + e^{(-)}$		$\Delta H = +264$ kcal/mole
Ethylene	$H_2C{=}CH_2 + Energy \rightarrow [H_2C{=}CH_2]^{\bullet(+)} + e^{(-)}$		$\Delta H = +244$ kcal/mole
Ethane	$H_3C{-}CH_3 + Energy \rightarrow [H_3C{-}CH_3]^{\bullet(+)} + e^{(-)}$		$\Delta H = +296$ kcal/mole

As defined by the preceding equations, an **ionization potential** is the minimum energy required to remove an electron from a molecule of a compound. Since pi-electrons are less tightly held than sigma-electrons, we expect the ionization potentials of ethylene and acetylene to be lower than that of ethane, as is the case. Gas-phase proton affinities show the same order, with ethylene being more basic than acetylene, and ethane being less basic than either. Since the initial interaction between an electrophile and an alkene or alkyne is the formation of a pi-complex, in which the electrophile accepts electrons from and becomes weakly bonded to the multiple bond, the relatively slower reactions of alkynes becomes understandable.

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. This intermediate has its positive charge localized on an unsaturated carbon, and such **vinyl cations** are less stable than their saturated analogs. Indeed, we can modify our earlier ordering of carbocation stability to include these vinyl cations in the manner shown below. It is possible that vinyl cations stabilized by conjugation with an aryl substituent are intermediates in HX addition to alkynes of the type Ar-C≡C-R, but such intermediates are not formed in all alkyne addition reactions.

Carbocation Stability	$CH_3^{(+)}$	≈	$RCH{=}CH^{(+)}$	<	$RCH_2^{(+)}$	≈	$RCH{=}CR^{(+)}$	<	$R_2CH^{(+)}$	≈	$CH_2{=}CH{-}CH_2^{(+)}$	<	$C_6H_5CH_2^{(+)}$	≈	$R_3C^{(+)}$
	Methyl		1°-Vinyl		1°		2°-Vinyl		2°		1°-Allyl		1°-Benzyl		3°

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. This is illustrated for alkenes versus alkynes by the following energy diagrams.



A Comparison of Energy Profiles for Electrophilic Addition to Alkenes and Alkynes

Despite these differences, electrophilic additions to alkynes have emerged as exceptionally useful synthetic transforms.

Addition of Hydrogen Halide to an Alkyne

Summary: Reactivity order of hydrogen halides: HI > HB r> HCl > HF.

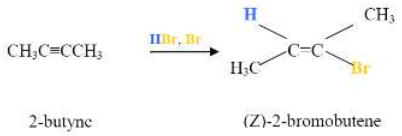
Follows Markovnikov's rule:

- Hydrogen adds to the carbon with the greatest number of hydrogens, the halogen adds to the carbon with fewest hydrogens.
- Protination occurs on the more stable carbocation. With the addition of HX, haloalkenes form.
- With the addition of excess HX, you get *anti* addition forming a geminal dihaloalkane.

Addition of a HX to an Internal Alkyne

As shown in Figure 2 below, the π electrons react with the hydrogen of the HBr and because the alkyne carbons are equivalent it does not matter which carbon adds the hydrogen. Once the hydrogen is covalently bonded to one of the carbons, the bromide will react with the carbocation intermediate to form a vinyl halide as shown in the example of forming 2-bromobutene from 2-butyne reacting with HBr. The reaction below assumes a 1:1 mole ratio of the alkyne and HBr.

Figure 2



2-butyne (Z)-2-bromobutene

Now, what happens if there is excess HBr?

Addition due to excess HX yields a geminal dihaloalkane

Figure 3

(Z)-2-bromobutene 2,2-Dibromobutane

Here, the electrophilic addition proceeds with the same steps used to achieve the product in Addition of a HX to an Internal Alkyne. The π electrons react with the hydrogen (shown in blue) adding it to the carbon on the left because the lone pair electrons of the bromine can help stabilize the carbocation intermediate that reacts with the bromide ions to form a geminal dihalide.

Addition of HX to Terminal Alkyne

For terminal alkynes, the carbon atoms sharing the triple bond are not equivalent. The addition of HX to terminal alkynes occurs in a Markovnikov-manner in which the halide attaches to the most substituted carbon. The pi electrons react with the hydrogen and it bonds to the terminal carbon. The bromide reacts with the resulting carbocation intermediate to form the vinyl halide. The overall reaction and mechanism are shown below.

Figure 4

Propyne 2-Bromopropene

Mechanism:

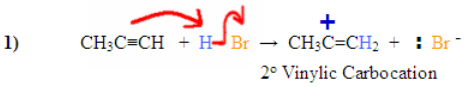
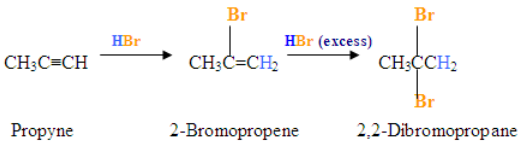


Figure4.2.bmp" />

Addition due to excess HBr present

Similar to the addition of excess HBr to internal alkynes, both halides will add to the same carbon to form a geminal dihalide.

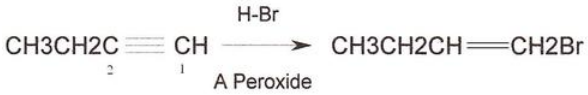
Figure 5



HBr Addition With Radical Mechanism

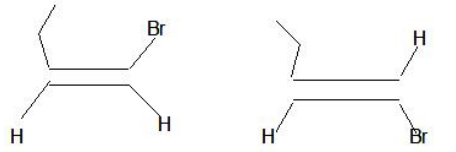
Most hydrogen halide reactions with terminal alkynes occur in a Markovnikov-manner in which the halide attaches to the most substituted carbon since it is the most positively polarized. However, there are two specific reactions among alkynes where anti-Markovnikov reactions take place: the radical addition of HBr and Hydroboration Oxidation reactions. For alkynes, an anti-Markovnikov addition takes place for terminal alkynes.

The Br of the Hydrogen Bromide (H-Br) attaches to the less substituted 1-carbon of the terminal alkyne shown below in an anti-Markovnikov manner while the Hydrogen proton attaches to the second carbon. As mentioned above, the first carbon is the less substituted carbon since it has fewer bonds attached to carbons and other substituents. The H-Br reagent must also be reacted with heat or some other radicial initiator such as a peroxide in order for this reaction to proceed in this manner. This presence of the radical or heat leads to the anti-Markovnikov addition since it produces the most stable reaction.



The product of a terminal alkyne that is reacted with a peroxide (or light) and H-Br is a 1-bromoalkene.

Regioselectivity: The Bromine can attach in a ***syn*** or ***anti*** manner which means the resulting alkene can be both ***cis*** and ***trans***. ***Syn*** addition is when both Hydrogens attach to the same face or side of the double bond (i.e. ***cis***) while the ***anti*** addition is when they attach on opposite sides of the bond (***trans***).



Halogenation of Alkynes

The additon of X_2 to alkynes is analogous to the addition of X2 to alkenes. The halogen molecule becomes polarized by the approach of the nucleophilic alkyne. The pi electrons of the alkyne react with the bromine to form a carbon-bromine bond and cyclic halonium ion with halide as the leaving group. The formation of the cyclic halonium ion requires anti-addition of the nucleophilic halide to produce a vicinal dihalide alkene as shown in the reaction below.

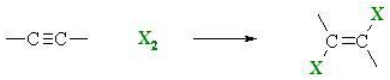
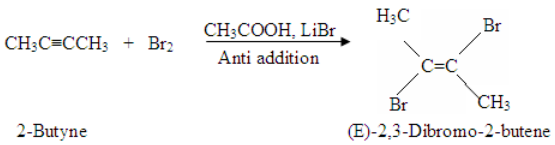
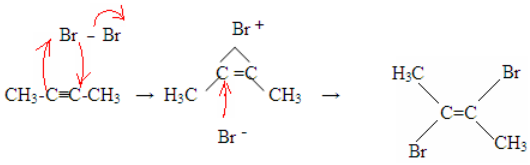


Figure 6 below shown the reaction of bromine with 2-buttyne to form (E)-2,3-ibromo-2-butene along with the mechanism.

Figure 6



Mechanism:



Exercise

1. Draw the structure, and give the IUPAC name, of the product formed in each of the reactions listed below.

a. $\mathrm{CH_3{-}C{\equiv}C{-}CH_3} \xrightarrow[\mathrm{HCl}]{\text{1 equiv}}$

b. $\mathrm{CH_3{-}C{\equiv}C{-}CH_3} \xrightarrow[\mathrm{HCl}]{\text{excess}}$

c. $\mathrm{CH_3{-}C{\equiv}C{-}CH_3} \xrightarrow[\mathrm{Br_2}]{\text{1 equiv}}$

d. $\mathrm{CH_3{-}C{\equiv}C{-}CH_3} \xrightarrow[\mathrm{Br_2}]{\text{excess}}$

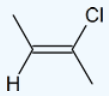
e. $\mathrm{CH_3CH_2{-}C{\equiv}C{-}H} \xrightarrow[\mathrm{HCl}]{\text{1 equiv}}$

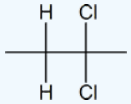
f. $\mathrm{CH_3CH_2{-}C{\equiv}C{-}H} \xrightarrow[\mathrm{HCl}]{\text{excess}}$

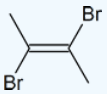
g. $\mathrm{CH_3CH_2CH_2{-}C{\equiv}C{-}H} \xrightarrow[\mathrm{Br_2}]{\text{1 equiv}}$

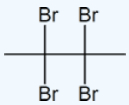
h. $\mathrm{CH_3CH_2CH_2{-}C{\equiv}C{-}H} \xrightarrow[\mathrm{Br_2}]{\text{excess}}$

Answer

a. (*Z*)-2-chloro-2-butene 

b. 2,2-dichlorobutane 

c. (*E*)-2,3-dibromo-2-butene 

d. 2,2,3,3-tetrabromobutane 

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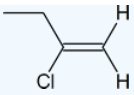
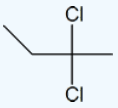
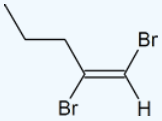
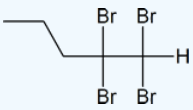
e. 2-chloro-1-butene 

f. 2,2-dichlorobutane 

g. (*E*)-1,2-dibromo-1-pentene 

h. 1,1,2,2-tetrabromopentane 

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

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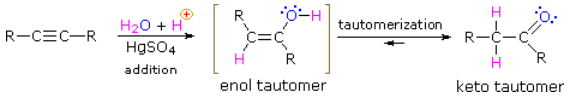
9.4: Hydration of Alkynes for Markovnikov Products

Learning Objective

- predict the products and specify the reagents for the Markovnikov-products of alkyne hydration

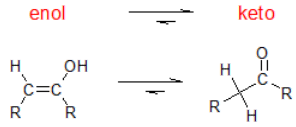
Reaction: Hydration of Alkynes (Markovnikov's Rule)

Hydration of alkynes begins similar to the hydration of alkenes through the addition of the first water molecule. However, this first hydration reaction forms an enol, an alcohol bonded to a vinyl carbon. Enols immediately undergo a special type of isomerization reaction called tautomerization to form carbonyl groups - aldehydes or ketones. To keep things simple, this reaction is called "enol-keto" tautomerization with the understanding that aldehydes form on terminal alkyne carbons. As with alkenes, hydration (addition of water) to alkynes requires a strong acid, usually sulfuric acid with a mercuric sulfate catalyst as shown below.



Enol-Keto Tautomers

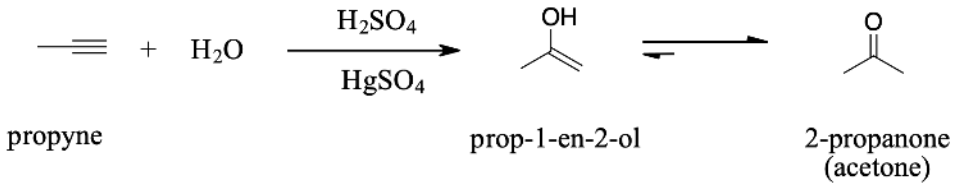
Tautomers are defined as rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom (colored red here) and a differently located double bond. The equilibrium between tautomers is not only rapid under normal conditions, but it often 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. The three examples shown below illustrate these reactions for different substitutions of the triple-bond. The tautomerization step is indicated by a red arrow. For terminal alkynes the addition of water follows the Markovnikov rule, as in the second example below, and the final product ia a methyl ketone (except for acetylene, shown in the first example). For internal alkynes (the triple-bond is within a longer chain) the addition of water is not regioselective. If the triple-bond is not symmetrically located (i.e. if R & R' in the third equation are not the same) two isomeric ketones will be formed.



With the addition of water, alkynes can be hydrated to form enols that spontaneously tautomerize to ketones. The reaction is catalyzed by mercury ions and follows Markovnikov’s Rule A useful functional group conversion for multiple -step syntheses is to hydrate terminal alkynes to produce methyl ketones.

Hydration of Alkyne Mechanism

The first step is an acid/base reaction where the π electrons of the triple bond acts as a Lewis base and reacts with the proton therefore protonating the carbon with the most hydrogen substituents as expected by Markovnikov's Rule. In the second step, the nucleophilic water molecule reacts with the electrophilic carbocation to produce an oxonium ion. The oxonium ion is deprotonated by a base to produce an enol which immediately tautomerizes into a ketone. The hydration reaction for propyne is shown below with its mechanism to illustrate the electron flow of the mechanism.



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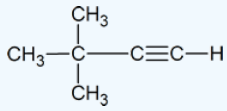
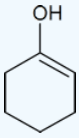
Exercise

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. CH_3CHCCH

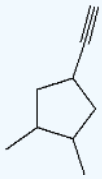
   b. 

2. Draw the structure of the keto form of the compound shown below. Which form would you expect to be the most stable?

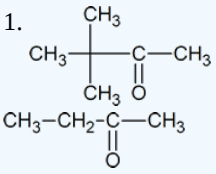


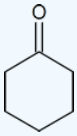
3. What alkyne would you start with to gain the following products, in an oxidation reaction? Keep in mind resonance.

4. Propose a reaction scheme for the following compound starting from the alkyne and showing required reagents and intermediates.

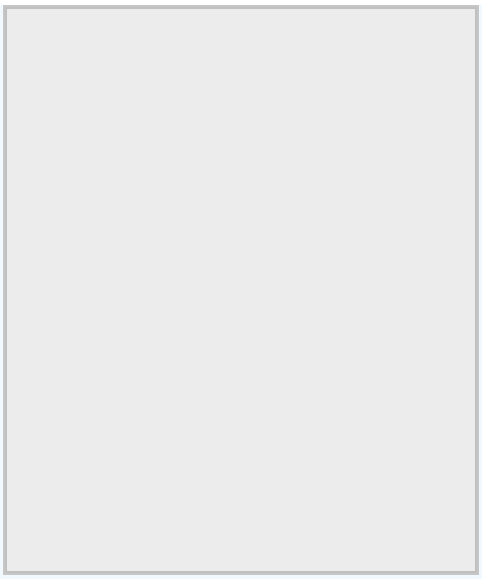


Answer

1. 

2.  ; The keto form should be the most stable.

3.



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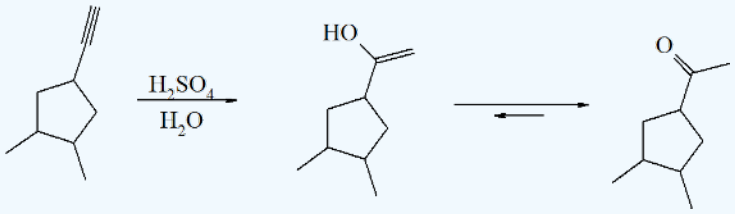

Contributors and Attributions

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9.5: Hydration of Alkynes for Anti-Markovnikov Products

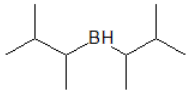
Learning Objective

- predict the products and specify the reagents for the anti-Markovnikov-products of alkyne hydration

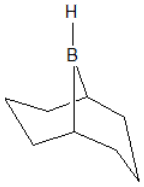
Introduction

The hydroboration-oxidation of alkynes is similar to the reaction with alkenes. However, there is one important difference. The alkyne has two pi bonds and both are capable of reacting with borane (BH_3). To limit the reactivity to only one of the pi bonds within the alkyne, a dialkyl borane reagent (R_2BH) is used. Replacing two of the hydrogens on the borane with alkyl groups also creates steric hindrance so that the hydroboration reaction produces the regioselective,

anti-Markovnikov product. Disiamylborane (Sia_2BH) and 9-borabicyclo[3.3.1]nonane (9-BBN) are two common reagents for the hydroboration step. Their structures are shown below.

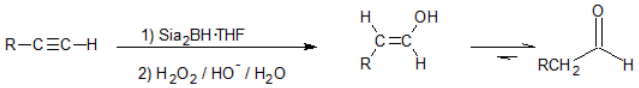


disiamylborane or Sia_2BH



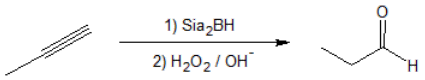
9-borabicyclo[3.3.1]nonane or 9-BBN

The oxidation reagents (a basic hydrogen peroxide solution) are the same for both alkenes and alkynes, The overall reaction is shown below.

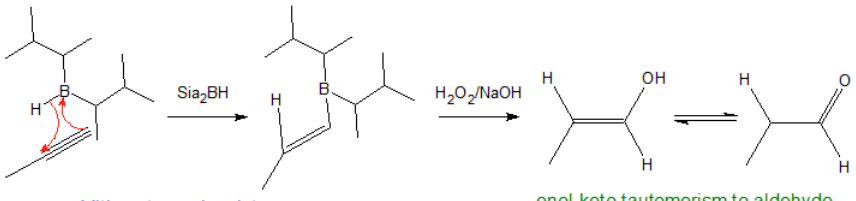


Mechanism

The hydroboration reaction of alkynes has the same stereo- and regiochemistry as the alkene reaction. The primary difference is the steric hindrance of the two isoamyl groups of the dialkyl borane creates anti-Markovnikov regeioselectivity. The hydrogen and boron bond with the same orientation to the alkyne carbon with syn-addition stereochemistry to form the enol. The enol immediately tautomerizes to the keto form which is an aldehyde for terminal alkynes. The hydration of 1-propyne is shown below along with the reaction mechanism.



mechanism



syn-addition stereochemistry
with H adding at the most substituted carbon
for anti-Markovikov regiochemistry

enol-keto tautomerism to aldehyde

Exercise

1. Draw the bond-line structure(s) for the product(s) of each reaction.

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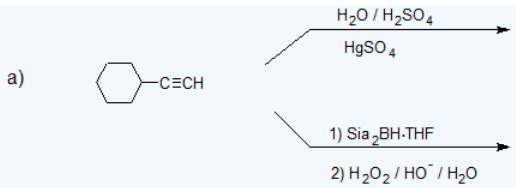
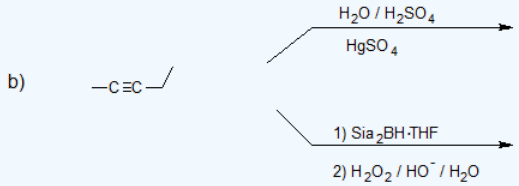
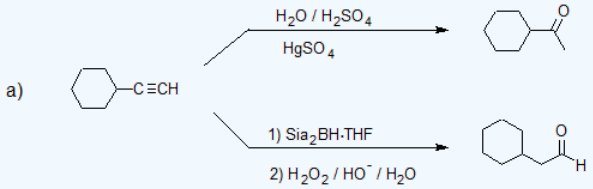
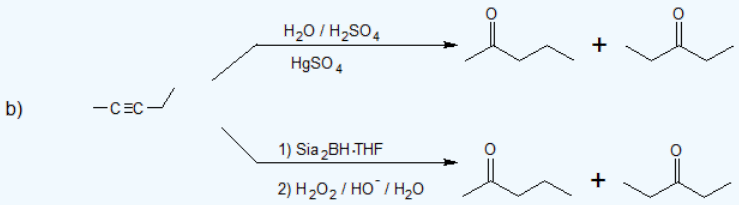




Answer





For internal alkynes, there is no difference in the reaction products.

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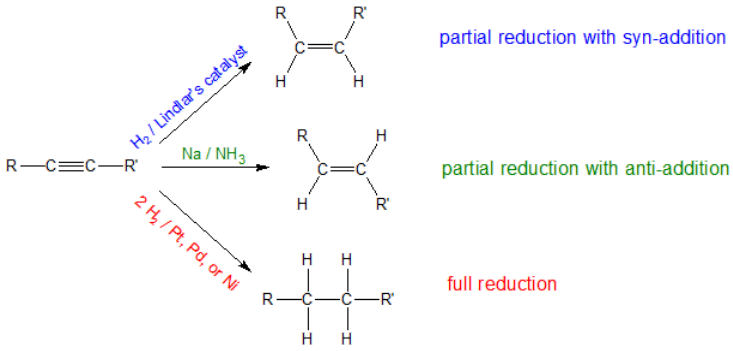
9.6: 10.6 Reduction of Alkynes

Learning Objective

- predict the products and specify the reagents for the full or partial reduction of alkynes

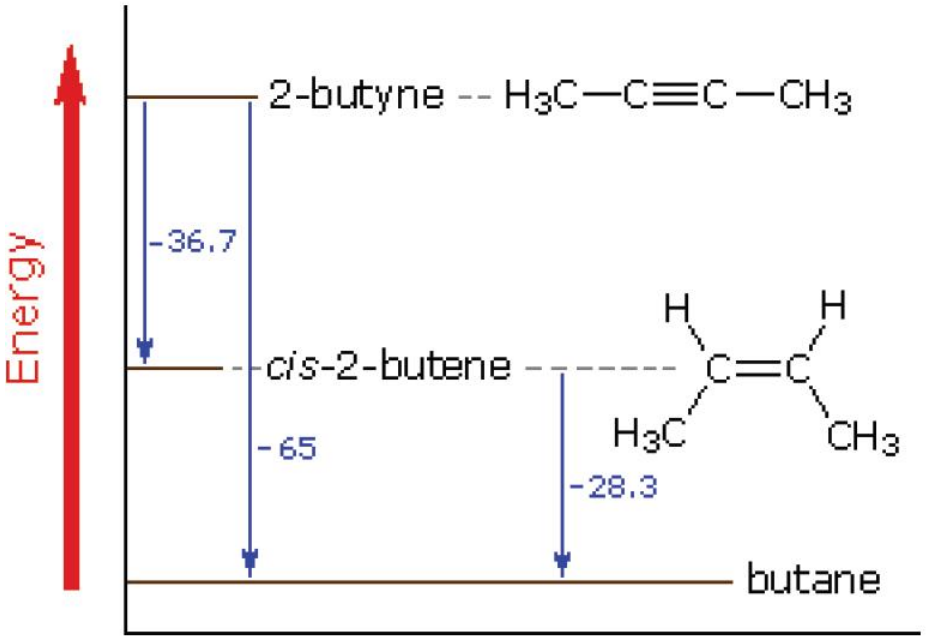
Introduction and Overview

Alkynes can undergo reduction reactions similar to alkenes. These reactions are also called hydrogenation reactions. With the presence of two pi bonds within the carbon-carbon triple bonds, the reduction reactions can be partial or complete depending on the reagents. Since partial reduction of an alkyne produces an alkene, the stereochemistry of the addition mechanism determines whether the cis- or trans- alkene is formed. The three most significant alkyne reduction reactions are summarized below.



Hydrogenation and the Relative Stability of Hydrocarbons

Like alkenes, alkynes readily undergo catalytic hydrogenation partially to cis- or trans- alkenes or fully to alkanes depending on the reaction employed.

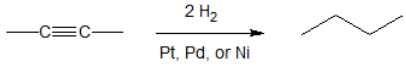


The catalytic addition of hydrogen to 2-butyne provides heat of reaction data that reflect the relative thermodynamic stabilities of these hydrocarbons, as shown above. From the heats of hydrogenation, shown in blue in units of kcal/mole, it would appear that alkynes are thermodynamically less stable 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).

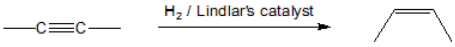
Catalytic Hydrogenation of an Alkyne

Alkynes can be fully hydrogenated into alkanes with the help of a platinum, paladium, or nickel catalyst. Because the reaction is catalyzed on the surface of the metal, it is common for these catalysts to dispersed on carbon (Pd/C) or finely dispersed as nickel (Raney-Ni). The full reduction of 2-butyne is shown below as an example.

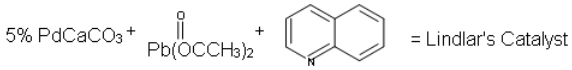


Hydrogenation of an Alkyne to a Cis-Alkene

Since alkynes are thermodynamically less stable than alkenes, we expect addition reactions of alkynes to be more exothermic and relatively faster than equivalent reactions of alkenes. For catalytic hydrogenation, the Pt, Pd, or Ni catalysts are so effective in promoting addition of hydrogen to both double and triple carbon-carbon bonds that the alkene intermediate formed by hydrogen addition to an alkyne cannot be isolated. A less efficient catalyst, 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 the hydrogenation reaction is occurring on the surface of the metal. Both hydrogen atoms are added to the same side of the alkyne as shown in the syn-addition mechanism for hydrogenation of alkenes in the previous chapter.

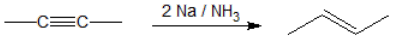


Lindlar's catalyst is prepared by deactivating (or poisoning) a conventional palladium catalyst. Lindlar's catalyst has three components: palladium-calcium carbonate, lead acetate and quinoline. The quinoline serves to prevent complete hydrogenation of the alkyne to an alkane. This approach is similar to the one used for hydration of alkynes using a dialkyl borane for hydroboration. A strong reagent is modified into a less reactive form.

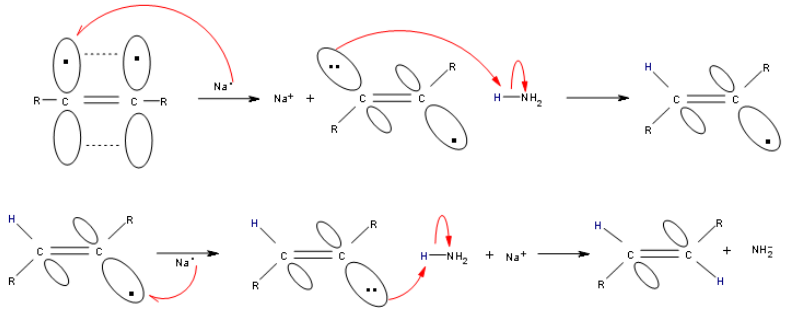


Hydrogenation of an Alkyne to a Trans-Alkene

Alkynes can be reduced to trans-alkenes with the use of sodium dissolved in an ammonia solvent. A sodium radical donates an electron to one of the p-orbitals in the carbon-carbon triple bond. This reaction forms an anion that can be protonated by a hydrogen atom in the ammonia solvent which prompts another sodium radical to donate an electron to the second p-orbital. The resulting anion is also protonated by a hydrogen from the ammonia solvent to produce a trans-alkene according to the mechanism shown below.



Mechanism for Hydrogenation of Alkynes to trans-Alkenes

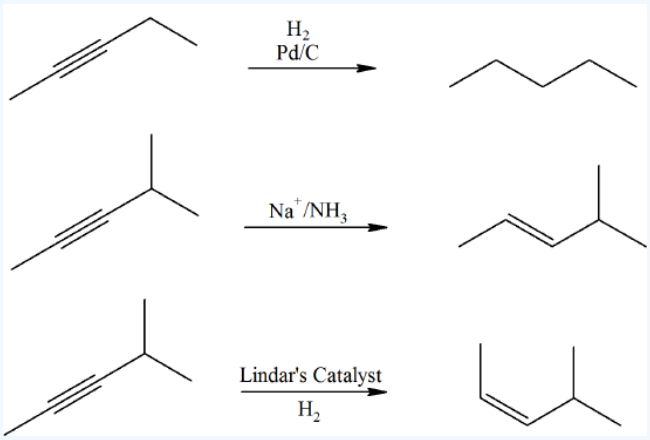


Exercise

1. Using any alkyne how would you prepare the following compounds: pentane, *trans*-4-methyl-2-pentene, *cis*-4-methyl-2-pentene.

Answer

1.



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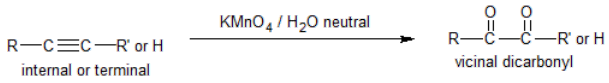
9.7: Oxidation of Alkynes

Learning Objective

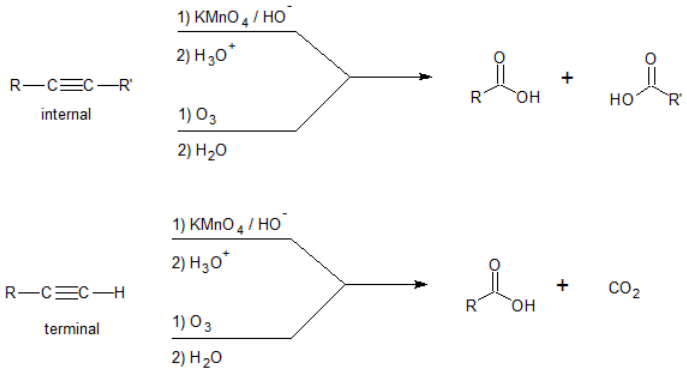
- predict the products and specify the reagents for the oxidation of alkynes

Alkynes, similar to alkenes, can be oxidized gently or strongly depending on the reaction environment. Since alkynes are less stable than alkenens, the reactions conditions can be gentler. For examples, alkynes form vicinal dicarbonyls in neutral permanganate solution. For the alkene reaction to vicinal dialcohols, the permanganate reaction requires a lightly basic environment for the reaction to occur. 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. The generic reactions are summarized below for the different oxidative conditions - gentle or strong.

Gentle Alkyne Oxidation

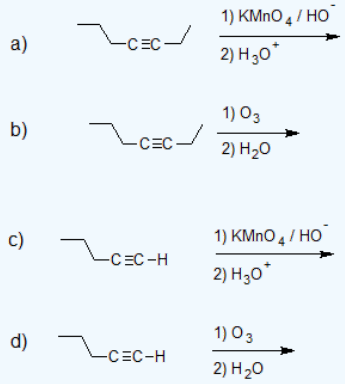


Strong Alkyne Oxidation - Oxidative Cleavage



Exercise

1. Draw the bond-line structures for the product(s) of the following reactions.



Answer

1.

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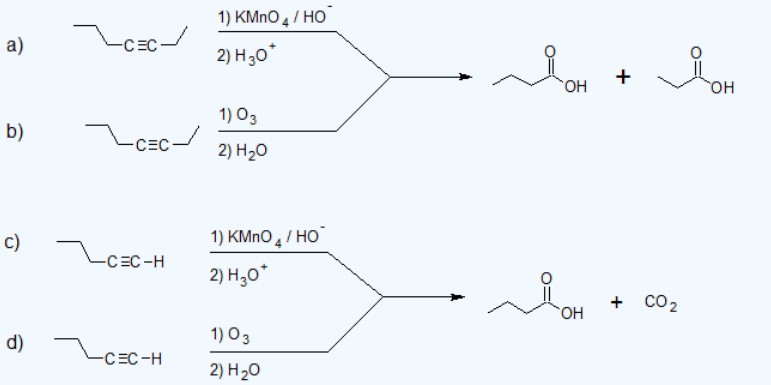

Oxidative cleavage of alkynes produces carboxylic acids and/or carbon dioxide. Aldehydes are not produced.

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9.8: Acidity of Terminal Alkynes

Learning Objectives

- explain why alkynes are more acidic than alkanes and alkenes
- predict the products and specify the reagents to generate nucleophilic acetylide ions and heavy metal acetylides

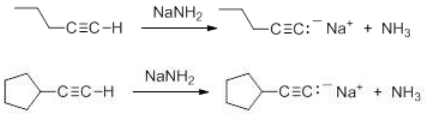
Acidity of Terminal Alkynes and Acetylilde Ion Formation

Terminal alkynes are much more acidic than most other hydrocarbons. Removal of the proton leads to the formation of an acetylide anion, $RC{\equiv}C{:}^-$. The origin of the enhanced acidity can be attributed to the stability of the acetylide anion, which has the unpaired electrons in an sp hybridized orbital. The stability results from occupying an orbital with a high degree of s-orbital character. 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 enhanced acidity with greater s-character occurs despite the fact that the homolytic C-H BDE is larger.

***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

Consequently, acetylide anions can be readily formed by deprotonation using a sufficiently strong base. Amide anion (NH_2^-), in the form of $NaNH_2$ is commonly used for the formation of acetylide anions.



Exercise

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.
    1. ethanol (p*K*a = 16)
    2. acetic acid (p*K*a = 4.72)
    3. acetylene (p*K*a = 25)

Answer

Answers:

1.

1. No, The p*K*a of ethanol is similar to the pKa of water so proton exchange is comparable for both protonation and deprotonation between alcohols and water. Alcohols can be considered "alkylated water" and share many similarities in both physical properties and chemical reactivity.
2. 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 with acetate as the predominate form of the original acetic acid.
3. No, hardly at all. The hydroxide ion is too weak a base to remove a proton from acetylene. The equilibrium lies so far to the left that it is considered a "No Reaction".

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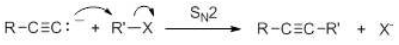
9.9: Synthesis of Larger Alkynes from Acetylides

Learning Objective

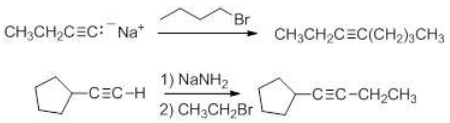
- predict the products and specify the reagents to synthesize larger alkynes with acetylide ions

Nucleophilic Substitution Reactions of Acetylides

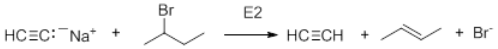
Acetylide anions are strong bases and strong nucleophiles. Therefore, they are able to displace halides and other leaving groups in substitution reactions. The product is a substituted alkyne with a longer, continuous carbon chain.



Because the ion is a very strong base, the substitution reaction follows the S_N2 mechanism and is most efficient with methyl or primary halides without substitution near the reaction center.

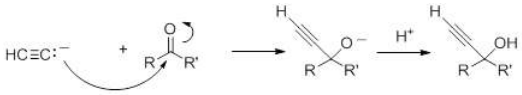


Secondary, tertiary or even bulky primary substrates will give elimination by the E2 mechanism.



Nucleophilic Addition of Acetylides to Carbonyls

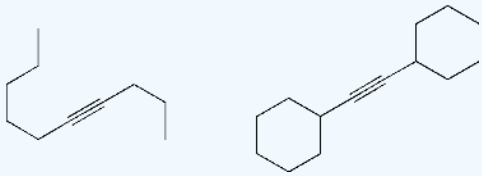
Acetylide anions will add to aldehydes and ketones to form alkoxides that are subsequently protonated to form propargyl alcohols.



With aldehydes and non-symmetric ketones, in the absence of chiral catalyst, the product will be a racemic mixture of the two enantiomers.

Exercise

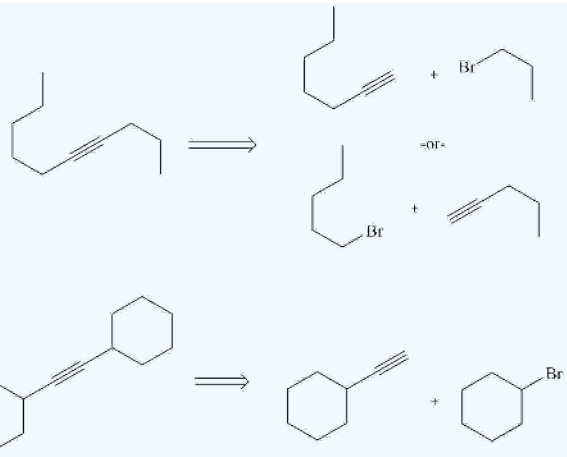
1. The pK_a of ammonia is 35. Estimate the equilibrium constant for the deprotonation of pent-1-yne by amide, as shown above.
2. Give the possible reactants for the following formations:



3. Propose a synthetic route to produce 2-pentene from propyne and an alkyl halide.

Answer

1. 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}.
2.



3.

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9.10: An Introduction to Multiple Step Synthesis

Learning Objective

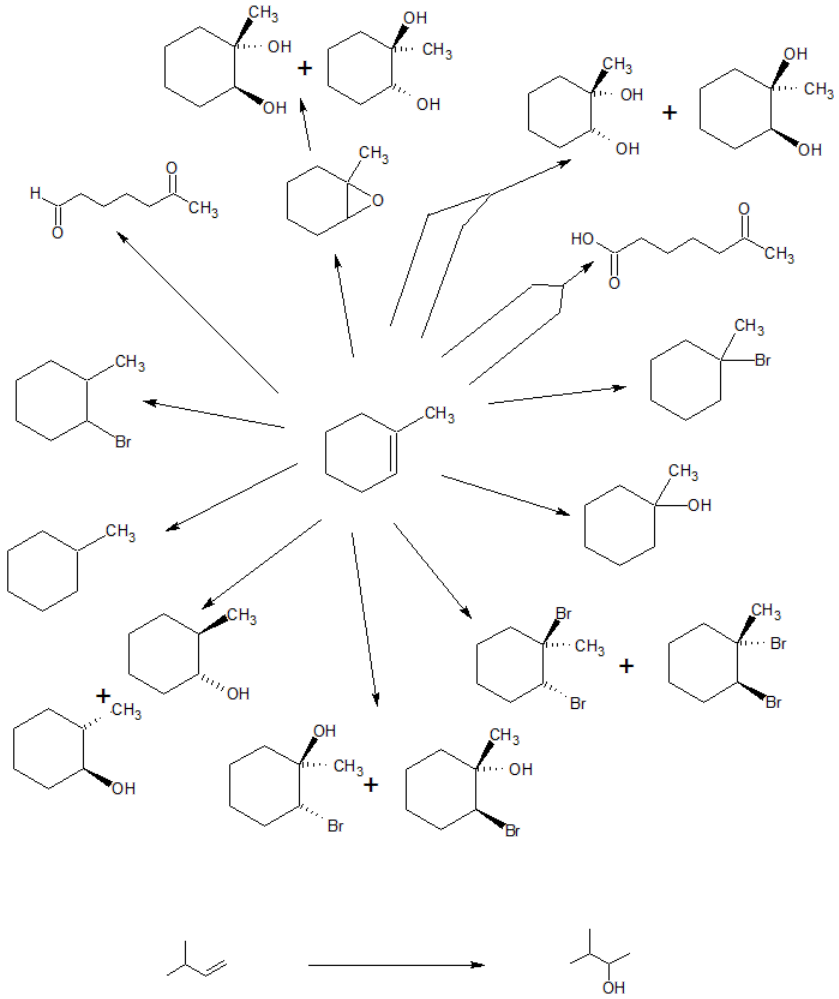
- use retrosynthetic analysis to design a multi-step synthesis with correct regiochemistry and stereochemistry using the reactions studied to date

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.

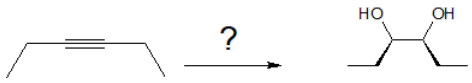
Alkene Reaction Map

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.

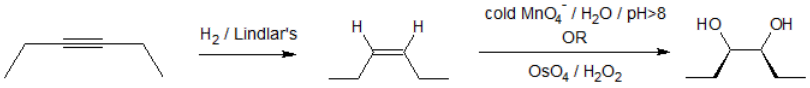


Simple Multi-Step Syntheses

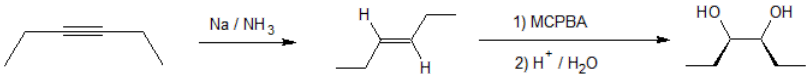
A one or two step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol from 3-hexyne can occur by more than one multi-step pathway.



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.

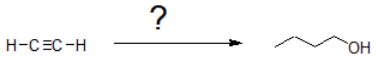


Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope 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

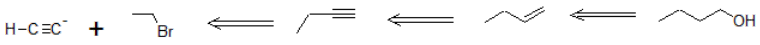
The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. 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.

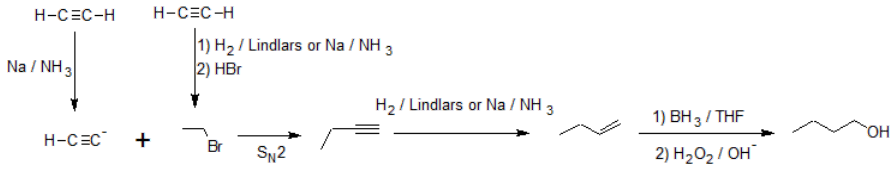


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol 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.

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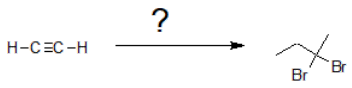
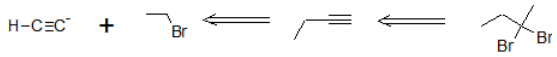
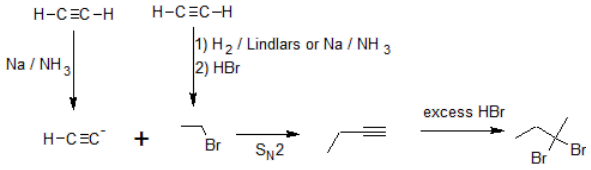


Once again there is an increase in the carbon chain length indicating an acetylide S_N2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne 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 halogenatioin because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

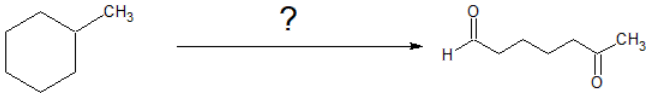
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.

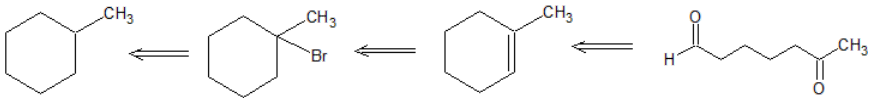


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.

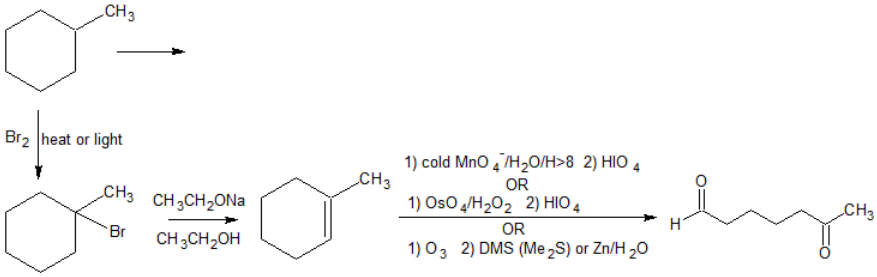


Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or 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 (Cl2) or bromine (Br2). Because methylcyclohexane has several different classifications of carbons, the selectivity of Br2 is more important than the faster reactivity of Cl2. An strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldhyde 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.

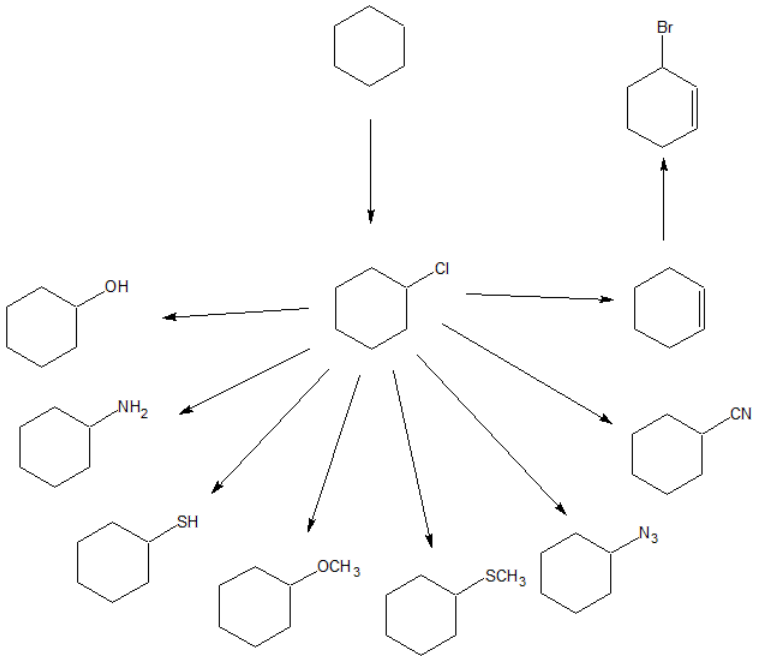


Reaction Maps to Build Functional Group Conversion Mastery

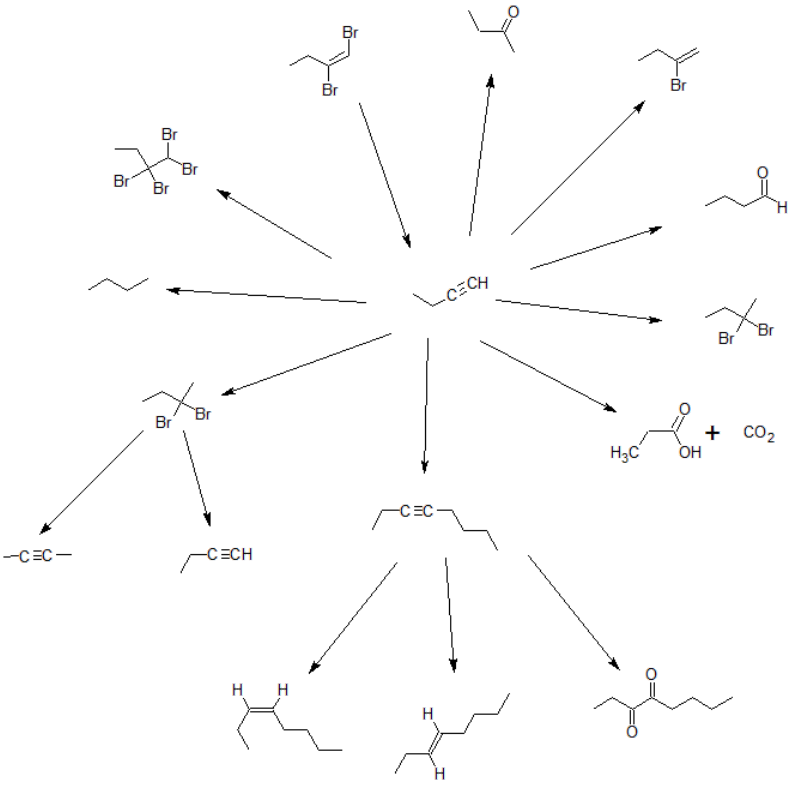
After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

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

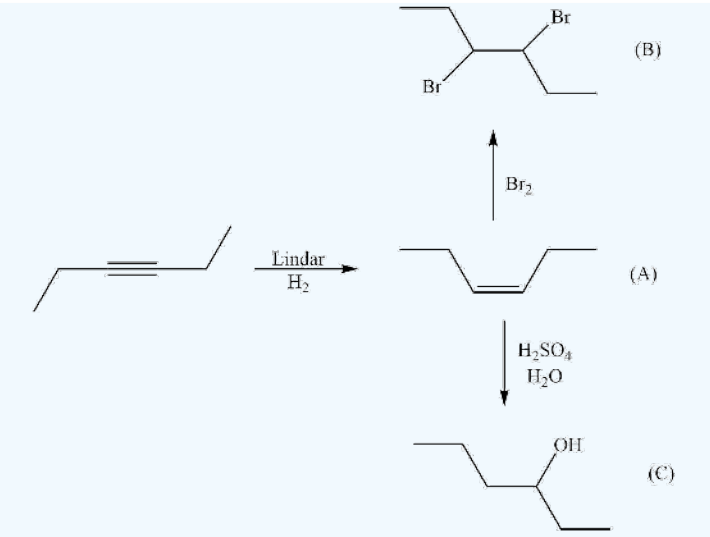
a) pentanal

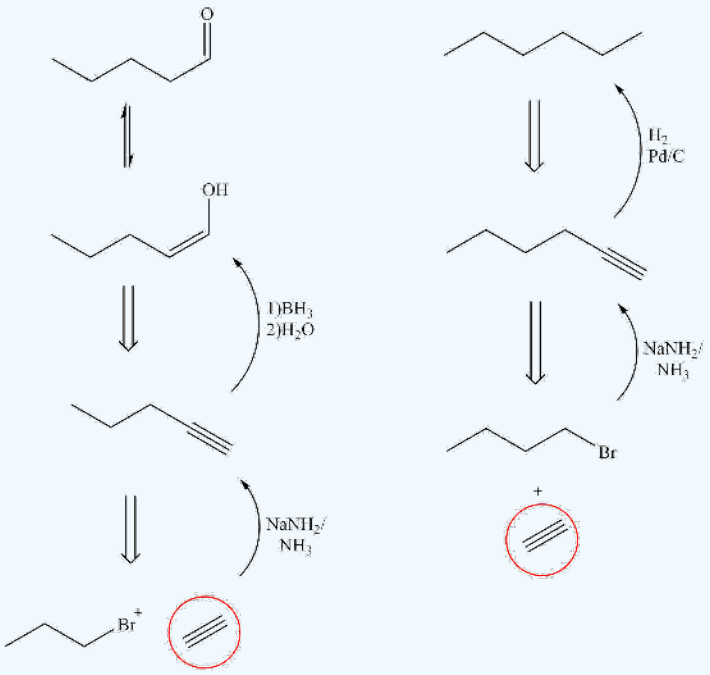
b) hexane.

Answer

1.

2.





Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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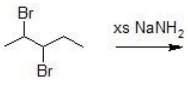
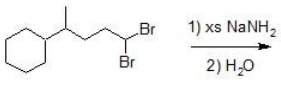
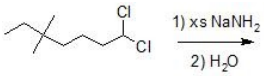
9.11: Additional Exercises

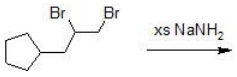
Alkyne Reactions

10-1 Predict the product of these following reactions:

a) 

b) 

c) 

d) 

10-2 Using acetylene as the starting material, show how you would synthesize the following compounds

a)

b) but-2-yne

c)

d)

10-3 Identify the reagents needed to turn hex-1-yne into the following compounds

a) hexane

b) oct-3-yne

c) cis-hept-2-ene

d) trans-hept-2-ene

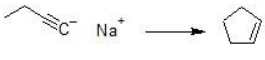
e) 2,2-dibromohexane

f) 1-bromohexene

10-4 Show how you would accomplish the following synthetic transformations.

a)

b)

c) 

d)

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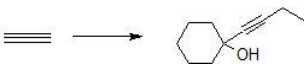
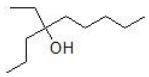
f) 

10-5 Deduce the structure of each unknown from the information given.

a) Upon catalytic hydrogenation, unknown **A** yields pentane. Ozonolysis of **A** yields butanoic acid, $HOOC(CH_2)_2CH_3$ and CO_2. Draw the structure of compound **A**

b) Upon catalytic hydrogenation, unknown **B** yields pentane. Ozonolysis of **B** yields acetaldehyde, CH_3CHO, and propionaldehyde, CH_3CH_2CHO.

10-6 Use compound **A** from the previous problem (**10-5**) and any additional reagents you may need to synthesize the following compound.



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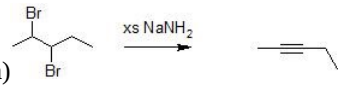
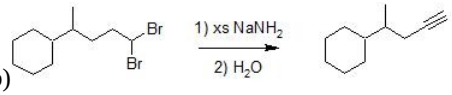
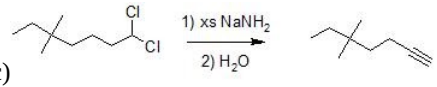
9.12: Solutions to Additional Exercises

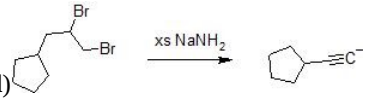
Alkyne Reactions

10-1

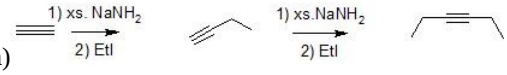
a) 

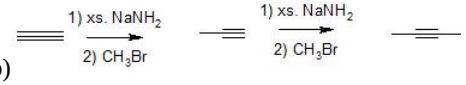
b) 

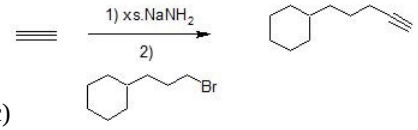
c) 

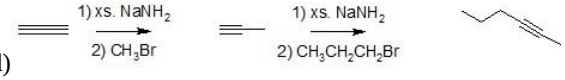
d) 

10-2

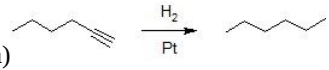
a) 

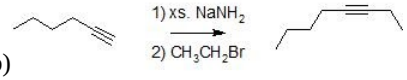
b) 

c) 

d) 

10-3

a) 

b) 

c)

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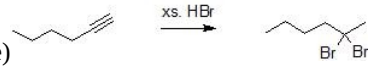
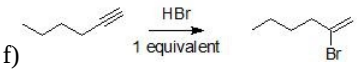
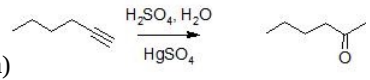
e) 

f) 

10-4

a)



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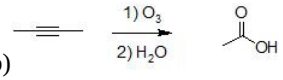

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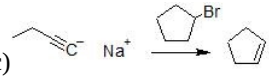

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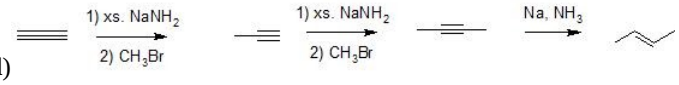

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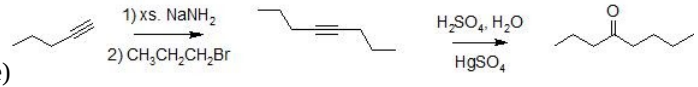

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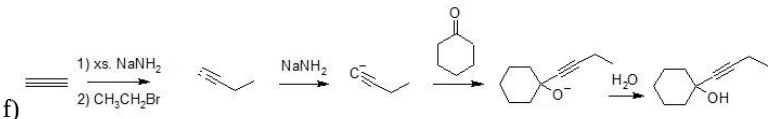
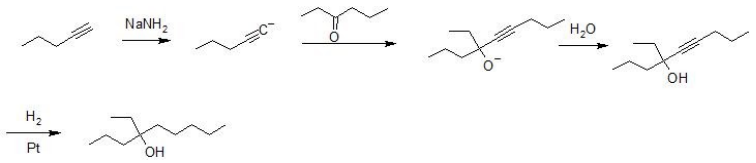


10-5

a)

b)

10-6



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CHAPTER OVERVIEW

10: Reactions of Alcohols

learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- predict the products, specify the reagents, and determine the mechanism of the reactions of alcohols with
    a. hydrohalic acids (refer to section 14.1)
    b. phosphorous halides (refer to section 14.2)
    c. thionyl chloride (refer to section 14.2)
    d. carboxylic acids, acid chlorides, and tosyl choride (refer to section 14.3)
    e. dehydrating reagents – H_2SO_4/heat or $POCl_3$/pyridine (refer to section 14.4)
    f. oxidizing agents (refer to section 14.6)
    g. sodium and potassium (refer to section 14.11)
- apply the most efficient and effective oxidizing agents (refer to section 14.6)
- determine the alcohol classification using laboratory experiments (refer to section 14.7)
- predict the products and specify the reagents of alcohol protecting group reactions (refer to section 14.9)
- predict the products and specify the reagents for diol cleavage reactions (refer to section 14.10)
- predict the products, specify the reagents for alkoxide ion reactions (refer to section 14.11)
- describe selected alcohol oxidation reactions in biology (refer to section 14.12)
- determine multiple-step synthetic pathways using alcohols (chapters 1-10 and 13-14)

10.1: 14.1 Reactions of Alcohols with Hydrohalic Acids
10.2: Reactions with Phosphorus Halides
10.3: Alcohol conversion to Esters - Tosylate and Carboxylate
10.4: Dehydration Reactions of Alcohols
10.5: Oxidation States of Alcohols and Related Functional Groups
10.6: Oxidation Reactions of Alcohols
10.7: Determining Alcohol Classifications in the Lab - alternate reactions
10.8: Protection of Alcohols
10.9: Cleavage of Diols
10.10: Reactions of Alkoxides
10.11: Biological Oxidation - an introduction
10.12: Additional Exercises
10.13: Solutions to Additional Exercises

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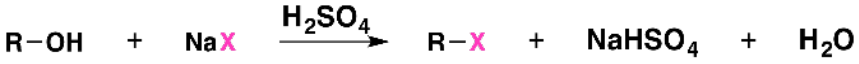
10.1: 14.1 Reactions of Alcohols with Hydrohalic Acids

Conversion of Alcohols into Alkyl Halides

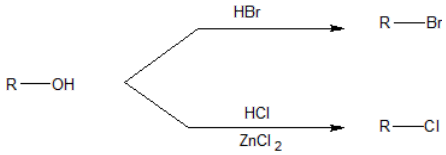
When alcohols react with a hydrogen halide, a substitution takes place producing an alkyl halide and water:

- 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:



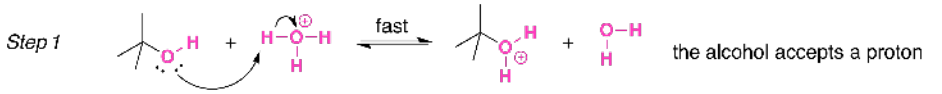
Because Cl- is a weaker nucleophile than Br-, the reaction with HCl requires a catalyst such as ZnCl2 as shown below.

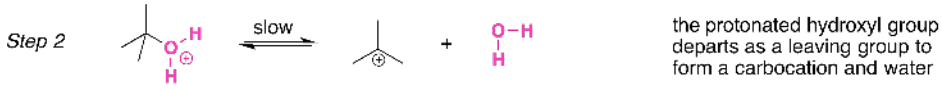


Mechanisms of the Reactions of Alcohols with HX

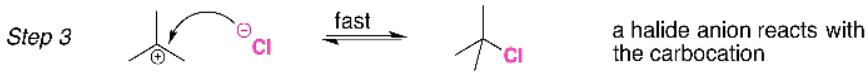
Secondary, tertiary, allylic, and benzylic alcohols appear to react by a mechanism that involves the formation of a carbocation, in an S_N1 reaction with the protonated alcohol acting as the substrate.

The S_N1 mechanism is illustrated by the reaction 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 water, H_2O, which makes the dissociation step of the S_N1 mechanism more favorable.





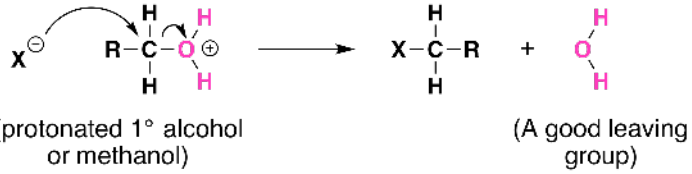
In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.



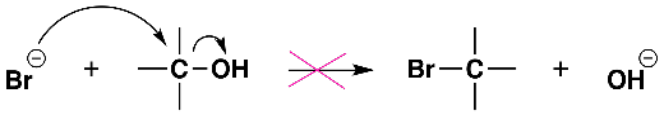
When we convert an alcohol to an alkyl halide, we carry out the reaction in the presence of acid and in the presence of halide ions, and not at elevated temperature. Halide ions are good nucleophiles (they are much stronger nucleophiles than water), and since halide ions are present in high concentration, 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:

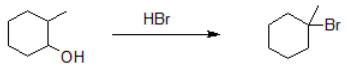


Again, acid is required. Although halide ions (particularly iodide and bromide ions) are strong nucleophiles, they are not strong enough to carry out substitution reactions with alcohols themselves. Direct displacement of the hydroxyl group does not occur because the leaving group would have to be a strongly basic hydroxide ion:



We can see now why the reactions of alcohols with hydrogen halides are acid-promoted.

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. However, this phenomenon is not as simple as it sounds.

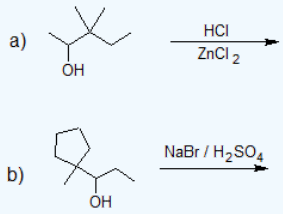


The carbocation intermediate undergoes a 1,2-hydride shift.

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. The alcohol reactions with thionyl chloride or phosphorus tribromide are discussed in the next section.

Exercises

1. Predict the product of each reaction below.



Answer

1.

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a)

b)

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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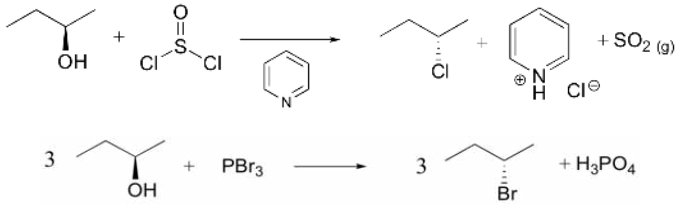
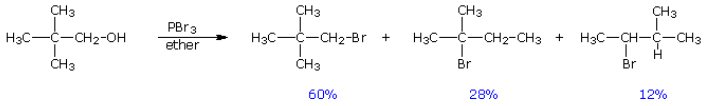
10.2: Reactions with Phosphorus Halides

Carbocation containment

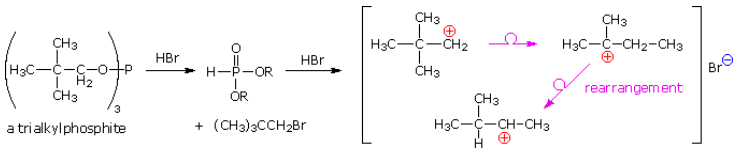
Synthetic organic chemists use phosphorus tribromide and thionyl chloride to convert an alcohol into a better leaving group without carbocation rearrangement.



Despite their general usefulness, phosphorous tribromide and thionyl chloride have shortcomings. Hindered 1º- and 2º-alcohols react sluggishly with the former, and may form rearrangement products, as noted in the following equation.



Below, an abbreviated mechanism for the reaction is displayed. The initially formed trialkylphosphite ester may be isolated if the HBr byproduct is scavenged by base. In the presence of HBr a series of acid-base and S_N2 reactions take place, along with the transient formation of carbocation intermediates. Rearrangement (pink arrows) of the carbocations leads to isomeric products.



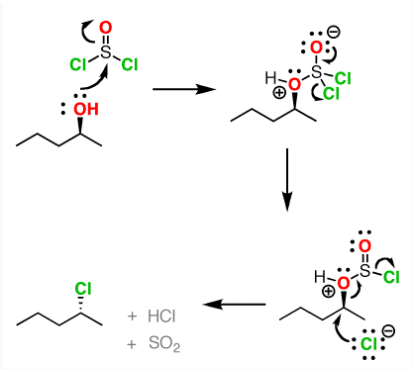
Reaction of thionyl chloride with chiral 2º-alcohols has been observed to proceed with either inversion or retention. In the presence of a base such as pyridine, the intermediate chlorosulfite ester reacts to form an "pyridinium" salt, which undergoes a relatively clean S_N2 reaction to the inverted chloride. In ether and similar solvents the chlorosulfite reacts with retention of configuration, presumably by way of a tight or intimate ion pair. This is classified as an **S_Ni** reaction (nucleophilic substitution internal). The carbocation partner in the ion pair may also rearrange. These reactions are illustrated by the following equations. An alternative explanation for the retention of configuration, involving an initial solvent molecule displacement of the chlorosulfite group (as SO_2 and chloride anion), followed by chloride ion displacement of the solvent moiety, has been suggested. In this case, two inversions lead to retention.

Example: Conversion of Alcohols to Alkyl Chlorides

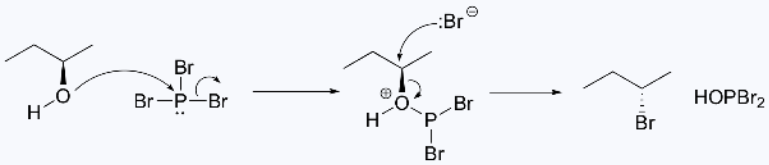
There's one important thing to note here: see the stereochemistry? It's been inverted.*(white lie alert – see below) That's an important difference between $SOCl_2$ and tosyl chloirde, TsCl, which leaves the stereochemistry alone. The TsCl reaction is studied in section 12.3.

Mechanisms

Since the reaction proceeds through a backside S_N2 reaction, there is inversion of configuration at the carbon



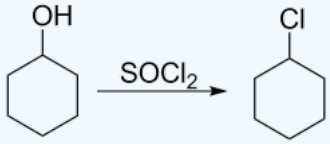
The PBr_3 reaction is thought to involve two successive S_N2-like steps:



Notice that these reactions result in inversion of stereochemistry in the resulting alkyl halide.

Exercises

2. Draw the mechanism of the reaction of thinoylchloride with cyclohexanol, given below.

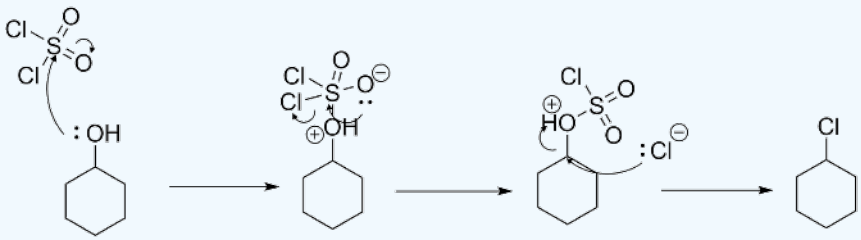


3. Draw the expected product of the reaction of cylohexanol with the following reagents.

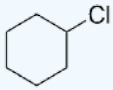
(a) $SOCl_2$ (b) PBr_3

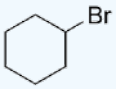
Answer

2.



3.

(a) 

(b) 

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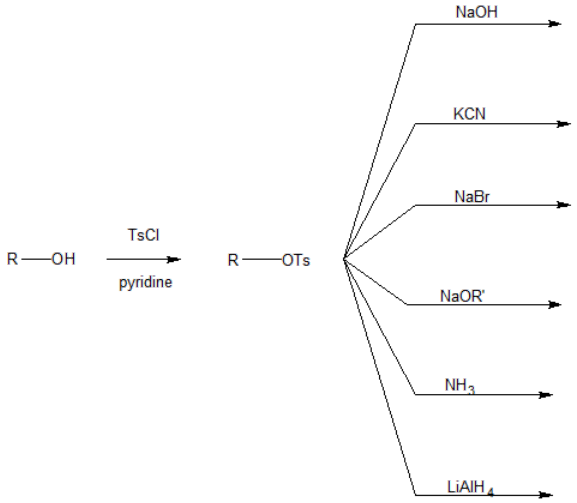
10.3: Alcohol conversion to Esters - Tosylate and Carboxylate

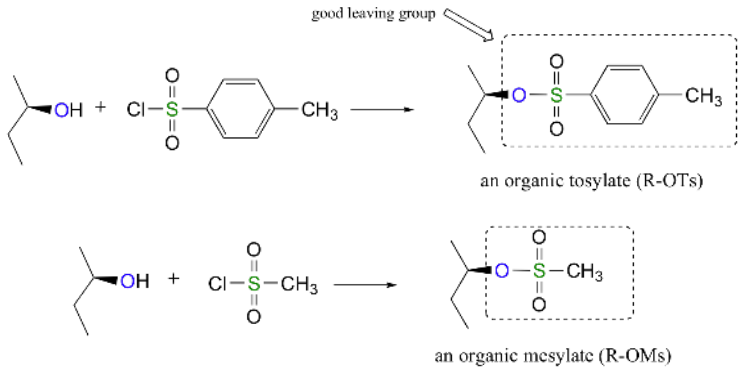
The poor leaving group of alcohols can be overcome by converting the hydroxyl group to a tosylate ester, an excellent leaving group. The tosylate ester undergoes subsequent reactions (typically S_N1 or S_N2) as part of a multiple step synthesis.



The synthesis of carboxylate esters (the other ester) is commonly the final step of a synthetic pathway.

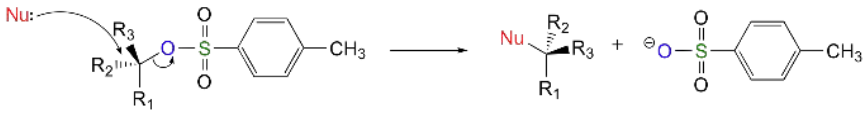
Tosylate Ester Formation

We can transform an alcohol group into a sulfonic ester using *para*-toluene sulfonyl chloride (Ts-Cl) or methanesulfonyl chloride (Ms-Cl), creating what is termed an organic **tosylate** or **mesylate:**

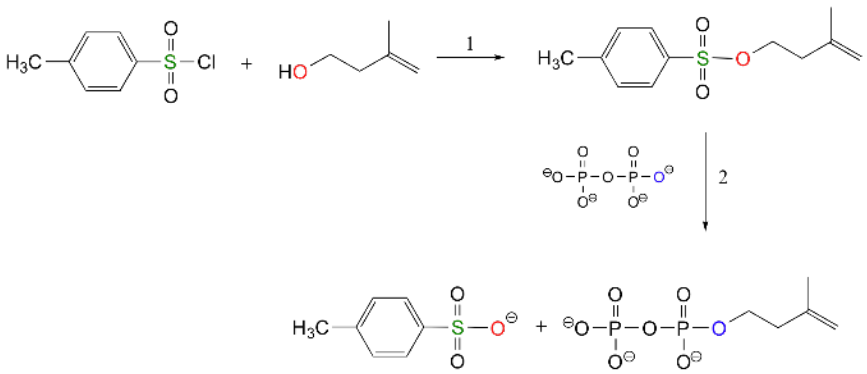


Notice that unlike the halogenation reactions of alcohols with thionyl chloride or phosphorous tribromide, conversion of an alcohol to a tosylate or mesylate proceeds with retention of configuration at the electrophilic carbon.

Tosylate/mesylate groups are excellent leaving groups in nucleophilic substitution reactions, due to resonance delocalization of the developing negative charge on the leaving oxygen.



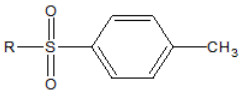
The laboratory synthesis of isopentenyl diphosphate - the 'building block' molecule used by nature for the construction of isoprenoid molecules such as cholesterol and b-carotene - was accomplished by first converting the alcohol into an organic tosylate (step 1), then displacing the tosylate group with an inorganic pyrophosphate nucleophile (step 2) (*J. Org. Chem* **1986**, *51*, 4768).



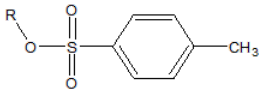
The major reactive species of tosylate chemistry are summarized below.

Tosyl Groups

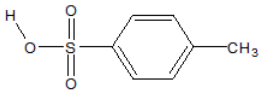
Ts
tosyl group



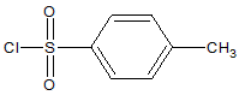
ROTs
tosylate ester



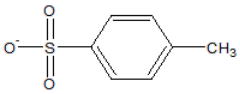
TsOH or p-TSA
tosic acid



TsCl
tosyl chloride

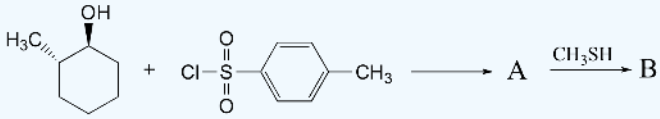


$^{-}$OTs
tosylate ion



Exercise

4. Predict the structures of A and B in the following reaction.



Answer

4.

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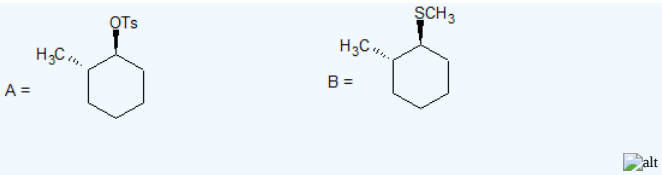
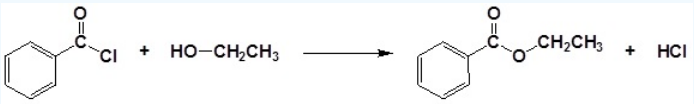


Conversion of Alcohols into Esters

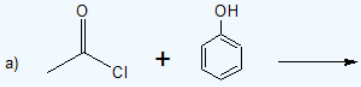
Acid chlorides react with alcohols to form esters

Example 10.3.1



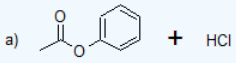
Exercise

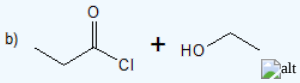
5. Predict the products or specify the reagents for the following reactions.



Answer

5.





Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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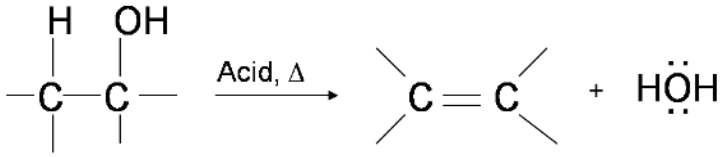
10.4: Dehydration Reactions of Alcohols

Dehydration of Alcohols to Yield Alkenes

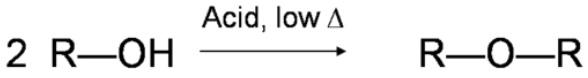
One way to synthesize alkenes is by dehydration of alcohols, a process in which alcohols undergo E1 or E2 mechanisms to lose water and form a double bond. The dehydration reaction of alcohols to generate alkene proceeds by heating the alcohols in the presence of a strong acid, such as sulfuric or phosphoric acid, at high temperatures.



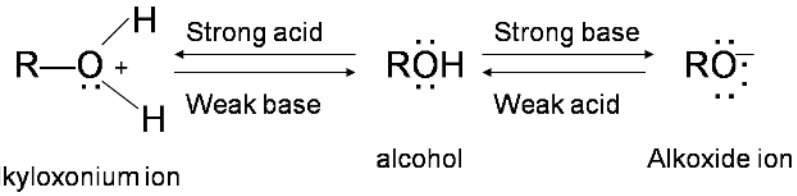
The required range of reaction temperature decreases with increasing substitution of the hydroxy-containing carbon:

- 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).



Alcohols are amphoteric; they can act as both acid or base. The lone pair of electrons on oxygen atom makes the –OH group weakly basic. Oxygen can donate two electrons to an electron-deficient proton. Thus, in the presence of a strong acid, R—OH acts as a base and protonates into the very acidic alkyloxonium ion +OH2 (The pKa value of a tertiary protonated alcohol can go as low as -3.8). This basic characteristic of alcohol is essential for its dehydration reaction with an acid to form alkenes.



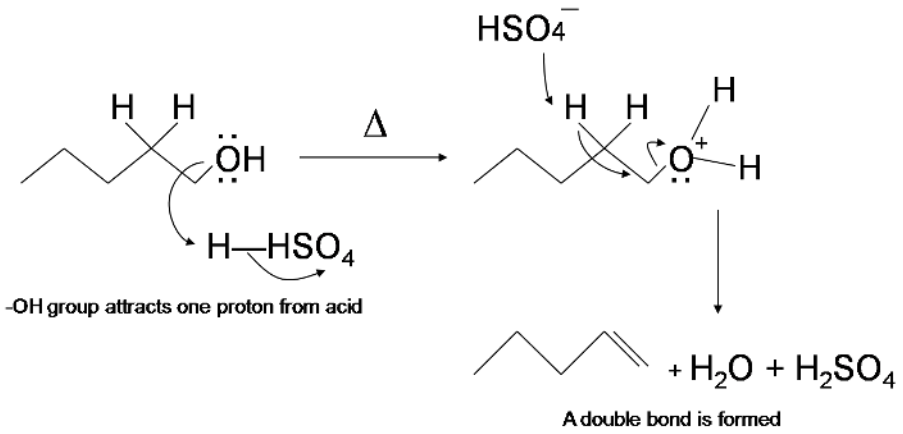
Mechanism for the Dehydration of Alcohol into Alkene

Different types of alcohols may dehydrate through a slightly different mechanism pathway. However, the general idea behind each dehydration reaction is that the –OH group in the alcohol donates two electrons to H^+ from the acid reagent, forming an alkyloxonium ion. This ion acts as a very good leaving group which leaves to form a carbocation. The deprotonated acid (the base) then reacts with the hydrogen adjacent to the carbocation and form a double bond.

Primary alcohols undergo bimolecular elimination (E2 mechanism) while secondary and tertiary alcohols undergo unimolecular elimination (E1 mechanism). The relative reactivity of alcohols in dehydration reactions is ranked as follows:

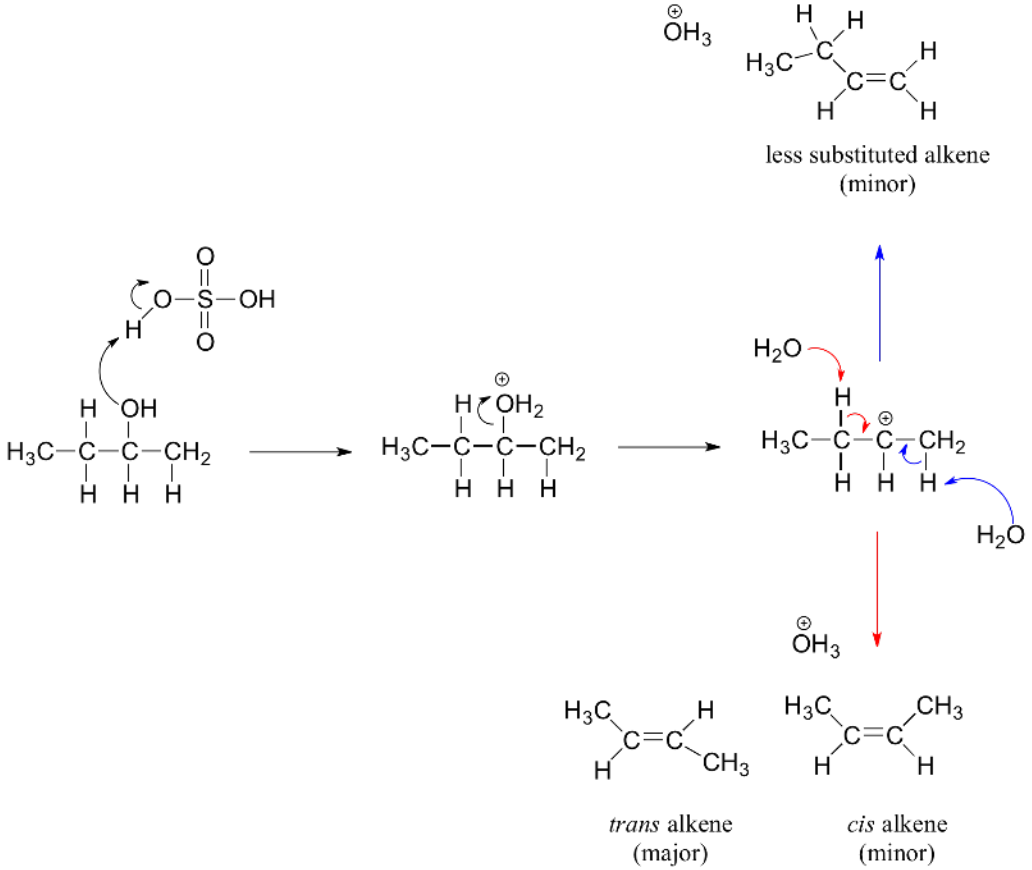
Methanol < *primary* < *secondary* < *tertiary*

Primary alcohols dehydrate through the E2 mechanism. The hydroxyl oxygen donates two electrons to a proton from sulfuric acid (H_2SO_4), forming an alkyloxonium ion. Then the conjugate base, HSO_4^-, reacts with one of the adjacent (beta) hydrogen atoms while the alkyloxonium ion leaves in a concerted process, forming a double bond.



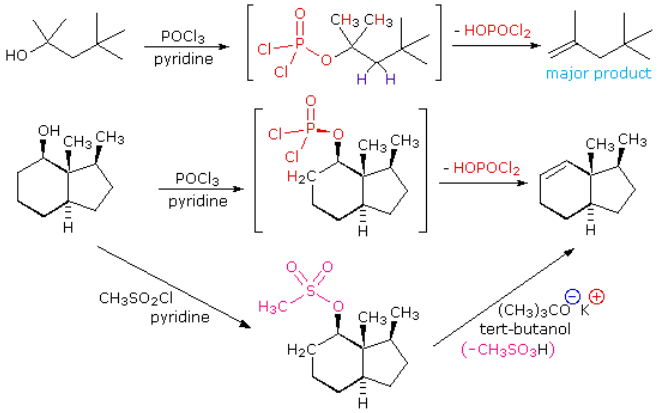
Secondary and tertiary alcohols dehydrate through the E1 mechanism. Similarly to the reaction above, secondary and tertiary –OH protonate to form alkyloxonium ions. However, in this case the ion leaves first and forms a carbocation as the reaction intermediate. The water molecule (which is a stronger base than the HSO_4^- ion) then abstracts a proton from an adjacent carbon to form a double bond. Notice in the mechanism below that the alkene formed depends on which 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. Recall that according to Zaitsev's Rule, the more substituted alkenes are formed preferentially because they are more stable than less substituted alkenes. Additionally, trans alkenes are more stable than cis alkenes and are also the major product formed. For the example below, the trans diastereomer of the 2-butene product is most abundant.

Dehydration reaction of secondary alcohol



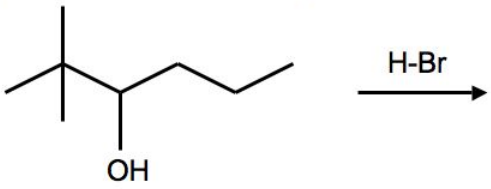
The dehydration mechanism for a tertiary alcohol is analogous to that shown above for a secondary alcohol.

The E2 elimination of 3º-alcohols under relatively non-acidic conditions may be accomplished by treatment with phosphorous oxychloride ($POCl_3$) in pyridine. This procedure is also effective with hindered 2º-alcohols, but for unhindered and 1º-alcohols an S_N2 chloride ion substitution of the chlorophosphate intermediate competes with elimination. Examples of these and related reactions are given in the following figure. The first equation shows the dehydration of a 3º-alcohol. The predominance of the non-Zaitsev product (less substituted double bond) is presumed due to steric hindrance of the methylene group hydrogen atoms, which interferes with the approach of base at that site. The second example shows two elimination procedures applied to the same 2º-alcohol. The first uses the single step POCl3 method, which works well in this case because SN2 substitution is retarded by steric hindrance. The second method is another example in which an intermediate sulfonate ester confers halogen-like reactivity on an alcohol. In every case the anionic leaving group is the conjugate base of a strong acid.

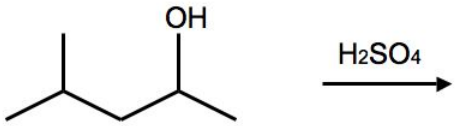


Practice Problems (aka Exercises)

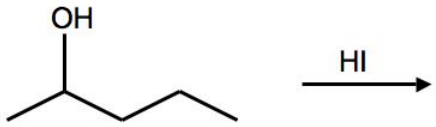
1) Please show the arrow pushing mechanism and the major final product:



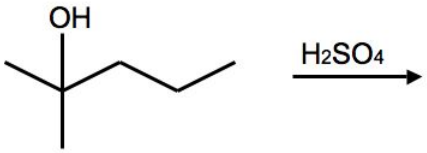
2) Please show the mechanism with **hydride shift** and show the final product:



3) Show both major and minor products of the given reaction:

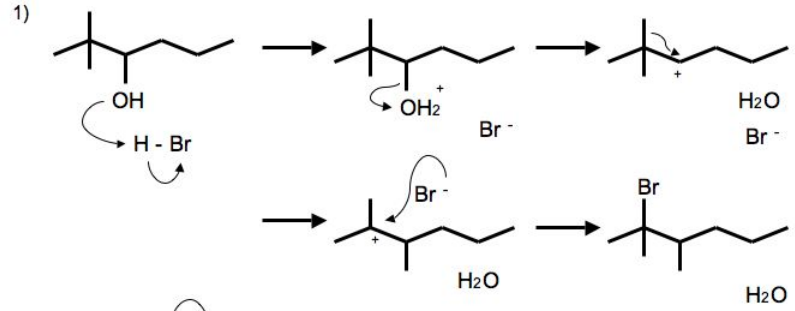


4) Show both major and minor products of the given reaction:

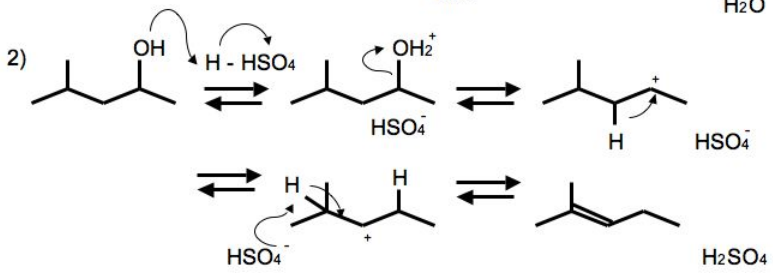


Answers to Practice Problems:

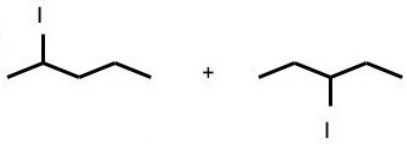
1)



2)



3)

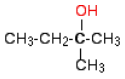


Equal amounts

4)

Major product Minor product

2-methylpropan-2-ol

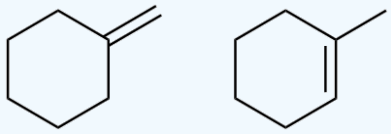


2-methylbutan-2-ol

Exercises

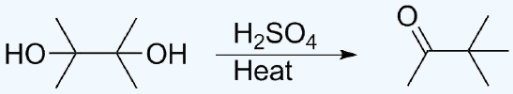
6. Starting with cyclohexanol, describe how you would prepare cyclohexene.

7. In the dehydration of 1-methylcyclohexanol, which product is favored?



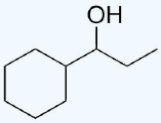
8.

In the dehydration of this diol the resulting product is a ketone. Draw the mechanism of its formation. (Hint a rearrangement occurs)



9.

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.



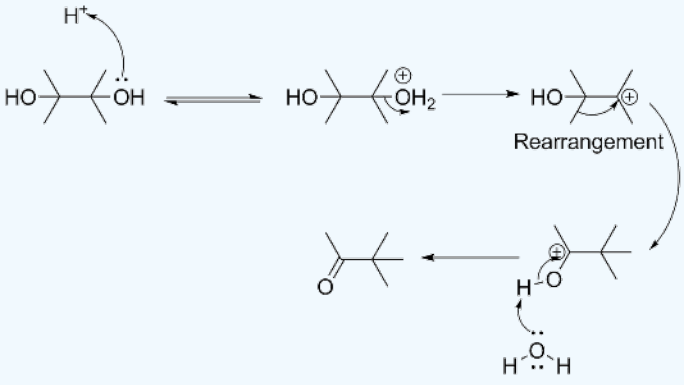
Answer

6. H_2SO_4 with heat since there are no concerns about C+ rearrangement

7. The more substituted alkene is favored, as more substituted alkenes are relatively lower in energy.

8.

This reaction is known as the Pinacol rearrangement.



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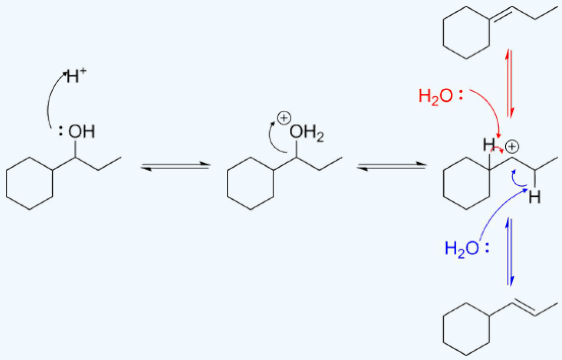
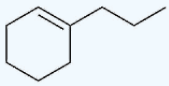
Note how the carbocation after the rearrangement is resonance stabilized by the oxygen

9. Note: While the mechanism is instructive for the first part of the this answer. The carbocation rearrangement would occur and determine the major and minor products as explained in the second part of this answer.



The major product of this mechanism would be the more highly substituted alkene, or the product formed from the red arrows.

Note: With the secondary carbocation adjacent a tertiary carbon center, a 1,2 hydride shift (rearrangement) would occur to form a tertiary carbocation and vcompound below would be the major product. The minor product being the same product as the one formed from the red arrows.



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10.5: Oxidation States of Alcohols and Related Functional Groups

Introduction

You are undoubtedly already familiar with the general idea of oxidation and reduction: you learned in general chemistry that when a compound or atom is oxidized it loses electrons, and when it is reduced it gains electrons. You also know that oxidation and reduction reactions occur in pairs: if one species is oxidized, another must be reduced at the same time - thus the term 'redox reaction'.

Most of the redox reactions you have seen previously in general chemistry probably involved the flow of electrons from one metal to another, such as the reaction between copper ion in solution and metallic zinc:

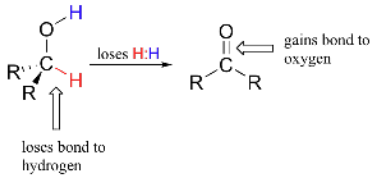
$$Cu^{+2}_{(aq)} + Zn_{(s)} \rightarrow Cu_{(s)} + Zn^{+2}_{(aq)} \tag{16.1.1}$$

In organic chemistry, redox reactions look a little different. Electrons in an organic redox reaction often are transferred in the form of a hydride ion - a proton and two electrons. Because they occur in conjunction with the transfer of a proton, these are commonly referred to as **hydrogenation** and **dehydrogenation** reactions: a hydride plus a proton adds up to a hydrogen (H_2) molecule. Be careful - do not confuse the terms **hydrogenation** and **dehydrogenation** with **hydration** and **dehydration** - the latter refer to the gain and loss of a *water* molecule (and are *not* redox reactions), while the former refer to the gain and loss of a *hydrogen* molecule.

Oxidation and Reduction - The Organic Chemistry View

When a carbon atom in an organic compound loses a bond to hydrogen and gains a new bond to a heteroatom (or to another carbon), we say the compound has been dehydrogenated, or oxidized. A very common biochemical example is the oxidation of an alcohol to a ketone or aldehyde:

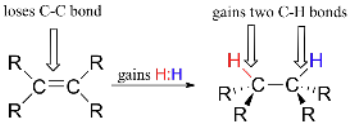
Dehydrogenation (oxidation) of an alcohol



When a carbon atom loses a bond to hydrogen and gains a bond to a heteroatom (or to another carbon atom), it is considered to be an oxidative process because hydrogen, of all the elements, is the least electronegative. Thus, in the process of dehydrogenation the carbon atom undergoes an overall loss of electron density - and loss of electrons is oxidation.

Conversely, when a carbon atom in an organic compound gains a bond to hydrogen and loses a bond to a heteroatom (or to another carbon atom), we say that the compound has been hydrogenated, or reduced. The hydrogenation of a ketone to an alcohol, for example, is overall the reverse of the alcohol dehydrogenation shown above. Illustrated below is another common possibility, the hydrogenation (reduction) of an alkene to an alkane.

Hydrogenation (reduction) of an alkene

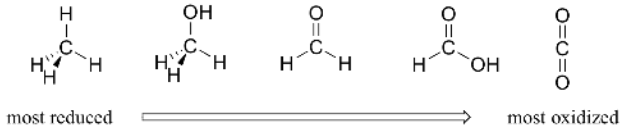


Hydrogenation results in *higher* electron density on a carbon atom(s), and thus we consider process to be one of reduction of the organic molecule.

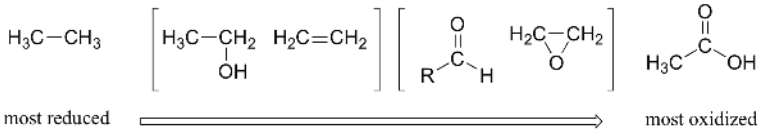
Notice that neither hydrogenation nor dehydrogenation involves the gain or loss of an oxygen *atom*. Reactions which *do* involve gain or loss of one or more oxygen atoms are usually referred to as 'oxygenase' and 'reductase' reactions.

For the most part, when talking about redox reactions in organic chemistry we are dealing with a small set of very recognizable functional group transformations. It is therefore very worthwhile to become familiar with the idea of 'oxidation states' as applied to organic functional groups. By comparing the relative number of bonds to hydrogen atoms, we can order the familiar functional groups according to oxidation state. We'll take a series of single carbon compounds as an example. Methane, with four carbon-

hydrogen bonds, is highly reduced. Next in the series is methanol (one less carbon-hydrogen bond, one more carbon-oxygen bond), followed by formaldehyde, formate, and finally carbon dioxide at the highly oxidized end of the group.



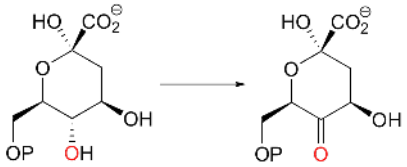
This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



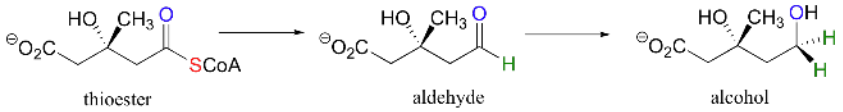
Alkanes are highly reduced, while alcohols - as well as alkenes, ethers, amines, sulfides, and phosphate esters - are one step up on the oxidation scale, followed by aldehydes/ketones/imines and epoxides, and finally by carboxylic acid derivatives (carbon dioxide, at the top of the oxidation list, is specific to the single carbon series).

Notice that in the series of two-carbon compounds above, ethanol and ethene are considered to be in the same oxidation state. You know already that alcohols and alkenes are interconverted by way of addition or elimination of water. When an alcohol is dehydrated to form an alkene, one of the two carbons loses a C-H bond and gains a C-C bond, and thus is oxidized. However, the other carbon loses a C-O bond and gains a C-C bond, and thus is considered to be reduced. Overall, therefore, there is no change to the oxidation state of the molecule.

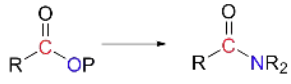
You should learn to recognize when a reaction involves a change in oxidation state in an organic reactant. Looking at the following transformation, for example, you should be able to quickly recognize that it is an oxidation: an alcohol functional group is converted to a ketone, which is one step up 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.



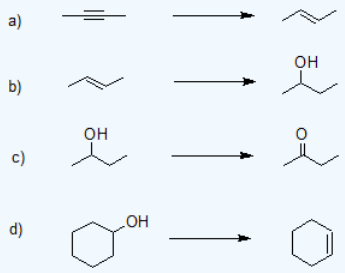
An acyl transfer reaction (for example the conversion of an acyl phosphate to an amide) is *not* considered to be a redox reaction - the oxidation state of the organic molecule is does not change as substrate is converted to product, because a bond to one heteroatom (oxygen) has simply been traded for a bond to another heteroatom (nitrogen).



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.

Exercises

10. Indicate whether the following reactions are oxidations [O], reductions [H], hydrations, or dehydrations.



Answer

10.

a) reduction

b) hydration

c) oxidation

d) dehydration

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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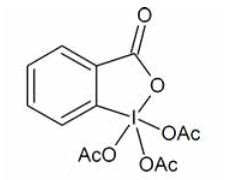
10.6: Oxidation Reactions of Alcohols

Oxidizing agents

The oxidizing agent commonly shown is a solution of sodium or potassium dichromate(VI) acidified with dilute sulfuric acid. If oxidation occurs, the orange solution containing the dichromate(VI) ions is reduced to a green solution containing chromium(III) ions. The electron-half-equation for this reaction is

$$Cr_2O_7^{2-} + 14H^+ + 6e^- \rightarrow 2Cr^{3+} + 7H_2O \tag{17.7.1}$$

- $K_2C_r2O_7$ potassium dichromate
- CrO_3 Chromium Trioxide
- 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. Both reagents are used along with H_2SO_4, H_2O



Dess–Martin periodinane (DMP)

Primary alcohols

Primary alcohols can be oxidized to either aldehydes or carboxylic acids depending on the reaction conditions. In the case of the formation of carboxylic acids, the alcohol is first oxidized to an aldehyde which is then oxidized further to the acid.

Full oxidation to carboxylic acids

You need to use an excess of the oxidizing agent and make sure that the aldehyde formed as the half-way product stays in the mixture. The alcohol is heated under reflux with an excess of the oxidizing agent. When the reaction is complete, the carboxylic acid is distilled off. The full equation for the oxidation of ethanol to ethanoic acid is:

$$3CH_3CH_2OH + 2Cr_2O_7^{2-} + 16H+ \rightarrow 3CH_3COOH + 4Cr^{3+} + 11H_2O \tag{17.7.1}$$

The more usual simplified version looks like this:

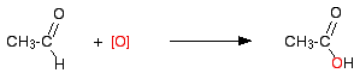
$$CH_3CH_2OH + 2[O] \rightarrow CH_3COOH + H_2O \tag{17.7.2}$$

Alternatively, you could write separate equations for the two stages of the reaction - the formation of ethanal and then its subsequent oxidation.

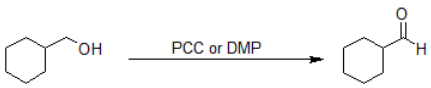
$$CH_3CH_2OH + [O] \rightarrow CH_3CHO + H_2O \tag{17.7.3}$$

$$CH_3CHO + [O] \rightarrow CH_3COOH \tag{17.7.4}$$

This is what is happening in the second stage:

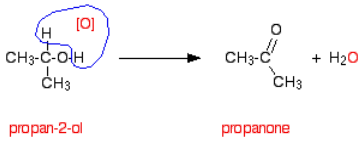


Partial oxidation to carboxylic acids



Secondary alcohols

Secondary alcohols are oxidized to ketones - and that's it. For example, if you heat the secondary alcohol propan-2-ol with sodium or potassium dichromate(VI) solution acidified with dilute sulfuric acid, you get propanone formed. Playing around with the reaction conditions makes no difference whatsoever to the product. Using the simple version of the equation and showing the relationship between the structures:

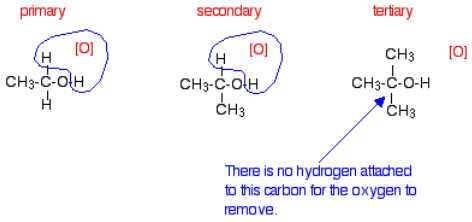


If you look back at the second stage of the primary alcohol reaction, you will see that an oxygen "slotted in" between the carbon and the hydrogen in the aldehyde group to produce the carboxylic acid. In this case, there is no such hydrogen - and the reaction has nowhere further to go.

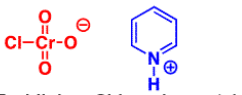
Tertiary alcohols

Tertiary alcohols are not oxidized by acidified sodium or potassium dichromate(VI) solution - there is no reaction whatsoever. If you look at what is happening with primary and secondary alcohols, you will see that the oxidizing agent is removing the hydrogen from the -OH group, and a hydrogen from the carbon atom attached to the -OH. Tertiary alcohols don't have a hydrogen atom attached to that carbon.

You need to be able to remove those two particular hydrogen atoms in order to set up the carbon-oxygen double bond.



Oxidation of Primary Alcohols by PCC - a closer look

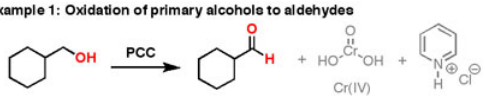


Pyridinium chlorochromate (PCC) is a milder version of chromic acid.

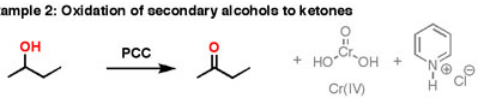
PCC oxidizes alcohols one rung up the oxidation ladder, from primary alcohols to aldehydes and from secondary alcohols to ketones. Unlike chromic acid, PCC will not oxidize aldehydes to carboxylic acids. Similar to or the same as: CrO_3 and pyridine (the Collins reagent) will also oxidize primary alcohols to aldehydes. Here are two examples of PCC in action.

- If you add one equivalent of PCC to either of these alcohols, you obtain the oxidized version. The byproducts (featured in grey) are Cr(IV) as well as pyridinium hydrochloride.
- One has to be careful with the amount of water present in the reaction. If water were present, it can ad to the aldehyde to make the hydrate, which could be further oxidized by a second equivalent of PCC were it present. This is not a concern with ketones, since there is no H directly bonded to C.

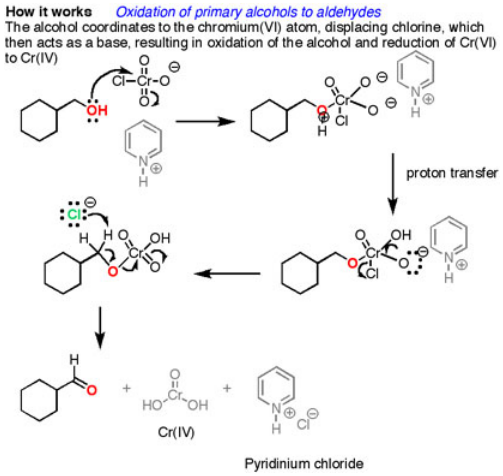
Example 1: Oxidation of primary alcohols to aldehydes



Example 2: Oxidation of secondary alcohols to ketones



How does it work? Oxidation reactions of this sort are actually a kind of elimination reaction. We're going from a carbon-oxygen single bond to a carbon-oxygen double bond. The elimination reaction can occur because we're putting a good leaving group on the oxygen, namely the chromium, which will be displaced when the neighboring C-H bond is broken with a base.

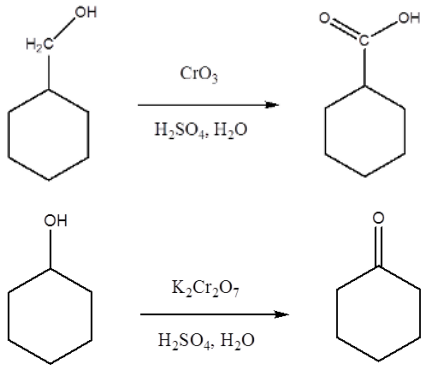


In the first step, the oxygen on the chromium reacts with the alcohol hydroxy group to form the Cr-O bond. Secondly, a proton on the (now positive) OH is transferred to one of the oxygens of the chromium, possibly through the intermediacy of the pyridinium salt. A chloride ion is then displaced, in a 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. [aside: I've drawn the base as Cl^- although there are certainly other species which could also act as bases here (such as an alcohol). 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.] The electrons from the C-H bond move to form the C-O bond, and in the process break the O-Cr bond, and Cr(VI) becomes Cr(IV) in the process (drawn here as O=Cr(OH)2).

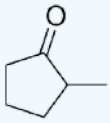
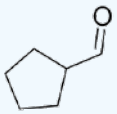
Real life notes: If you end up using PCC in the lab, don't forget to add molecular sieves or Celite or some other solid to the bottom of the flask, because otherwise you get a nasty brown tar that is a real major pain to clean up. The toxicity and mess associated with chromium has spurred the development of other alternatives like TPAP, IBX, DMP, and a host of other neat reagents you generally don't learn about until grad school.

Examples



Exercises

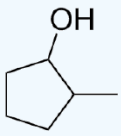
11. Draw the alcohol that the following ketones/aldehydes would have resulted from if oxidized. What oxidant could be used?

(a)  (b) 

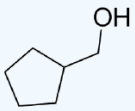
12. Show the products of the oxidation of 1-propanol and 2-propanol with chromic acid in aqueous solution.

Answer

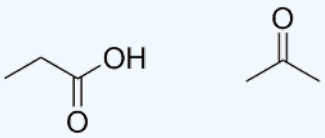
11. Any oxidant capable of oxidizing an alcohol to a ketone would work, such as the Jones reagent (CrO_3, H_2SO_4, H_2O), PCC, or Dess-Martin periodinane.

(a) 

(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.



12. The answers are correlated with the question.



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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

James Ashenhurst (MasterOrganicChemistry.com)

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10.7: Determining Alcohol Classifications in the Lab - alternate reactions

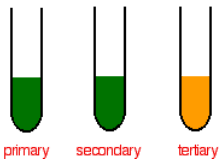
Using alcohol reactivity to distinguish between classifications

The presence of an alcohol can be determined with test reagents that react with the -OH group. The initial test to identify alcohols is to take the neutral liquid, free of water and add solid phosphorus(V) chloride. A a burst of acidic steamy hydrogen chloride fumes indicate the presence of an alcohol. Subsequent tests are needed to distinguish between alcohol classifications.

Determining the tertiary alcohol

A few drops of the alcohol are added to a test tube containing potassium dichromate(VI) solution acidified with dilute sulfuric acid. The tube is warmed in a hot water bath.

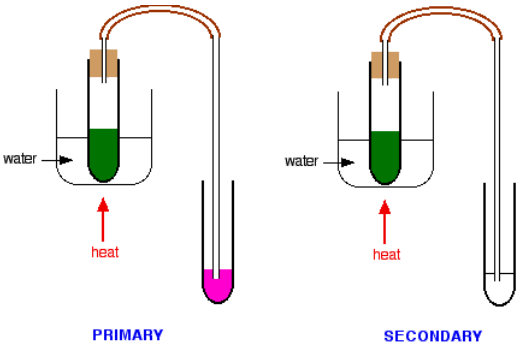
After heating, the following colors are observed:



In the case of a primary or secondary alcohols, the orange solution turns green. The Schiff's test will need to be performed to distinguish between the primary and secondary alcohols. With a tertiary alcohol, there is no color change.

Schiff's Reagent - Distinguishing between the primary and secondary alcohols

Schiff's reagent is a fuchsian dye decolorized by passing sulfur dioxide through it. In the presence of even small amounts of an aldehyde, it turns bright magenta. It must, however, be used absolutely cold, because ketones react with it very slowly to give the same color. Heat obviously causes a faster color change, but is potentially confusing because of the competing ketone reaction. While warming the reaction mixture in the hot water bath, pass any vapors produced through some Schiff's reagent.



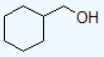
- If the Schiff's reagent quickly becomes magenta, then an aldehyde was produced from a primary alcohol.
- If there is no color change in the Schiff's reagent, or only a trace of pink color within a minute or so, then no aldehyde was produced and a primary alcohol is not present.

A secondary alcohol is identified by the color change with the acidified potassium dichromate(VI) solution and the absence of a color change with the Schiff's reagent might.

Exercise

13. The chromic acid oxidation test and Schiff's test are performed on the three alcohols shown below. Describe the expected test results.

a)

b) 

c)

Answer

13.

a) The chromic acid solution turns green, but the Schiff's reagent remains colorless.

b) The chromic acid solution turns green, and the Schiff's reagent turns magenta.

c) The chromic acid solution remains orance, and the Schiffs reagent remains colorless.

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- Jim Clark (Chemguide.co.uk)

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10.8: Protection of Alcohols

Introduction

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.

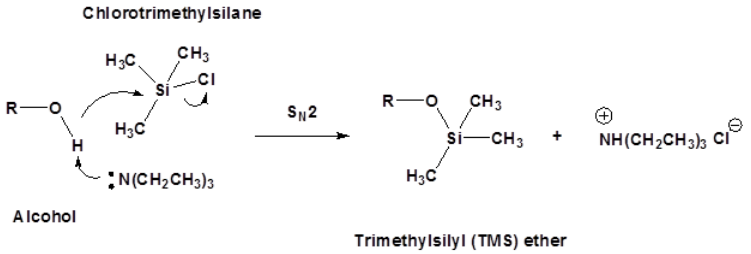
When situations like this occurs, chemists circumvent the problem by protecting the interfering functional group.

Functional group protection involves three steps:

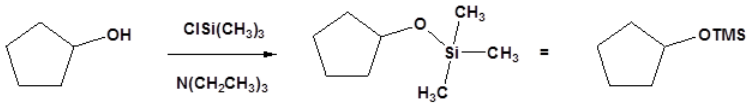
1. Blocking the interfering functionality by introducing a protecting group.
2. Performing the intended reaction.
3. Removing the protecting group and reforming the original functional group.

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. Chlorotrimethylsilane is often used in conjuction with a base, such as triethylamine, The base helps to form the alkoxide anion and remove the HCl produced by the reaction.

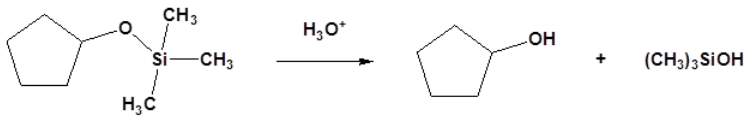
General Reaction



Example

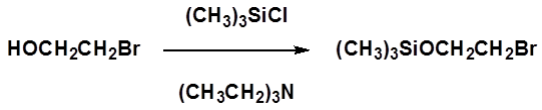


The silyl ether protecting group can be removed by reaction with an aqueous acid or the fluoride ion.



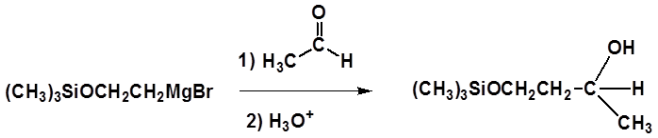
By utilizing a protecting group a Grignad reagent can be formed and reacted on a halo alcohol.

1) Protect the Alcohol

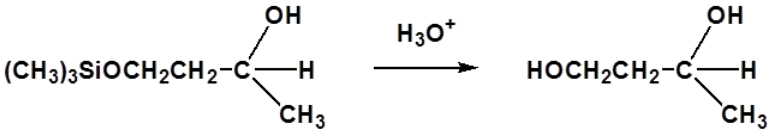


2) Form the Grignard Reagent

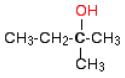
3) Perform the Grignard Reaction



4) Deprotection



2-methylpropan-2-ol



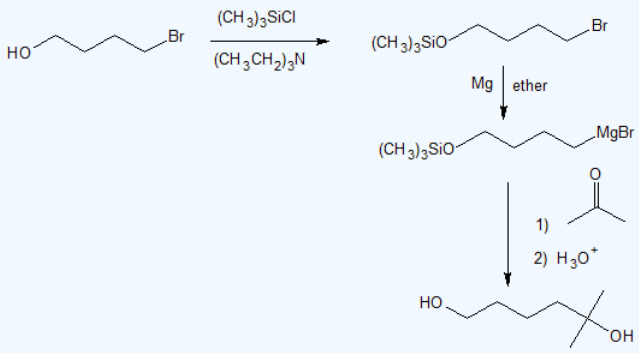
2-methylbutan-2-ol

Exercise

14. Propose a multiple-step synthesis to transform 4-bromo-1-butanol into 5-methylhexane-1,5-diol.

Answer

14.



Contributors and Attributions

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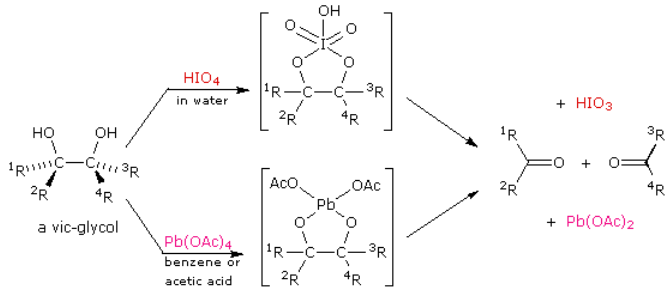
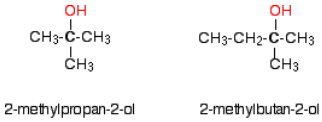
10.9: Cleavage of Diols

Glycol Cleavage

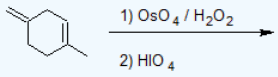
The vicinal glycols prepared by alkene hydroxylation (reaction with osmium tetroxide or permanganate) are cleaved to aldehydes and ketones in high yield by the action of **lead tetraacetate** ($Pb(OAc)_4$) or **periodic acid** (HIO_4). This oxidative cleavage of a carbon-carbon single bond provides a two-step, high-yield alternative to ozonolysis, that is often preferred for small scale work involving precious compounds. A general equation for these oxidations is shown below. As a rule, cis-glycols react more rapidly than trans-glycols, and there is evidence for the intermediacy of heterocyclic intermediates (as shown), although their formation is not necessary for reaction to occur.





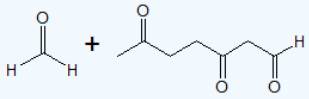
Exercise

15. Predict the product of the reaction below.



Answer

15.



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10.10: Reactions of Alkoxides

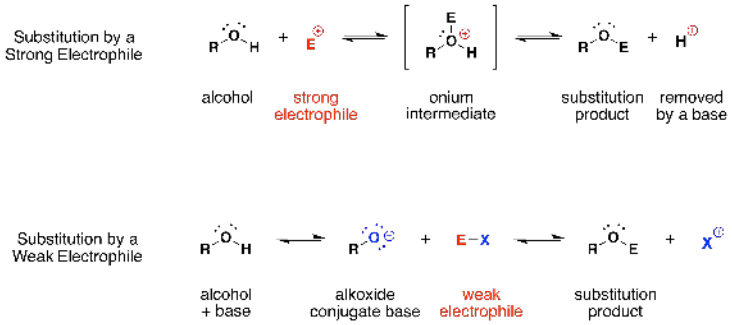
Introduction

The hydrogen atom of a hydroxyl group is ionizable and can be replaced by other substituents as illustrated in the reactions below. The first reaction shows simple alcohols with sodium (and sodium hydride). The second reaction shows the isotopic exchange that occurs when mixing an alcohol with deuterium oxide (heavy water). This exchange, which is catalyzed by acid or base, is rapid under normal conditions because it is difficult to avoid traces of these catalysts in most experimental systems.

$$2\ R–O–H + 2\ Na \longrightarrow 2\ R–O^{(-)}Na^{(+)} + H_2$$

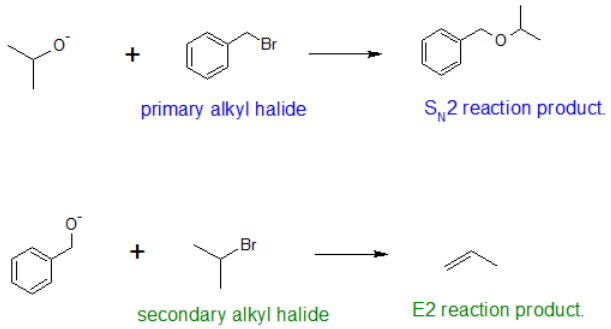
$$R–O–H + D_2O \rightleftharpoons R–O–D + D–O–H$$

The mechanism by which these substitution reactions proceed is straightforward. The oxygen atom of an alcohol is nucleophilic; therefore, it is prone to react with electrophiles. The resulting "onium" intermediate then loses a proton to a base, forming the substitution product. If a strong electrophile is not present, then the nucleophilicity of the oxygen may be enhanced by conversion to its conjugate base (an alkoxide). This powerful nucleophile then reacts with weak electrophiles. These two variations of the substitution mechanism are illustrated in the following diagram.



Williamson Ether Synthesis

Alkyl substitution of the hydroxyl group creates ethers. This reaction provides examples of both strong electrophilic substitution (first equation below) and weak electrophilic substitution (second equation). The latter S_N2 reaction is known as the **Williamson ether synthesis** and is generally only used with 1º alkyl halide reactants because the strong alkoxide base leads to E2 elimination with 2º and 3º alkyl halides.

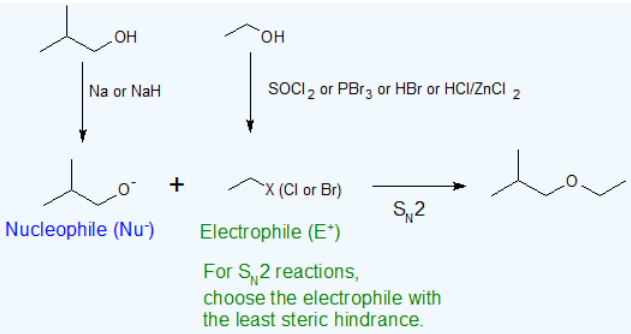


Exercise

16. Show how you would use the Williamson Ether synthesis to make 1-ethoxy-2-methylpropane from isobutyl alcohol and ethanol.

Answer

16.



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10.11: Biological Oxidation - an introduction

Foundation

All reactions which involve electron flow are considered oxidation-reduction reactions. The basic definition can be defined as: One reactant is oxidized (loses electrons), while another is reduced (gains electrons). A couple of basic oxidation-reduction or "redox" example's are given here.

Example 1

The reaction of magnesium metal with oxygen, involves the oxidation of magnesium

$$2Mg(s) + O_2(g) \rightarrow 2MgO(s) \tag{10.11.1}$$

Since the magnesium solid is oxidized, we expect to see a loss of electrons. Similarly, since oxygen must therefore be reduced, we should see a gain of electrons.

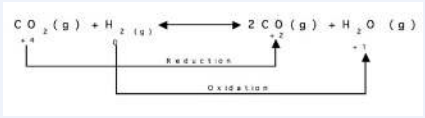
As the magnesium is oxidized there is a loss of 2 electrons while simultaneously, oxygen gains those two electrons. Another example of a redox reaction is with the two gasses CO_2 and H_2. This redox reaction also demonstrates the importance of implementing "oxidation numbers" in the methodology of redox reactions, allowing for the determination of which reactant is being reduced and which reactant is being oxidized.

Example 2

The reaction of carbon dioxide gas with hydrogen gas, involving the oxidation of hydrogen

$$CO_2(g) + H_2(g) \rightarrow 2CO(g) + H_2O(g) \tag{10.11.2}$$

Since the hydrogen gas is being oxidized (reductant), we expect to see an overall loss of electrons for the resulting molecule. Similarly, we expect to see a gain in the overall number of electrons for the resulting molecule of the oxidant (CO_2).



Here it is possible to infer that the carbon of CO_2 is being reduced by review of its unique oxidation number. Such that, C (of CO_2) goes from an oxidation number of +4 to C (of CO) having an oxidation number of +2, representing a loss of two electrons. Similarly, H_2 is noted as going from an oxidation number of 0 to +1, or gaining one electron in a reduction process. For more information on oxidation numbers, review the following link: Oxidation-Reduction Reactions

A Basic Biological Model

The flow of electrons is a vital process that provides the necessary energy for the survival of all organisms. The primary source of energy that drives the electron flow in nearly all of these organisms is the radiant energy of the sun, in the form of electromagnetic radiation or Light. Through a series of nuclear reactions, the sun is able to generate thermal energy (which we can feel as warmth) from electromagnetic radiation (which we perceive as light). However, the particular wavelength of the electromagnetic spectrum we are able to detect with the human eye is only between 400 and 700 nm in wavelength. It should therefore be noted that the visible part of the electromagnetic spectrum is actually a small percentage of the whole; where a much greater percentage remains undetectable for the human eye.

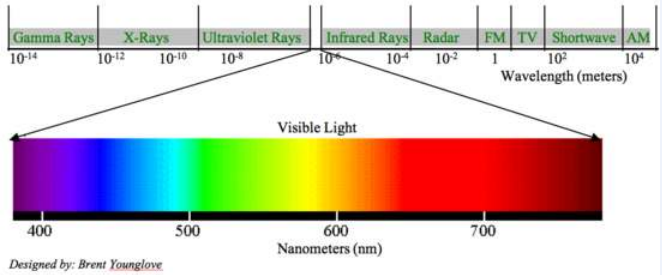


Figure 1: The electromagnetic spectrum with an emphasis on the visible light region

In physics, the use of the term "light" refers to electromagnetic radiation of any wavelength, independent of its detectability for the human eye. For plants, the upper and lower ends of the visible spectrum are the wavelengths that help drive the process of splitting water (H_2O) during photosynthesis, to release its electrons for the biological reduction of carbon dioxide (CO_2) and the release of diatomic oxygen (O_2) to the atmosphere. It is through the process of photosynthesis that plants are able to use the energy from light to convert carbon dioxide and water into the chemical energy storage form called glucose.

Plants represent one of the most basic examples of biological oxidation and reduction. The chemical conversion of carbon dioxide and water into sugar (glucose) and oxygen is a light-driven reduction process:

$$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2 \tag{10.11.3}$$

The process by which non photosynthetic organisms and cells obtain energy, is through the consumption of the energy rich products of photosynthesis. By oxidizing these products, electrons are passed along to make the products carbon dioxide, and water, in an environmental recycling process. The process of oxidizing glucose and atmospheric oxygen allowed energy to be captured for use by the organism that consumes these products of the plant. The following reaction represents this process:

$$C_6H_{12}O_6 + O_2 \rightarrow 6CO_2 + 6H_2O + Energy \tag{10.11.4}$$

It is therefore through this process that heterotrophs (most generally "animals" which consume other organisms obtain energy) and autotrophs (plants which are able to produce their own energy) participate in an environmental cycle of exchanging carbon dioxide and water to produce energy containing glucose for organismal oxidation and energy production, and subsequently allowing the regeneration of the byproducts carbon dioxide and water, to begin the cycle again. Therefore, these two groups of organisms have been allowed to diverge interdependently through this natural life cycle.

Physical Chemistry's Understanding

Biological oxidation-reduction reactions, or simply *biological oxidations* utilize multiple stages or processes of oxidation to produce large amounts of Gibbs energy, which is used to synthesize the energy unit called adenosine triphosphate or ATP. To efficiently produce ATP, the process of glycolysis must be near an abundance of oxygen. Since glycolysis by nature is not an efficient process, if it lacks sufficient amounts of oxygen the end product pyruvate, is reduced to lactate with NADH as the reducing agent. However, in a more favorable aerobic process, the degradation of glucose through glycolysis proceeds with two additional processes known as the *citric acid cycle* and the terminal *respiratory chain;* yielding the end products carbon dioxide and water, which we exhale with each breath.

Figure 2: The three main processes for the breakdown of glucose into carbon dioxide and water

The products NADH and $FADH_2$ formed during glycolysis and the citric acid cycle are able to reduce molecular oxygen (O_2) thereby releasing large amounts of Gibbs energy used to make ATP. The process by which electrons are transferred from NADH or $FADH_2$ to O_2 by a series of electron transfer carriers, is known as *oxidative phosphorylation*. It is through this process that ATP is able to form as a result of the transfer of electrons.

Thee specific examples of redox reactions that are used in biological processes, involving the transfer of electrons and hydrogen ions as follows. During some biological oxidation reactions, there is a simultaneous transfer of hydrogen ions with electrons (1). In other instances, hydrogen ions may be lost by the substance being oxidized while transferring only its electrons to the substance being reduced (2). A third type of biological oxidation might involve only a transfer of electrons (3). It should be noted that biological oxidation rarely proceeds in a direct manner, and generally involves complex mechanisms of several enzymes. The outline below recaps the three processes of biological oxidation stated above, in descending order.

***Table 1**: Transfer of hydrogen ions and electrons for the general reaction scheme of A + B with intermediate stage shown*

Reactants	Intermediate Stage	Products
$AH_2 + B$	$[A + 2H^+ + 2e^- + B]$	$A + BH_2$
$AH_2 + B$	$[A + 2H^+ + 2e^- + B]$	$A + B^{2-} + 2H^+$
$A^{2-} + B$	$[A + 2e^- + B]$	$A + B^{2-}$

In the last stage of the metabolic process (the terminal respiratory chain), the sequence by which electrons are carried is determined by relative redox potentials. The carrier molecules used to transfer electrons in this stage are called cytochromes, which are an electron-carrying protein containing a heme group. The iron atom of each cytochrome molecule can exist either in the oxidized (Fe^{3+}) or reduced (Fe^{2+}) form. Within the terminal respiratory chain, each carrier molecule alternates between the reduced state and the oxidized state, with molecular oxygen as the final electron acceptor at the end.

Figure 3. The terminal respitory chain showing electron transport and phosphorylation. Electrons from the citric acid cycle are transferred from one carrier to another, where each carrier alternates between the reduced and oxidized state. Molecular oxygen represents the final electron acceptor.

It is through the knowledge of redox potentials, that the knowledge of biological processes can be further expanded. The standard reduction potential is denoted as $E^{o'}$ and is often based on the hydrogen electrode scale of pH 7, rather than pH 0, a common reference point for listed values. Moreover, the superscript symbol (^{o}) denotes standard-state conditions, while the adjacent superscript symbol (') denotes the pH scale of 7 for biochemical processes.

It therefore becomes possible to trace the energy transfer in cells back to the fundamental flow of electrons from one particular molecule to another. Where this electron flow occurs via the physics principle of higher potential to lower potential; similar to a ball rolling down a hill, as opposed to the opposite direction. All of these reactions involving electron flow can be attributed to the basic definition of the oxidation-reduction pathway stated above.

References

1. Chang, Raymond. *PHYSICAL CHEMISTRY for the Chemical and Biological Sciences* . 3rd. Sausalito, CA: University Science Books , 373-389. Print.
2. Nelson, David, and Michael Cox. *LEHNINGER PRINCIPLES OF BIOCHEMISTRY* . 5th . New York, NY: Freeman and Company, 22. Print.

Contributors and Attributions

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DS — DekiScript —

No description

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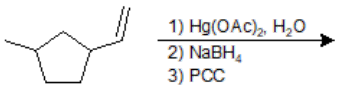
10.12: Additional Exercises

14-1 What is the IUPAC name for the product of the following reaction?



a) 1-(3-methylcyclopentyl)ethan-1-ol

b) (3-methylcyclopentyl)acetaldehyde

c) 1-(3-methylcyclopentyl)ethan-1-one

d) 1-(3-methylcyclopentyl)ethane-1,2-diol

14-2 Convert 3-chlorocyclohexanol to the following products. Any of these products can be used as the reactant in any subsequent part.

(a) 3-chlorocyclohexane

(b) 3-chlorocyclohexyl tosylate

(c) 3-chlorohexanone

d) sodium 3-chlorocyclohexan-1-olate

(e) 3-chloro-1-methylcyclohexanol

(f) 1-bromo-3-chlorocyclohexane

(g) 3-chlorocyclohexyl acetate

(h) 1-chloro-3-ethoxycyclohexane

14-3 Show how you would synthesis the chloride, bromide, and iodide from the corresponding alcohols

(a) 1-halopentane (halo=chloro, bromo, iodo)

(b) halocyclobutane

(c) 1-halo-1-ethylcyclopentane

(d) 1-halo-2-propylcyclopentane

14-4 Predict the major products of the following reactions. Clearly indicate stereochemistry where appropriate.

(a) (R)-pentan-2-ol + TsCl in pyridine

(b) (R)-2-pentyl tosylate + NaBr

(c) cyclopentanol + CrO3/H2SO4

(d) 2-cyclopenttylethanol +CrO3.pyridine.HCl

(e) 2-cyclopenttylethanol+ CrO3/H2SO4

(f) 1-propanol + HCl/ZnCl2

(g) 2-methylpropan-2-ol +HBr

(h) ethanol + CH3MgCl

(i) potassium *tert*-butoxide + ethyl iodide

(j) tert-butyl tosylate + sodium ethoxide

(k) 1-methylcyclohexanol + H2SO4/heat

(l) product from (k) + OsO4/H2O2, then HIO4

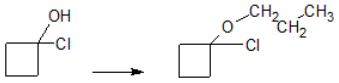
(m) sodium cyclohexoxide + 1-iodopropane

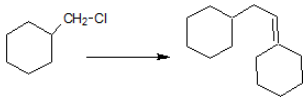
(n) sodium ethoxide + isopropyl tosylate

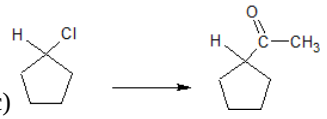
(o) cyclopentylmethanol + DMSO+ oxalyl chloride

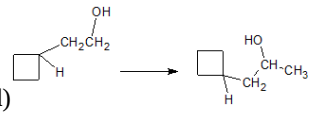
(p) cyclopropanol + DMP reagent

14-5 Propose an efficient synthesis for each of the following transformation

(a) 

(b) 

(c) 

(d) 

14-6 Predict the major products of sulfuric acid catalyzed dehydration

(a) butan-1-ol

(b) 2-methyl-3-pentanol

(c) cyclohexanol

(d) 1-cyclopentylethanol

(d) cyclohexylmethanol

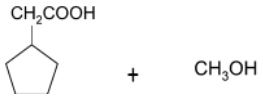
(e) 2-methylcyclohexanol

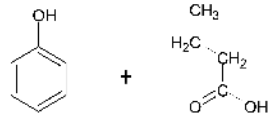
14-7 Predict the products of the following ester synthesis reactions

(a) $CH_3CH_2COOH + CH_3CH_2CH_2OH$

(b) $CH_3CH_2OH + HNO_3$

(c) $CH_3OH + H_3PO_4$

(d) 

(e) 

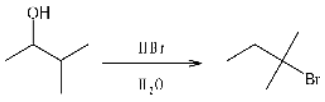
14-8 Show how you would convert (R)-2-pentanol to:

(a) (S)-2-chloropentane

(b) (R)-2-bromopentane

(c) (S)-2-pentanol

14-9 When 3-methyl-2-butanol reacts with concentrated aqueous HBr, the major product is 2-bromo-2-methylbutane



a) Propose a plausible mechanism for the above reaction

b) Show how you would convert 3-methyl-2-butanol into 2-bromo-3-methylbutane:

14-10 Predict the major products when trans-2-ethylcyclopentanol reacts with the following reagents. Include stereochemistry if necessary.

(a) PBr_3

(b) $SOCl_2$

(c) Lucas reagent

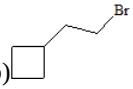
(d) concentrated HBr

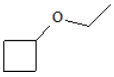
(e) TsCl/py then NaCN

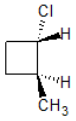
(f)TsCl/py then NaOEt

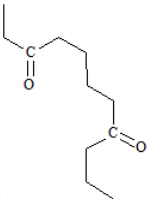
14-11 Using an alcohol of your choice, show how you would synthesis each following compound.

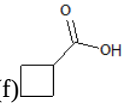
(a)

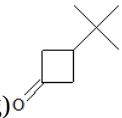
(b) 

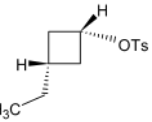
(c) 

(d) 

(e) 

(f) 

(g) 

(h) 

14-12 Describe chemical tests that can be used to distinguish the following pairs of compounds. Include the reagents, reaction conditions, observations, and chemical equations in your answers.

(a) 2-propanol and 2-methyl-2-propanol

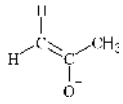
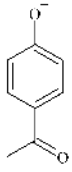
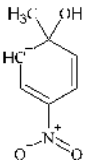
(b) 1-propanol and 2-propanol

(c) cyclopentanol and cyclopentene

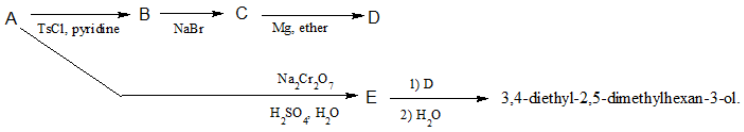
(d) cyclopentanol and 1-cyclopentylethanone

(e) cyclopentanone and 1-methylcyclopentanol

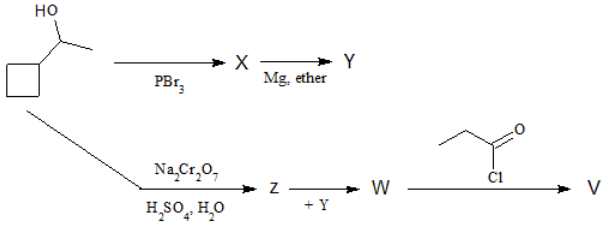
14-13 Draw important resonance structures for the following compounds

(a)  (b)  (c) 

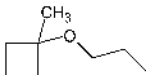
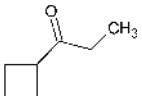
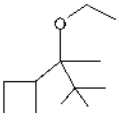
14-14 The following sequence of reaction transforms alcohol A to 3,4-diethyl-2,5-dimethylhexan-3-ol. Propose structure for compounds A, B, C, D, and E.

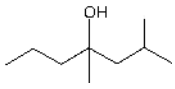
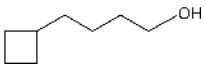
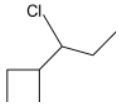


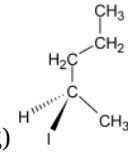
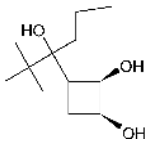
14-15 Consider the following transformation. Identify the structures of compound X, Y, Z, W, and V.



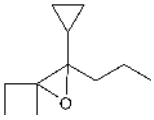
14-16 Show how each of the following compounds can be synthesized. You might use any alcohol containing five or fewer carbon atoms as your starting materials.

(a)  (b)  (c) 

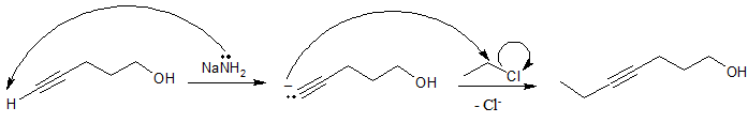
(d)  (e)  (f) 

(g)  (h) 

14-17 Show how you would synthesize the following compound. Only use alcohols containing four or fewer carbons as your organic materials. You might use any necessary solvents and inorganic reagents.



14-18



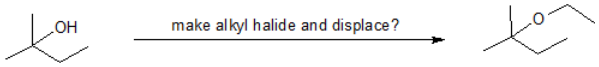
a) The above transformation does not work because of a common conceptual error. What is the conceptual error implicit in this transformation?

b) Show how you could accomplish the transformation in good yield?

14-19 X and Y are constitutional isomers of molecular formula C3H6O. Given the following results with four chemical test, propose structures and assign IUPAC names for X and Y.

	$SOCl_2$	**$K_2Cr_2O_7$**	**Br_2 (liquid)**	**Tollens' reagent**
Compound X	No Rxn	Orange -> Green	No Rxn	No Rxn
Compound Y	Bubbles	Orange -> Green	Decolorize	Grey precipitate of Silver

14-20 The Williamson ether synthesis converts an alkyl halide or tosylate to an ether. Would the following synthesis be possible? If not, explain why not and show an alternative synthesis that would be more likely to work.



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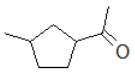
10.13: Solutions to Additional Exercises

14-1

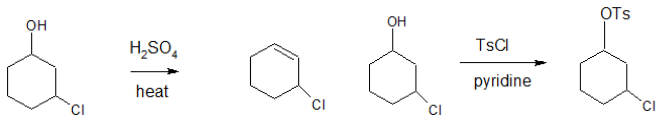
C.



1-(3-methylcyclopentyl)ethan-1-one

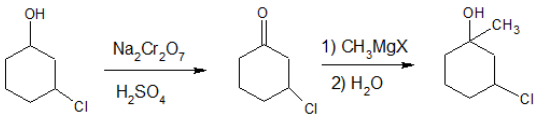
14-2

(a) (b)

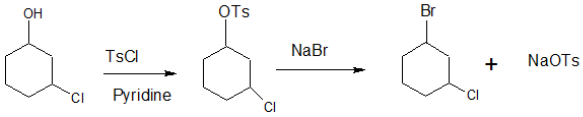


(c) (d)

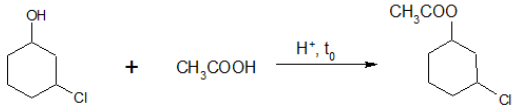
(e)



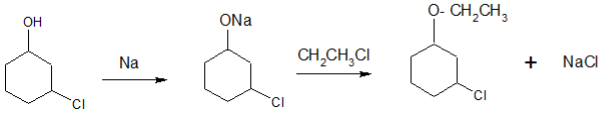
(f)



(g)

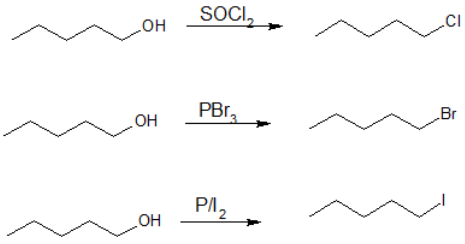


(h)

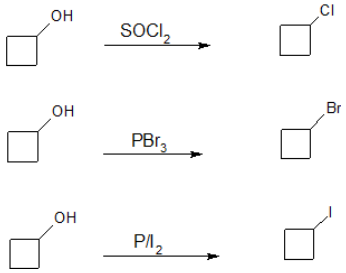


14-3

(a)


OH
SOCl2
Cl
OH
PBr3
Br
OH
P/I2
I

(b)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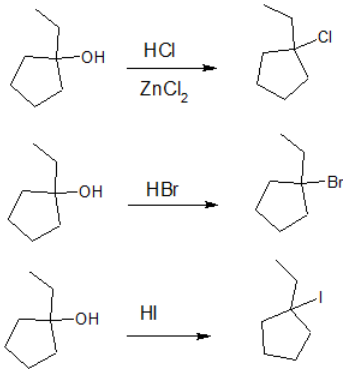
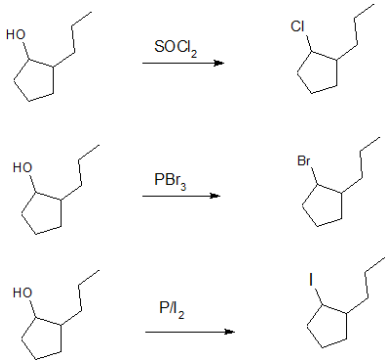
SOCl2
Cl
OH
PBr3
Br
OH
P/I2
I

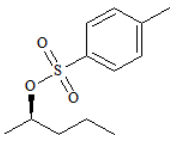
(c)

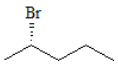

OH
HCl
ZnCl2
Cl
OH
HBr
Br
OH
HI
I

(d)


HO
SOCl2
Cl
HO
PBr3
Br
HO
P/I2
I

14-4

(a) 
O
S
O
O

(b) 

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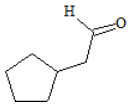
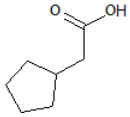
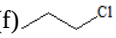
(d) 

(e) 

(f) 

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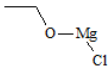
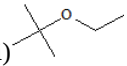
(h) 

(i) 

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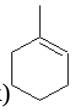
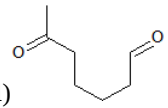
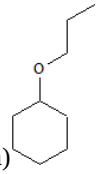
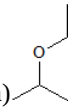
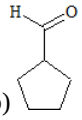
(k) 

(l) 

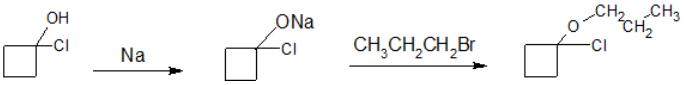
(m) 

(n) 

(o) 

(p)

14-5

(a) 

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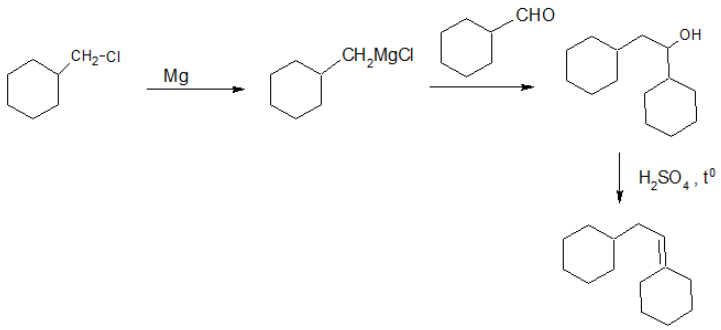
(b)



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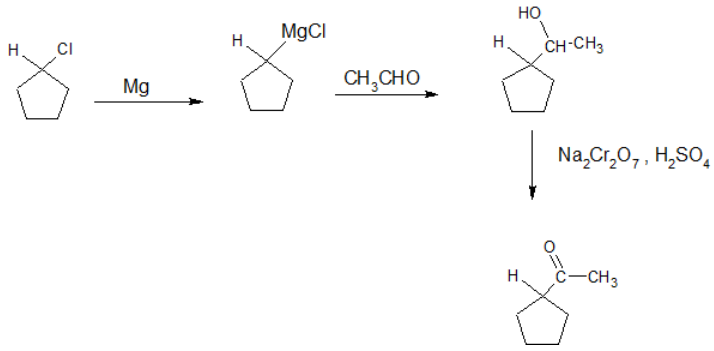
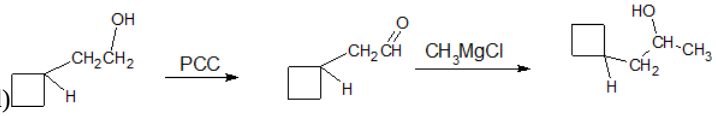
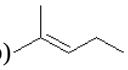
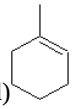
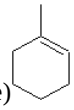
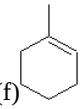


(d)



14-6

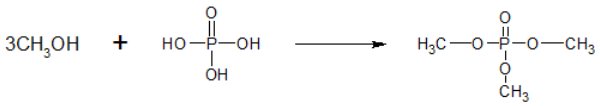
(a) (b)  (c)

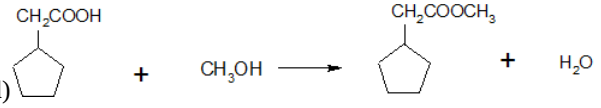
(d)  (e)  (f) 

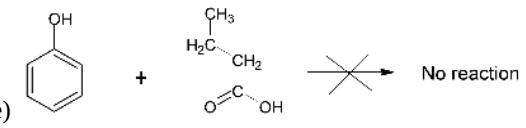
14-7

(a) $CH_3CH_2COOH + CH_3CH_2CH_2OH \longrightarrow CH_3CH_2COOCH_2CH_2CH_3$

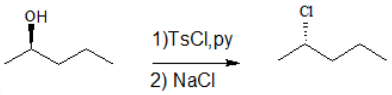
(b) $HNO_3 + CH_3CH_2OH \longrightarrow CH_3CH_2ONO_2 + H_2O$

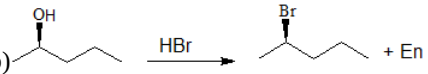
(c) 

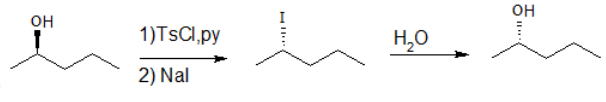
(d) 

(e) 

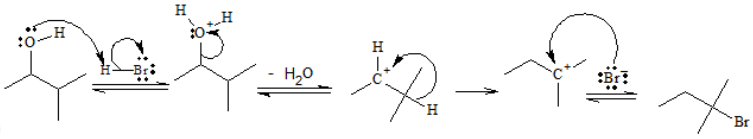
14-8

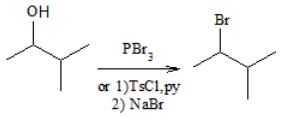
(a) 

(b) 

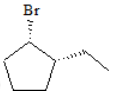
(c) 

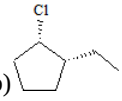
14-9

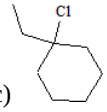
(a) 

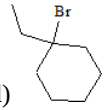
(b) 

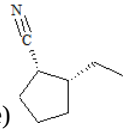
14-10

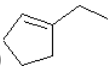
(a) 

(b) 

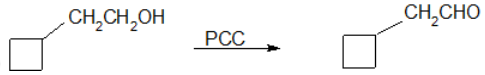
(c) 

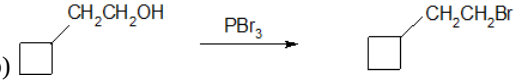
(d) 

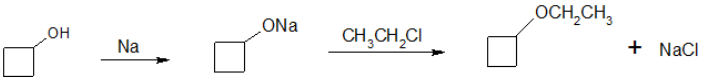
(e) 

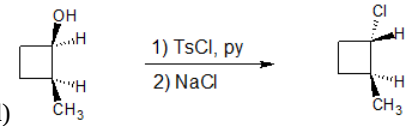
(f) 

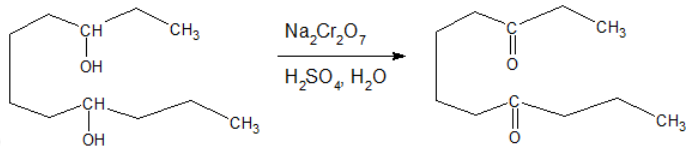
14-11

(a) 

(b) 

(c) 

(d) 

(e) 

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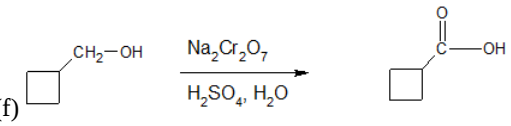
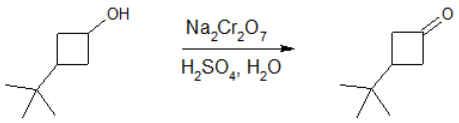
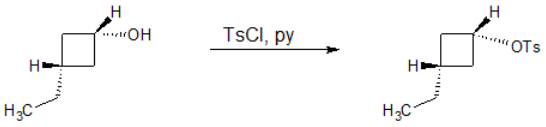
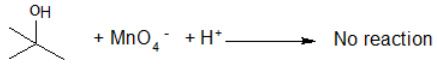
(f) 

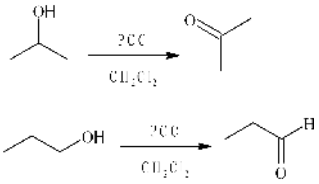
(g) 

(h) 

14-12

(a) We can use potassium permanganate solution to distinguish between 2-propanol and 2-methyl-2-propanol. In acidic condition, KMnO4 oxidizes 2-propanol into acetone which forms the MnO2 brown precipitate and vanishes KMnO4 purple. As tertiary alcohol cannot be oxidized, 2-methyl-2-propanol remains purple.

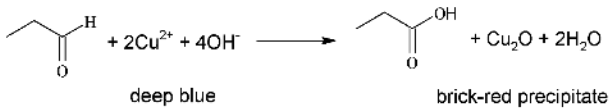


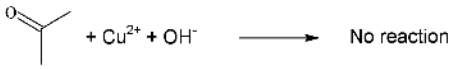


(b) 1-propanol and 2-propanol first need to be oxidized into propanal and acetone respectively.

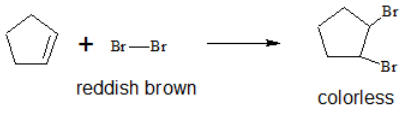
Note: we use pyridinium chlorochromate (PCC) in methylene chloride CH2Cl2 to produce aldehyde without further oxidation.

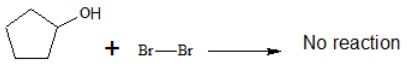
Fehling's test then can be used to determine the presence of an aldehyde. Propanal reacts with Fehling's reagent (Cu2+ in basic solution), forming a brick-red precipitate Cu2O, while acetone cannot react to Fehling's solution, remaining a deep transparent blue color.





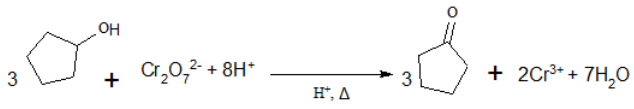
(c) We can use Bromine test to distinguished between cyclopentanol and cyclopentene. Bromine reacts rapidly with cyclopentene, in which the reddish brown color disappears quickly without forming HBr gas bubble. Cyclopentanol does not react with bromine.

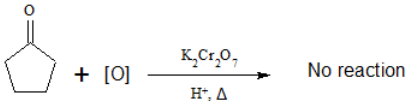




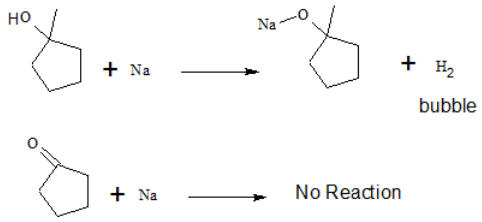
(d) Besides KMnO4, K2Cr2O7 in acidic condition is another oxidizing agent that can be used to distinguish between cyclopentanol and cyclopentanone. Acidified K2Cr2O7 oxidizes cyclopentanol into cyclopentanone. Evidence for the reaction is the orange

solution (Cr2O72-) turns green solution (Cr3+).
1-cyclopentylethanone cannot be oxidized, remaining the orange solution.



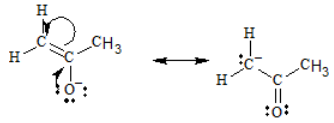


(e) Sodium metal can be used to distinguish between cyclopentanone and 1-methylcyclopentanol. 1-methylcyclopentanol reacts with Na, forming sodium 1-methylcyclopentanolate and releasing H2 bubbles. Cyclopentanone does not react with sodium metal.



14-13

(a)



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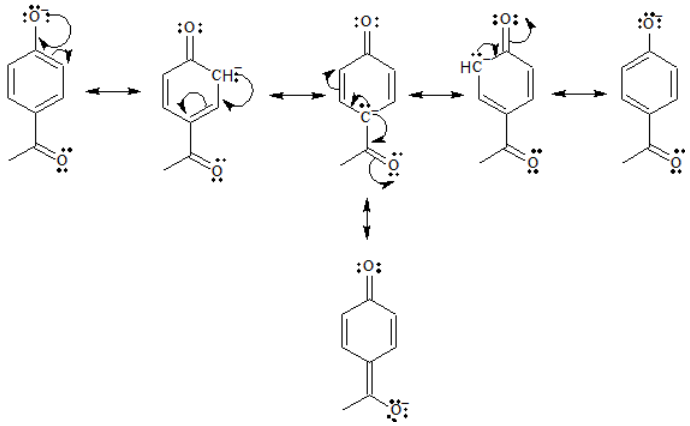

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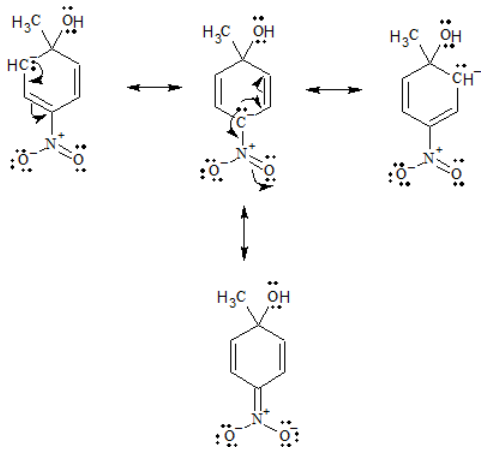
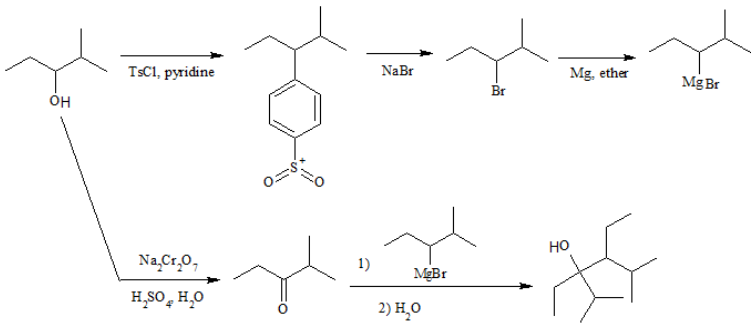


14-14



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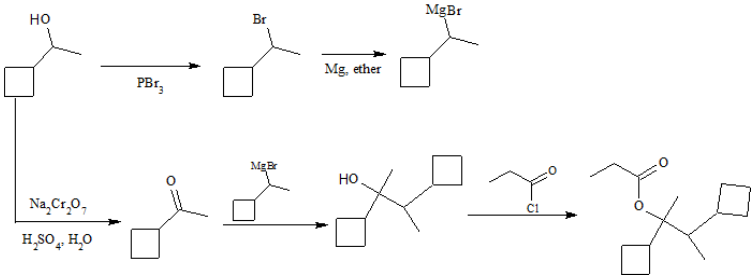
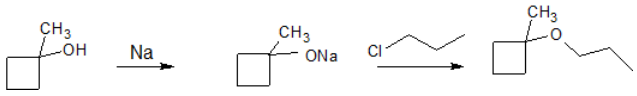


14-16

(a)



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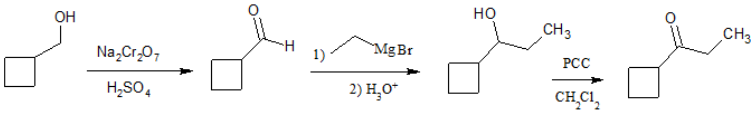

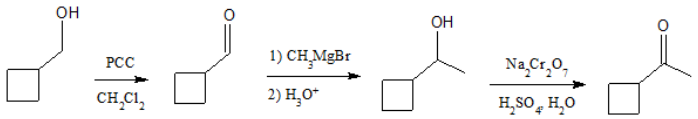

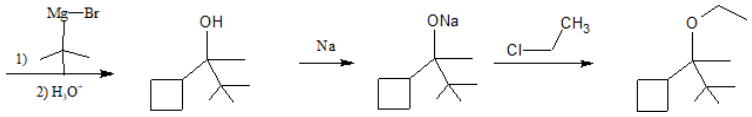

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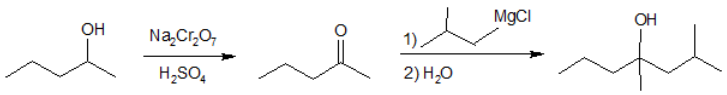

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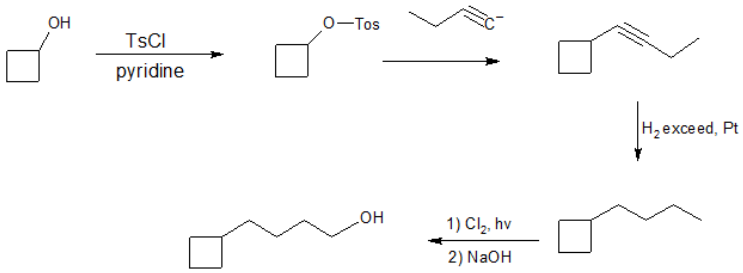

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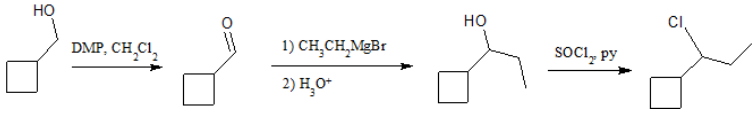

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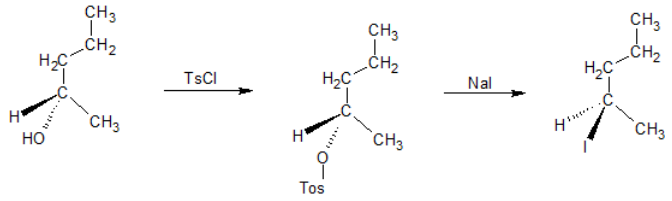

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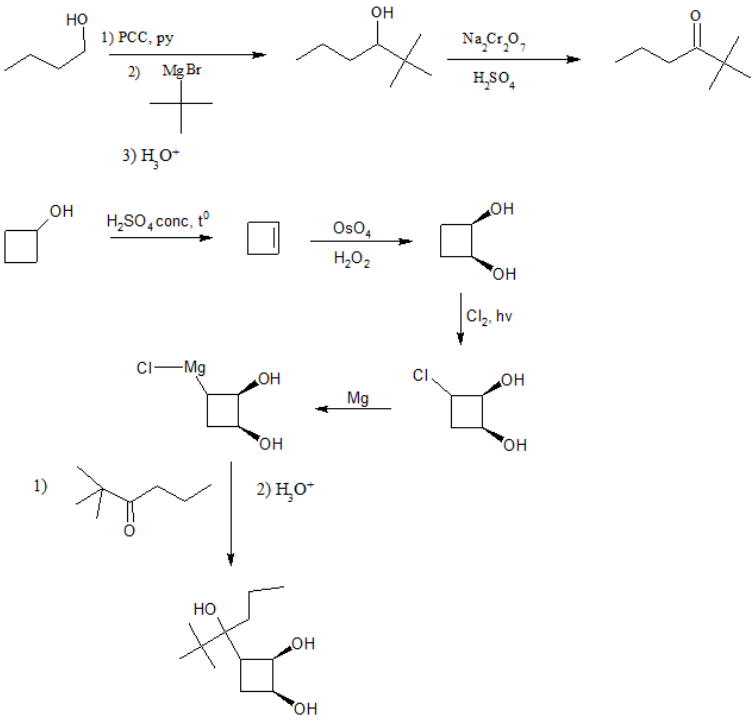
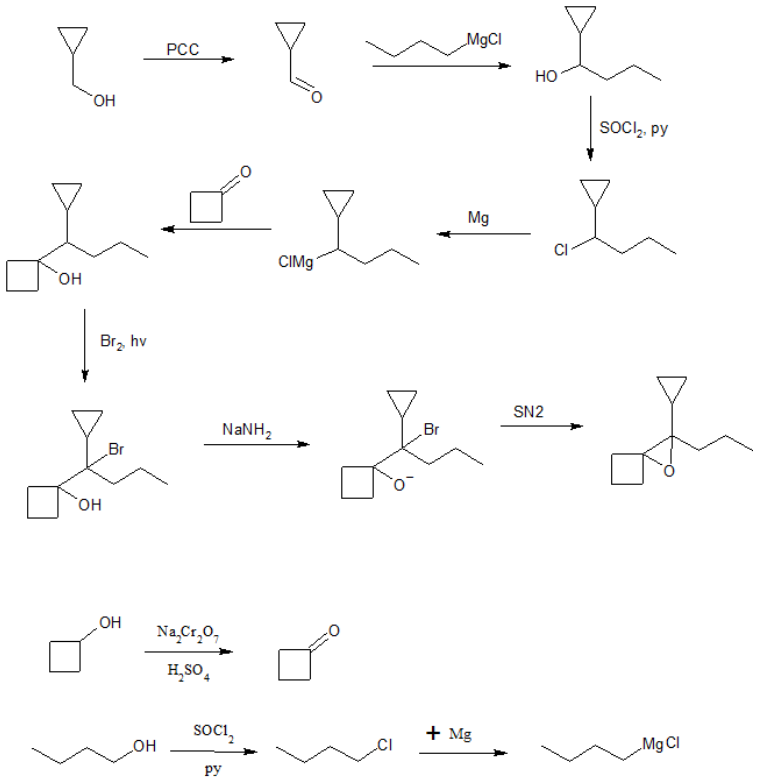


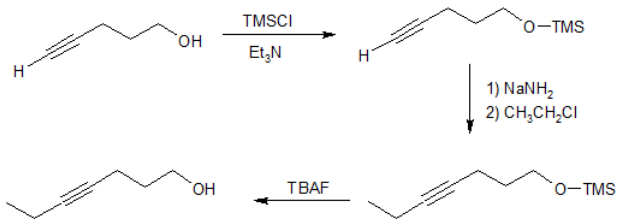
14-17



14-18

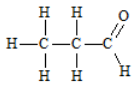
a) Alcohol functional group typically has pKa of 16 while the pKa of a terminal alkyne is usually about 25. The strong base NaNH2 would deprotonate the stronger acid, which in this case is the terminal alkyne. The resulting alkoxide then react with the alkyl halide CH3CH2Cl

b)



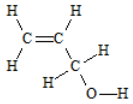
14-19

Compound X



propanal

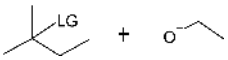
Compound Y



prop-2-en-1-ol

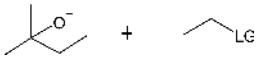
14-20

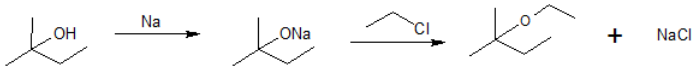
Williamson ether synthesis is an SN2 reaction, which favors strong nucleophile and a primary substrate for back-side attack. Since a tertiary alcohol is given, the resulting alkyl halide is also tertiary, which is sterically hindered for SN2 reaction to occur.



The alkoxide then would function as a base, and an elimination reaction would happen instead of SN2 reaction.

An alternative synthesis that is more likely to occur involving the reaction between a tertiary alkoxide and a primary alkyl halide:





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CHAPTER OVERVIEW

11: Structure and Synthesis of Alcohols
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- distinguish between alcohols, phenols, enols, and carboxylic acids - refer to section 13.1
- classify alcohols as primary, secondary, or tertiary - refer to section 13.2
- predict relative physical properties of alcohols, such as relative boiling points and solubility in a specified solvent - refer to section 13.3
- determine the structure of alcohols and phenols from spectroscopic data - refer to section 13.4
- predict the relative acidity of alcohols - refer to section 13.5
- use resonance to explain why phenols are more acidic than alcohols - refer to section 13.5
- specify the base needed to ionize an alcohol or phenol - refer to section 13.5
- predict the products and specify the reagents for alcohol and diol synthesis from alkyl halides, alkenes, and alkynes from the previous chapters - refer to section 13.6
- predict the products and specify the reagents to synthesize alcohols from the reduction of carbonyls - refer to section 13.7
- predict the products and specify the reagents to prepare Grignard and organolithium reagents - refer to section 13.8
- predict the products and specify the reagents for alcohol synthesis from organometallic reagents with aldehydes, ketones, esters, acyl halides, & epoxides - section 13.9
- distinguish between the structure and reactivity of thiols and sulfides - refer to section 13.10
- explain the commercial synthesis of alcohols - refer to section 13.11

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

11.1: Introduction to Structure and Synthesis of Alcohols
11.2: Classification of Alcohols
11.3: Physical Properties of Alcohols
11.4: Spectroscopy of Alcohols
11.5: Acidity of Alcohols and Phenols
11.6: Synthesis of Alcohols - Review
11.7: Reduction of the Carbonyl Group - Synthesis of 1º and 2º Alcohols
11.8: Organometallic Reagents
11.9: Organometallic Reagents in Alcohol Synthesis
11.10: Thiols (Mercaptans)
11.11: Commercially Important Alcohols
11.12: 13.12 Additional Exercises
11.13: Solutions to Additional Exercises

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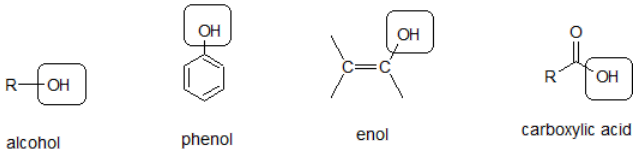
11.1: Introduction to Structure and Synthesis of Alcohols

Introduction

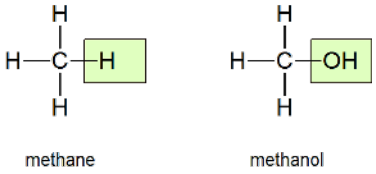
Alcohols, phenols, enols, and carboxylic acids all contain a hydroxyl group. However, the chemistry of these four different functional groups are different.



Alcohols

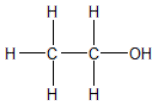
Molecules of alcohols contain one or more hydroxyl groups (OH groups) substituted for hydrogen atoms along the carbon chain.

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:



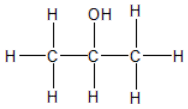
Methanol is also called wood alcohol because it can be obtained by heating wood in the absence of air, a process called **destructive distillation**. Methanol vapor given off when the wood is heated can be condensed to a liquid by cooling below its boiling point of 65°C. Methanol is highly toxic. In 1986, there were six deaths of residents of Peerless Lake, Alberta, 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."

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.) 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 labeled "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. 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.

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.

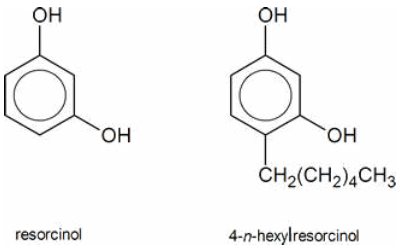


isopropanol

Phenols

A phenol is an organic compound in which a hydroxyl group is directly bonded to one of the carbon atoms of an aromatic ring. 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.

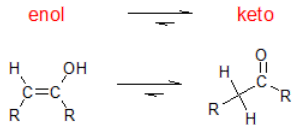
Until the late nineteenth century, a person undergoing surgery had to face the fact that he or she might suffer the consequences of what we now know to be bacterial infection, contracted during the course of the operation. The physicians of the time did not know that bacteria existed, and had no way 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

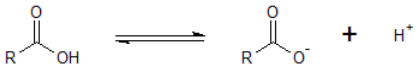
Enols

When a hydroxyl group is bonded to a vinyl carbon, the functional group is called an enol. As discussed in Chapter 10, alkyne hydration can result in enol formation. Enols undergo tautomerization to form ketones, In most cases, the keto-form is more stable and predominates the equilibrium. Phenol is an important exception to this trend.



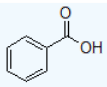
Carboxylic Acids

In carboxylic acids, the hydroxyl group is bonded to a carbonyl carbon. As the name implies, this functional group is acidic and can readily donate the proton on the hydroxyl group.



Exercise

1. Classify the following compounds as alcohols, phenols, enols, or carboxylic acids. One compound can be classified by two of the options.

a) 

b)

c)

Answer

1.

a) carboxylic acid

b) phenol and enol

c) alcohol

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- 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.

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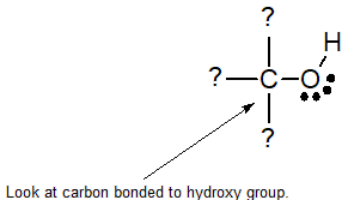
11.2: Classification of Alcohols

Alcohol classification is an application of the neutral bonding patterns for organic compounds. Oxygen can only form two bonds. The alcohol functional group requires that one of these bonds form with hydrogen to create the hydroxyl group and the other bond needs to be with carbon to create an alcohol. All of the oxygen atoms of all the alcohols look the same, so a different distinction is needed. To classify alcohols, we look at the carbon atom bonded to the hydroxyl group.



methyl alcohol = no (0) other carbon atoms (CH_3OH)

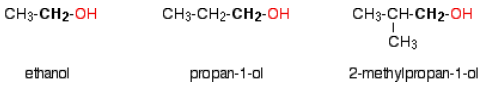
primary alcohols (1°) = 1 other carbon atoms

secondary alcohols (2°) = 2 other carbon atom

tertiary alcohols (3°) = 3 other carbon atoms

Primary alcohols

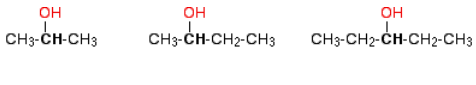
In a primary (1°) alcohol, the carbon which carries the -OH group is only attached to one alkyl group. Some examples of primary alcohols include:



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.

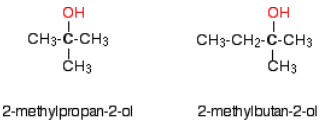
Secondary alcohols

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:



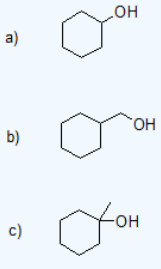
Tertiary alcohols

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:



Exercise

2. Classify the following alcohols as primary, secondary, or tertiary.



Answer

2.

a) secondary

b) primary

c) tertiary

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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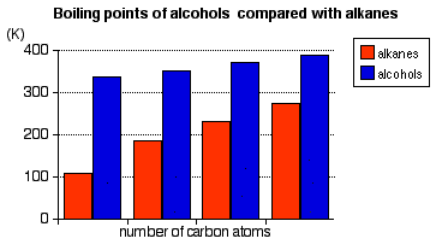
11.3: Physical Properties of Alcohols

Boiling Points

The chart below shows the boiling points of the following simple primary alcohols with up to 4 carbon atoms:

CH_3OH	CH_3CH_2OH	$CH_3CH_2CH_2OH$	$CH_3CH_2CH_2CH_2OH$
methanol	ethanol	propan-1-ol	butan-1-ol

These boiling points are compared with those of the equivalent alkanes (methane to butane) with the same number of carbon atoms.



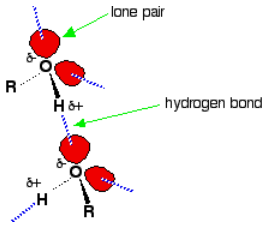
Notice that:

- The boiling points of the alcohols increase as the number of carbon atoms increases.

The patterns in boiling point reflect the patterns in intermolecular attractions.

Hydrogen bonding

Hydrogen bonding occurs between molecules in which a hydrogen atom is attached to a strongly electronegative element: fluorine, oxygen or nitrogen. In the case of alcohols, hydrogen bonds occur between the partially-positive hydrogen atoms and lone pairs on oxygen atoms of other molecules.



The hydrogen atoms are slightly positive because the bonding electrons are pulled toward the very electronegative oxygen atoms. In alkanes, the only intermolecular forces are van der Waals dispersion forces. Hydrogen bonds are much stronger than these, and therefore it takes more energy to separate alcohol molecules than it does to separate alkane molecules. This the main reason for higher boiling points in alcohols.

The effect of van der Waals forces

- **Comparison between alkanes and alcohols**: Even without any hydrogen bonding or dipole-dipole interactions, the boiling point of the alcohol would be higher than the corresponding alkane with the same number of carbon atoms.

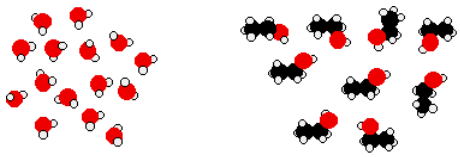
Compare ethane and ethanol:

Ethanol is a longer molecule, and the oxygen atom brings with it an extra 8 electrons. Both of these increase the size of the van der Waals dispersion forces, and subsequently the boiling point. A more accurate measurement of the effect of the hydrogen bonding on boiling point would be a comparison of ethanol with propane rather than ethane. The lengths of the two molecules are more similar, and the number of electrons is exactly the same.

Solubility of alcohols in water

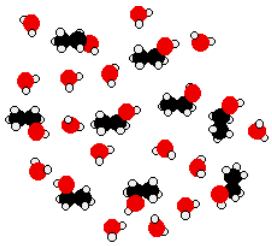
Small alcohols are completely soluble in water; mixing the two in any proportion generates a single solution. However, solubility decreases as the length of the hydrocarbon chain in the alcohol increases. At four carbon atoms and beyond, the decrease in solubility is noticeable; a two-layered substance may appear in a test tube when the two are mixed.

Consider ethanol as a typical small alcohol. In both pure water and pure ethanol the main intermolecular attractions are hydrogen bonds.



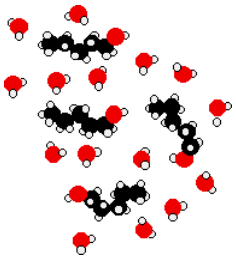
Both of these are held together mainly by hydrogen bonding.

In order to mix the two, the hydrogen bonds between water molecules and the hydrogen bonds between ethanol molecules must be broken. Energy is required for both of these processes. However, when the molecules are mixed, new hydrogen bonds are formed between water molecules and ethanol molecules.



New hydrogen bonds are set up between ethanol and water molecules.

The energy released when these new hydrogen bonds form approximately compensates for the energy needed to break the original interactions. In addition, there is an increase in the disorder of the system, an increase in entropy. This is another factor in deciding whether chemical processes occur. Consider a hypothetical situation involving 5-carbon alcohol molecules.

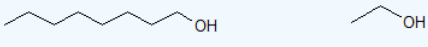


The hydrocarbon chains are forced between water molecules, breaking hydrogen bonds between those water molecules. The -OH ends of the alcohol molecules can form new hydrogen bonds with water molecules, but the hydrocarbon "tail" does not form hydrogen bonds. This means that many of the original hydrogen bonds being broken are never replaced by new ones.

In place of those original hydrogen bonds are merely van der Waals dispersion forces between the water and the hydrocarbon "tails." These attractions are much weaker, and unable to furnish enough energy to compensate for the broken hydrogen bonds. Even allowing for the increase in disorder, the process becomes less feasible. As the length of the alcohol increases, this situation becomes more pronounced, and thus the solubility decreases.

Exercise

Use 1-octanol and ethanol, shown below, to answer the following questions.



3. Which compound is more water soluble?

4. Which compound has the highest boiling point?

5. Explain why the answers above are not in conflict using your understanding of intermolecular forces, relative boiling points, and solubility.

Answer

3. ethanol

4. octanol

5. While both compounds exhibit H-bonding, the smaller, hydrophobic carbon chain of ethanol results in higher water solubility of ethanol while the longer carbon chain of octanol increases the surface area resulting in a higher boiling point.

Contributors

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)
- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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11.4: Spectroscopy of Alcohols

Infrared Spectroscopy

If you look at an IR spectrum of 1-butanol, you will see:

- there are sp^3 C-H stretching and CH_2 bending modes at 2900 and 1500 cm^{-1}.
- there is a strong C-O stretching mode near 1000 cm^{-1}.
- there is a very large peak around 3400 cm^{-1}. O-H peaks are usually very broad like this one.

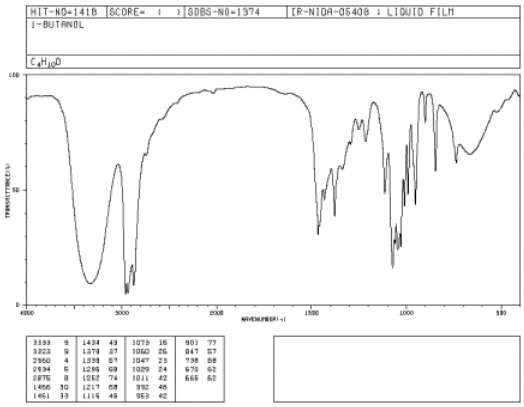


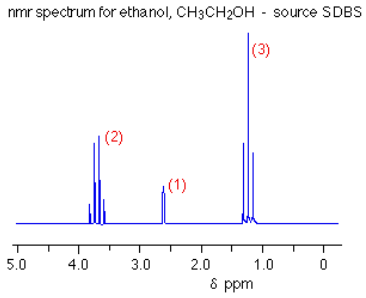
Figure IR8. IR spectrum of 1-butanol. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

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 whole lot of them all smeared out into one broad blob. Since C-H bonds don't hydrogen bond very well, you don't see that phenomenon in an ether, and an O-H peak is very easy to distinguish in the IR spectrum.

Nuclear Magnetic Resonance Spectroscopy

Alcohols

Where is the -O-H peak? This is very confusing! Different sources quote totally different chemical shifts for the hydrogen atom in the -OH group in alcohols - often inconsistently. For example:



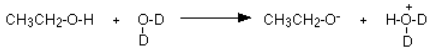
- The Nuffield Data Book quotes 2.0 - 4.0, but the Nuffield text book shows a peak at about 5.4.
- The OCR Data Sheet for use in their exams quotes 3.5 - 5.5.
- A reliable degree level organic chemistry text book quotes1.0 - 5.0, but then shows an NMR spectrum for ethanol with a peak at about 6.1.
- The SDBS database (used throughout this site) gives the -OH peak in ethanol at about 2.6.

The problem seems to be that the position of the -OH peak varies dramatically depending on the conditions - for example, what solvent is used, the concentration, and the purity of the alcohol - especially on whether or not it is totally dry.

A clever way of picking out the -OH peak

If you measure an NMR spectrum for an alcohol like ethanol, and then add a few drops of deuterium oxide, D_2O, to the solution, allow it to settle and then re-measure the spectrum, the -OH peak disappears! By comparing the two spectra, you can tell immediately which peak was due to the -OH group.

The reason for the loss of the peak lies in the interaction between the deuterium oxide and the alcohol. All alcohols, such as ethanol, are very, very slightly acidic. The hydrogen on the -OH group transfers to one of the lone pairs on the oxygen of the water molecule. The fact that here we've got "heavy water" makes no difference to that.



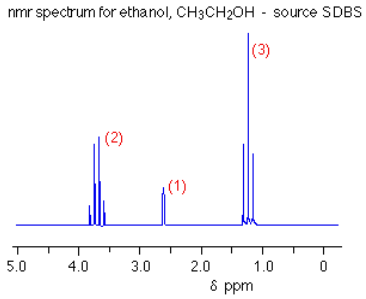
The negative ion formed is most likely to bump into a simple deuterium oxide molecule to regenerate the alcohol - except that now the -OH group has turned into an -OD group.

Deuterium atoms don't produce peaks in the same region of an NMR spectrum as ordinary hydrogen atoms, and so the peak disappears. You might wonder what happens to the positive ion in the first equation and the OD^- in the second one. These get lost into the normal equilibrium which exists wherever you have water molecules - heavy or otherwise.

$$2D_2O \rightleftharpoons D_3O^+ + OH^- \tag{11.4.1}$$

The lack of splitting with -OH groups

Unless the alcohol is absolutely free of any water, the hydrogen on the -OH group and any hydrogens on the next door carbon don't interact to produce any splitting. The -OH peak is a singlet and you don't have to worry about its effect on the next door hydrogens.



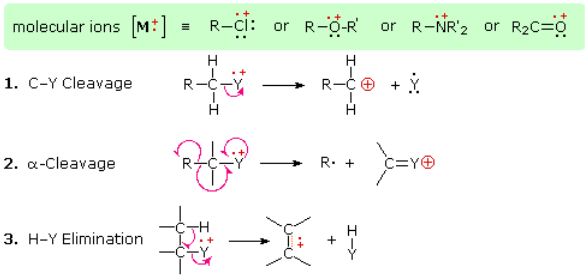
The left-hand cluster of peaks is due to the CH_2 group. It is a quartet because of the 3 hydrogens on the next door CH_3 group. You can ignore the effect of the -OH hydrogen. Similarly, the -OH peak in the middle of the spectrum is a singlet. It hasn't turned into a triplet because of the influence of the CH_2 group.

Mass Spectra Fragmentation Patterns

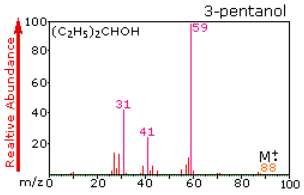
The fragmentation of molecular ions into an assortment of fragment ions is a mixed blessing. The nature of the fragments often provides a clue to the molecular structure, but if the molecular ion has a lifetime of less than a few microseconds it will not survive long enough to be observed. Without a molecular ion peak as a reference, the difficulty of interpreting a mass spectrum increases markedly. Fortunately, most organic compounds give mass spectra that include a molecular ion, and those that do not often respond successfully to the use of milder ionization conditions. Among simple organic compounds, the most stable molecular ions are those from aromatic rings, other conjugated pi-electron systems and cycloalkanes. Alcohols, ethers and highly branched alkanes generally show the greatest tendency toward fragmentation.

The presence of a functional group, particularly one having a heteroatom Y with non-bonding valence electrons (Y = N, O, S, X etc.), can dramatically alter the fragmentation pattern of a compound. This influence is thought to occur because of a "localization"

of the radical cation component of the molecular ion on the heteroatom. After all, it is easier to remove (ionize) a non-bonding electron than one that is part of a covalent bond. By localizing the reactive moiety, certain fragmentation processes will be favored. These are summarized in the following diagram, where the green shaded box at the top displays examples of such "localized" molecular ions. The first two fragmentation paths lead to even-electron ions, and the elimination (path #3) gives an odd-electron ion. Note the use of different curved arrows to show single electron shifts compared with electron pair shifts.

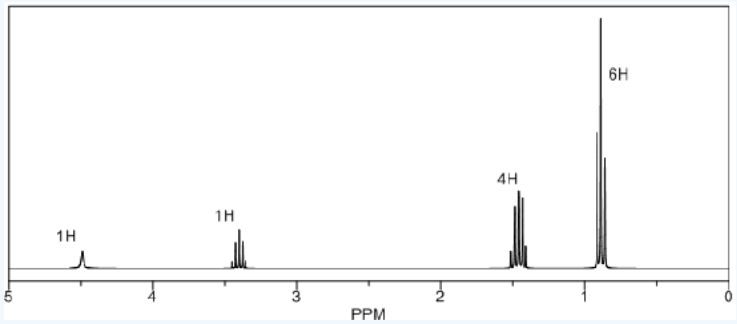


3-Pentanol shows three significant fragment ions. Alpha-fragmentation (loss of an ethyl radical) forms the m/z=59 base peak. Loss of water from this gives a m/z=41 fragment, and loss of ethene from m/z=59 gives a m/z=31 fragment.



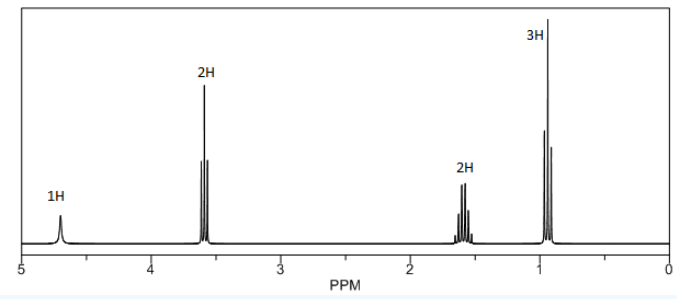
Exercise

6. 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.



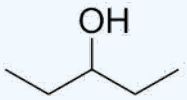
7. Given that alcohols are relatively acidic and the protons transfer in solution, what would you expect to happen to the NMR spectrum if D_2O was used as a solvent.

8. 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

6.



7.

The alcohol proton signal's intensity in the ^{1}H NMR would be expected to diminish and likely disappear. This is due to the fact that NMR can only probe the spin changes of nuclei with an odd number of protons.

8.

1-propanol

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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11.5: Acidity of Alcohols and Phenols

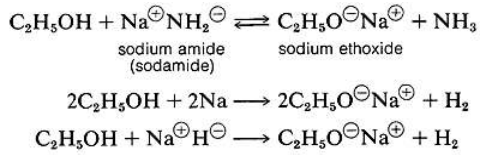
Overview - Aqueous vs Organic Solvents

In aqueous solutions, phenols are weakly acidic and lower the pH of a solution. Sodium hydroxide can be used to fully deprotonate a phenol. Water soluble alcohols do not change the pH of the solution and are considered neutral. Aqueous solutions of sodium hydroxide can NOT deprotonate alcohols to a high enough concentration to be synthetically useful.

In solutions of organic solvents, more extreme reaction conditions can be created. Sodium metal can be added to an alcohol in an organic solvent system to fully deprotonate the alcohol to form alkoxide ions.

Acidity of Alcohols

Several important chemical reactions of alcohols involving the O-H bond or oxygen-hydrogen bond only and leave the carbon-oxygen bond intact. An important example is salt formation with acids and bases. Alcohols, like water, are both weak bases and weak acids. The acid ionization constant (Ka) of ethanol is about 10~18, slightly less than that of water. Ethanol can be converted to its conjugate base by the conjugate base of a weaker acid such as ammonia {Ka — 10~35), or hydrogen (Ka ~ 10-38). It is convenient to employ sodium metal or sodium hydride, which react vigorously but controllably with alcohols:



The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the equilibrium position for the proton-transfer reaction lies more on the side of ROH as R is changed from primary to secondary to tertiary; therefore, tert-butyl alcohol is considered less acidic than ethanol:

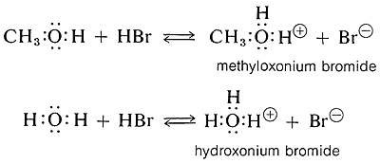
$$ROH + OH^- \rightleftharpoons RO^- + HOH \tag{11.5.1}$$

However, in the gas phase the order of acidity is reversed, and the equilibrium position for lies increasingly on the side of the alkoxide as R is changed from primary to secondary to tertiary, tert-butyl alcohol is therefore more acidic than ethanol in the gas phase. This seeming contradiction appears more reasonable when one considers what effect solvation (or the lack of it) has on equilibria. In solution, the larger alkoxide ions, probably 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. However, “naked” gaseous ions are more stable the larger the associated R groups, probably because the larger R groups can stabilize the charge on the oxygen atom better than the smaller R groups. They do this by polarization of their bonding electrons, and the bigger the group, the more polarizable it is.

Basicity of Alcohols

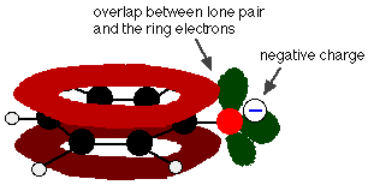
Alcohols are bases similar in strength to water and accept protons from strong acids. An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide with hydrogen bromide and water:



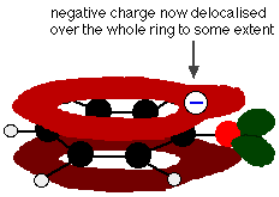
Acidity of Phenol

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 solution in water:

Phenol is a very weak acid and the position of equilibrium lies well to the left. Phenol can lose a hydrogen ion because the phenoxide ion formed is stabilised to some extent. The negative charge on the oxygen atom is delocalised around the ring. The more stable the ion is, the more likely it is to form. One of the lone pairs on the oxygen atom overlaps with the delocalised electrons on the benzene ring.



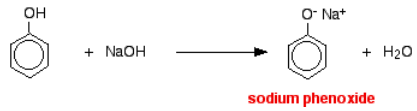
This overlap leads to a delocalization which extends from the ring out over the oxygen atom. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread out around the whole ion.



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.

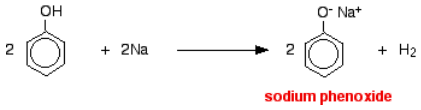
Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.

The resonance stabilization in these two cases is very different. An important principle of resonance is that charge separation diminishes the importance of canonical contributors to the resonance hybrid and reduces the overall stabilization. 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.



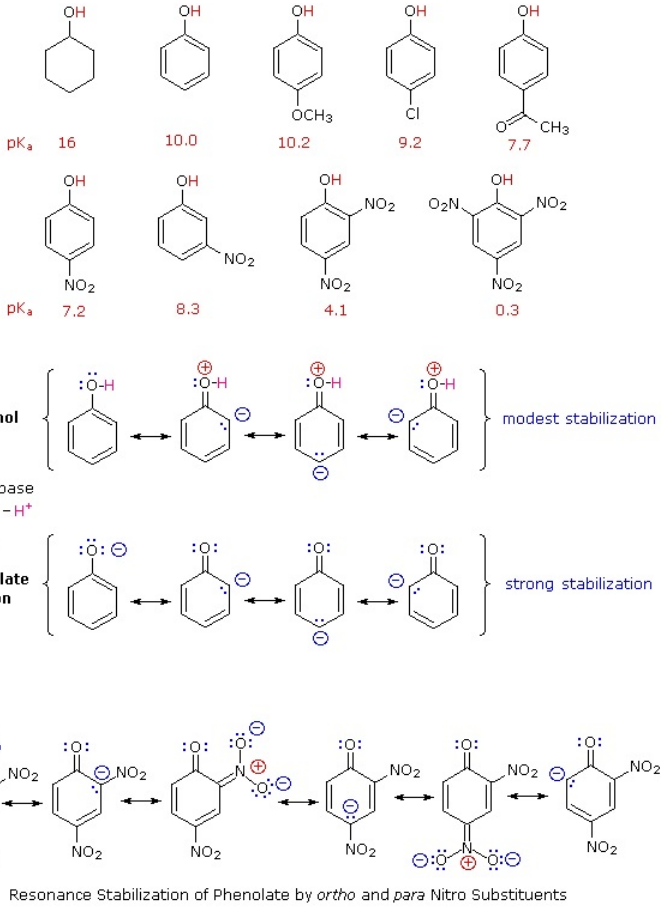
In this reaction, the hydrogen ion has been removed by the strongly basic hydroxide ion in the sodium hydroxide solution.

Acids react with the more reactive metals to give hydrogen gas. Phenol is no exception - the only difference is the slow reaction because phenol is such a weak acid. Phenol is warmed in a dry tube until it is molten, and a small piece of sodium added. There is some fizzing as hydrogen gas is given off. The mixture left in the tube will contain sodium phenoxide.



Acidity of Substituted Phenols

Substitution of the hydroxyl hydrogen atom is even more facile with phenols, which are roughly a million times more acidic than equivalent alcohols. This phenolic acidity is further enhanced by electron-withdrawing substituents ortho and para to the hydroxyl group, as displayed in the following diagram. The alcohol cyclohexanol is shown for reference at the top left. 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. Furthermore additional nitro groups have an additive influence if they are positioned in ortho or para locations. The trinitro compound shown at the lower right is a very strong acid called picric acid.

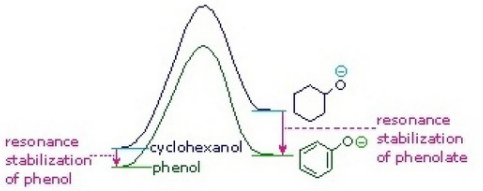


Resonance Stabilization of Phenolate by *ortho* and *para* Nitro Substituents

Comparing the Acidity of Alcohols with Phenols

Why is phenol a much stronger acid than cyclohexanol? To answer this question we must evaluate the manner in which an oxygen substituent interacts with the benzene ring. As noted in our earlier treatment of electrophilic aromatic substitution reactions, an

oxygen substituent enhances the reactivity of the ring and favors electrophile attack at ortho and para sites. It was proposed that resonance delocalization of an oxygen non-bonded electron pair into the pi-electron system of the aromatic ring was responsible for this substituent effect. Formulas illustrating this electron delocalization will be displayed when the "Resonance Structures" button beneath the previous diagram is clicked. A similar set of resonance structures for the phenolate anion conjugate base appears below the phenol structures.



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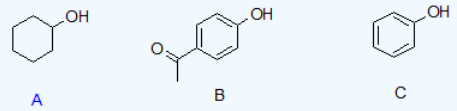
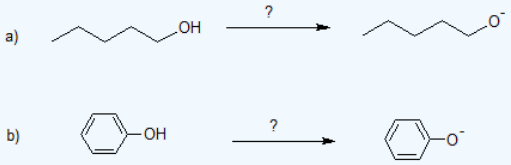
Exercise

9. Arrange the following compounds in order of decreasing acidity when they are in solution.



10. Specify the base needed to deprotonate each reactant.



Answer

9. B > C > A

10. a) Na or NaH or NNH_2

b) NaOH or KOH or LiOH

Contributors

- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

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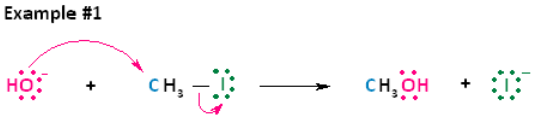
11.6: Synthesis of Alcohols - Review

Alcohols are prepared by S_N2 & S_N1 (solvolysis) reactions

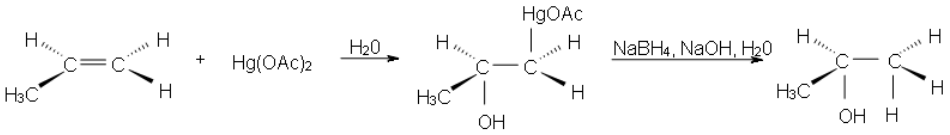
Alkyl halides can be converted to alcohols by using S_N2 reactions with OH^- as a nucleophile. Substrates that undergo substitution by SN1 reaction can be converted to alcohols using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents.



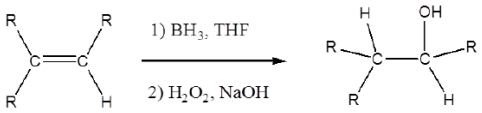
Alcohols from alkenes

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.

Carbocation rearrangement is a process in which the carbocation intermediate can form a more stable ion. With carbocation rearrangement, the reaction would not be able to hydrate quickly under mild conditions and be produced in high yields. This reaction is very fast and proceeds with 90% yield.

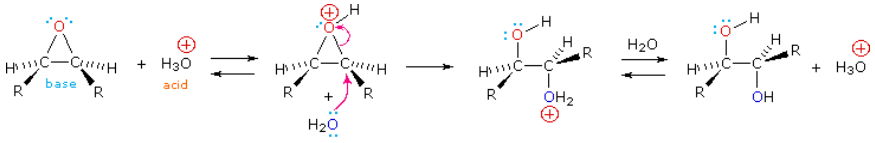


Hydroboration-Oxidation is a two step pathway used to produce alcohols. The reaction proceeds in an Anti-Markovnikov manner, where the hydrogen (from BH_3 or BHR_2) attaches to the more substituted carbon and the boron attaches to the least substituted carbon in the alkene bouble bond. Furthermore, the 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.

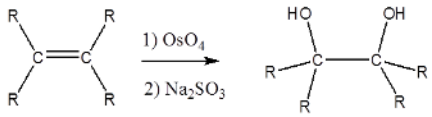


Diols from alkenes

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.



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.



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.

Contributors and Attributions

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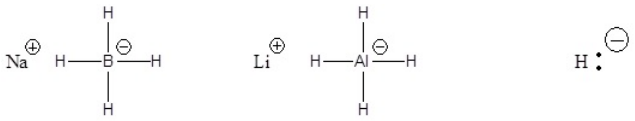
11.7: Reduction of the Carbonyl Group - Synthesis of 1º and 2º Alcohols

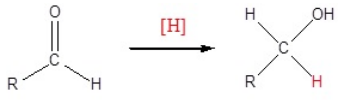
Reduction of Aldehydes and Ketones

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.

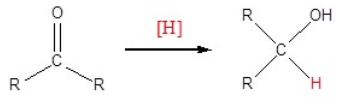


Sodium Borohydride **Lithium Aluminum Hydride** **Hydride Nucleophile**

Addition of a hydride anion ($H:^-$) to an aldehyde or ketone gives an alkoxide anion, which upon protonation yields the corresponding alcohol. Aldehydes produce 1º-alcohols and ketones produce 2º-alcohols.



Aldehyde **1° Alcohol**

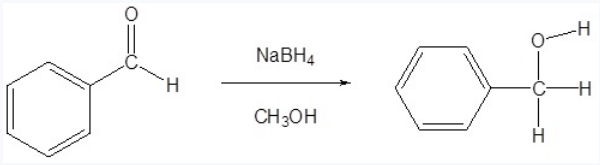


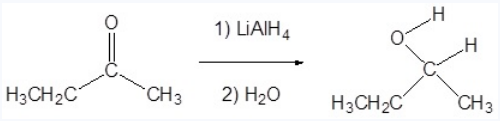
Ketone **2° Alcohol**

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. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

Formally, that process is referred to as a reduction. Reduction generally means a reaction in which electrons are added to a compound; the compound that gains electrons is said to be reduced. Because hydride can be thought of as a proton plus two electrons, we can think of conversion of a ketone or an aldehyde to an alcohol as a two-electron reduction. A carbonyl (aldehyde or ketone) plus two electrons and two protons becomes an alcohol.

Example 1

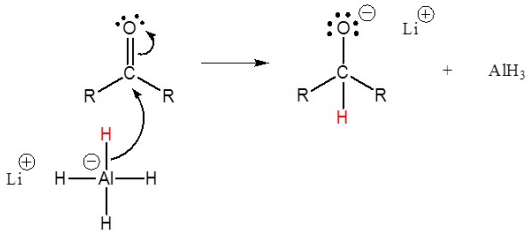




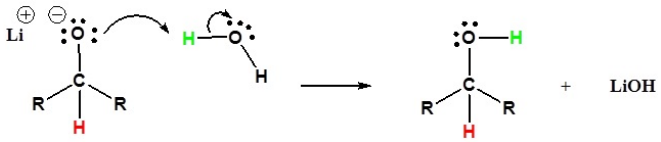
Mechanism

This mechanism is for a $LiAlH_4$ reduction. The mechanism for a $NaBH_4$ reduction is the same except methanol is the proton source used in the second step.

1) Nucleopilic hydride anion reacts with the electrophilic carbonyl carbon forcing the pi electrons onto the electronegative oxygen atom.



2) The alkoxide is protonated.



Biological Reduction

Addition to a carbonyl by a semi-anionic hydride, such as $NaBH_4$, results in conversion of the carbonyl compound to an alcohol. The hydride from the BH_4^- anion acts as a nucleophile, adding H^- to the carbonyl carbon. A proton source can then protonate the oxygen of the resulting alkoxide ion, forming an alcohol.

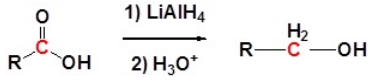
CONADH2.png

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.

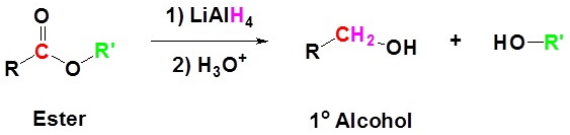
NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Insetad of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms 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 can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$). Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride (***$NaBH_4$***) is not a strong enough reducing agent to perform this reaction.

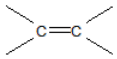
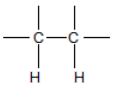


Ester — 1° Alcohol

Reduction Reaction Summary

The table below summarize the reduction reactions covered so far in our text. It is important to distinguish between functional group reactivity as we add more multiple-step synthetic pathways.

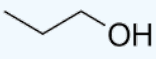
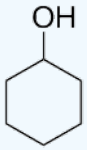
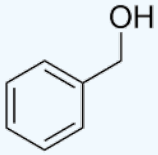
Reduction Reaction Summary

Reactant	Reduction Product with Specified Reagents: H_2 with Pt, Pd or Ni	1) $NaBH_4$ 2) H_3O^+	1) $LiAlH_4$ 2) H_3O^+
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	$RCH_2—OH$	$RCH_2—OH$	$RCH_2—OH$
	no rxn	no rxn	$RCH_2—OH$
	no rxn	no rxn	

Exercise

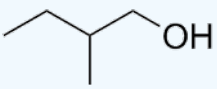
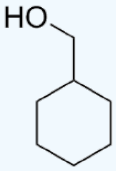
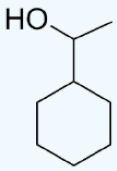
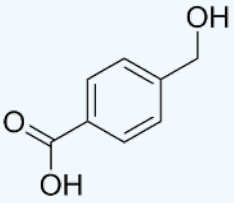
11.

Give the aldehyde, ketone, or carboxyllic acid (there can be multiple answers) that could be reduced to form the following alcohols.

(a) (b)  (c)  (d) 

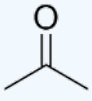
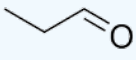
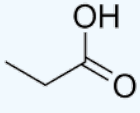
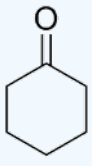
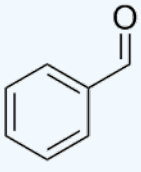
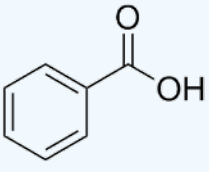
12.

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$

(a)  (b)  (c)  (d) 

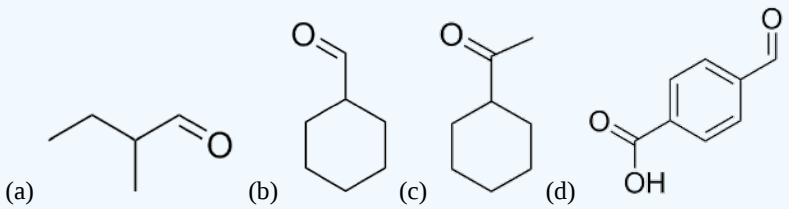
Answer

11.

(a)  (b)  or  (c)  (d)  or 

12.

Note, $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.



Contributors and Attributions

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11.8: Organometallic Reagents

Introduction

A Grignard reagent has a formula **RMgX** where **X** is a halogen, and **R** is an alkyl or aryl (based on a benzene ring) group. For the purposes of this page, we shall take R to be an alkyl group. A typical Grignard reagent might be $\mathbf{CH_3CH_2MgBr}$. Organolithium reagents have the chemical formula RLi. A typical reagent might be $\mathbf{CH_3CH_2Li}$.

Formation of Organometallic Reagents

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).

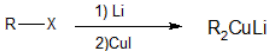
- **An Alkyl Lithium Reagent**

$$\mathbf{R_3C{-}X + 2\,Li \rightarrow R_3C{-}Li + LiX} \tag{11.8.1}$$

- **A Grignard Reagent**

$$\mathbf{R_3C{-}X + Mg \rightarrow R_3C{-}MgX} \tag{11.8.2}$$

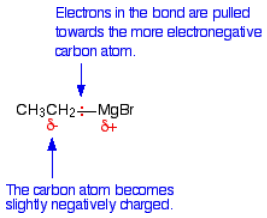
- **An Organocuprate Reagent**



Halide reactivity in these reactions increases in the order: Cl < Br < I and Fluorides are usually not used. The alkyl magnesium halides described in the second 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 other metals mentioned above react in a similar manner, but Grignard and Alky Lithium Reagents most widely used. Although the formulas 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. Organocuprate reagents have limited reactivity and will be used for ketone synthesis.

Organometallic Reagents are Strong Nucleophiles

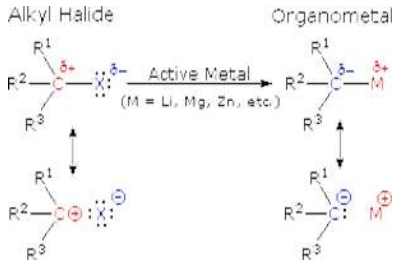
The bond between the carbon atom and the metal atom is polar. Therefore, organometallic reagents are strong nucleophiles. Using the Grignard reagent as an example, the carbon is more electronegative than magnesium, so the bonding pair of electrons is pulled towards the carbon creating a partial negative charge. Grignard reagents are strong nucleophiles. Nucleophilic carbon atoms are very useful in building carbon chains in multiple step systhesis.



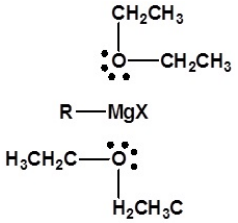
Grignard reactions create the possibility for substitution reactions at vinylic carbons. This reaction pathway is very useful since vinyl halides cannot react by the SN1 and SN2 mechanisms.

Organometallic Reagents and Protic Solvents (like water)

Everything **must** be perfectly dry because organometallic reagents react with water (see below) or any protic solvent. Reactions using the Grignard reagent must use an ether as the solvent. Organolithium reactions also require aprotic solvents, but ethers are not required and alkanes can be used as solvents. The resulting reaction mixture is used directly for the next reaction. There are no separation and isolation procedures between reaction steps. Organometallic reagents react with water or any protic solvent to produce alkanes. For this reason, everything has to be **very dry** during the preparation above. The term **dry** means that no water or other protonated solvents are present. There is still a **liquid** ether solvent.

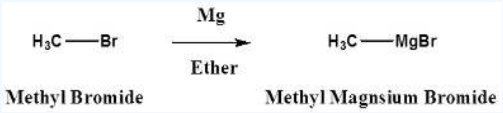


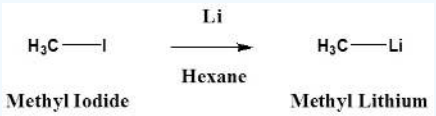
A suitable solvent must be used. For alkyl lithium formation pentane or hexane are usually used. Diethyl ether can also be used but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Ethyl ether or THF are essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (As pictured below). This complex helps stabilize the organometallic and increases its ability to react.



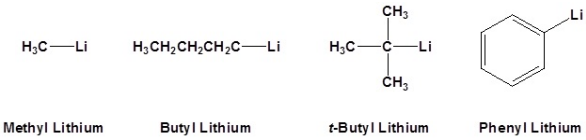
These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents excellent nucleophiles and useful reactants in synthesis.

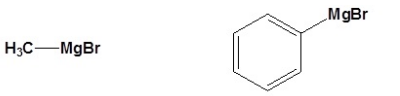
Example:





Common Organometallic Reagents



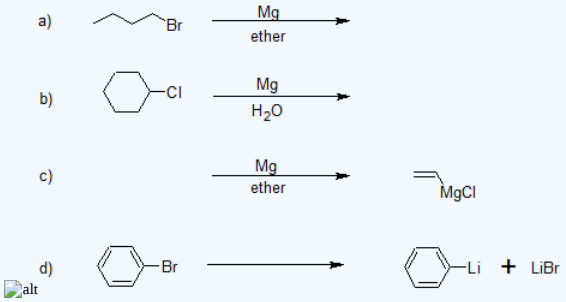


Methyl Magnesium Bromide Phenylmagnesium Bromide

Exercises

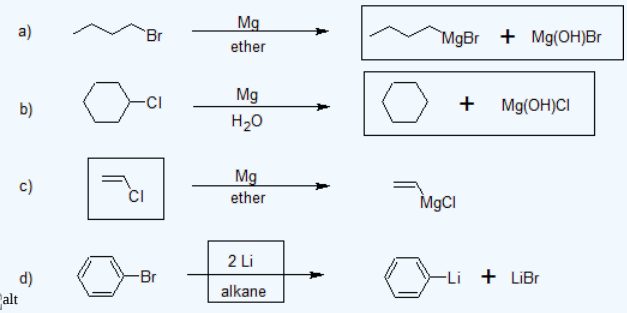
13.

Predict the product or specify the missing regent(s) in the reactions below.



Answer

13.



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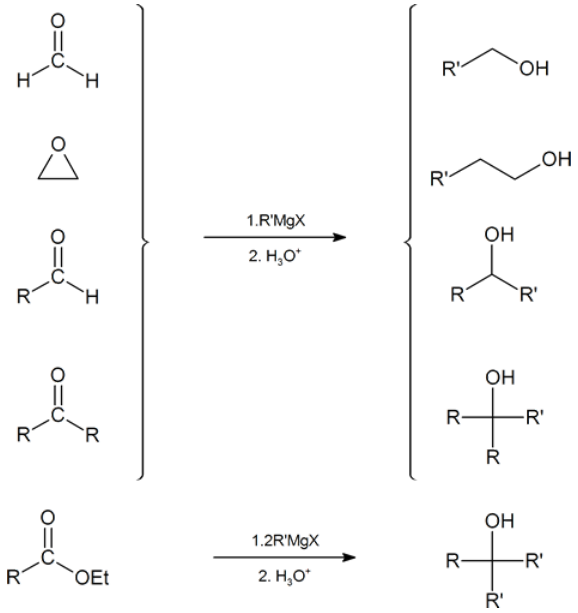
11.9: Organometallic Reagents in Alcohol Synthesis

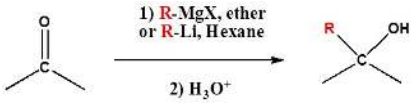
Introduction

The nucleophilic carbon atoms of organometallic reagents react with the electrophilic carbon atoms of aldehydes, ketones, acyl halides, esters, and epoxides to build larger carbon chains. In the process, an alcohol is formed. The ability to build larger organic molecules is an important and useful skill for multi-step synthesis. These various reaction pathways are summarized below showing the Grignard reagent.



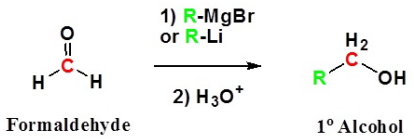
Organometallic Reactions with Aldehydes and Ketones

Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic reaction of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.

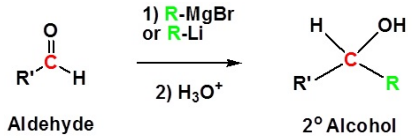


Both Grignard and Organolithium Reagents will perform these reactions.

Addition to formaldehyde gives 1° alcohols.



Addition to aldehydes gives 2° alcohols.



Addition to ketones gives 3° alcohols

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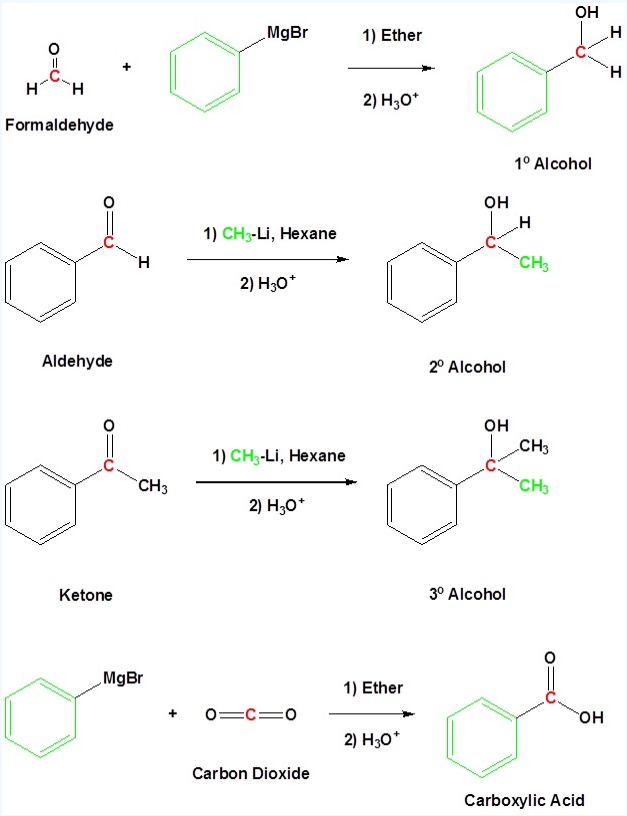
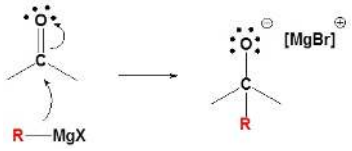
Examples



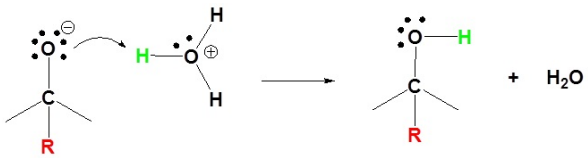
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown. The mechanism for an organolithium reagent is the same.

1) Nucleophilic reaction

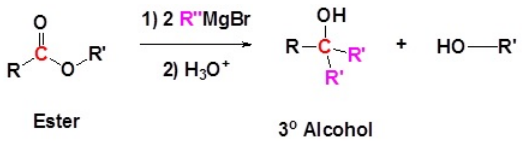


2) Protonation



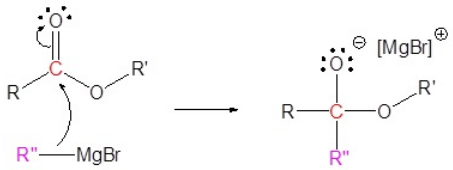
Grignard reagents convert esters to 3° alcohols

After the first Grignard reaction, the carbonyl reforms creating a ketones which can then react with the Grignard. In effect, the Grignard reagent adds twice.

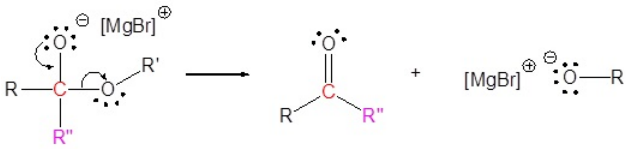


Mechanism

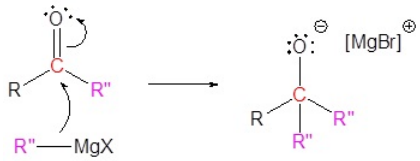
1) Nucleophilic reaction



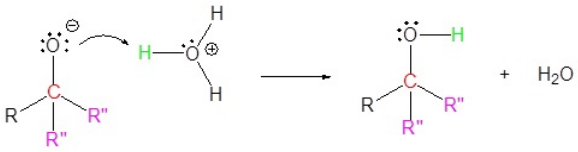
2) Carbonyl reforms with leaving group removal



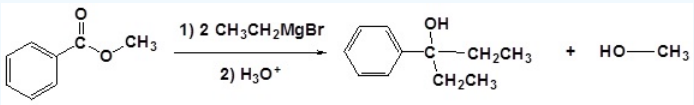
3) Nucleophilic reaction



4) Protonation

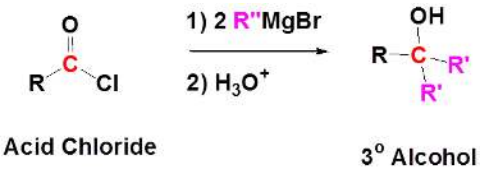


Example

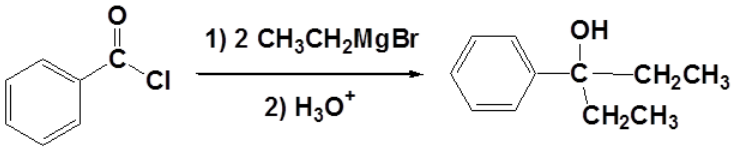


Grignard reagents convert Acyl Halides to 3° alcohols

Grignard reagents react with acyl halides similar to the reaction with esters. The first reaction produces a ketone which them undergoes a second reaction to form a tertiary alcohol following the analogous mechanism shown above for esters.

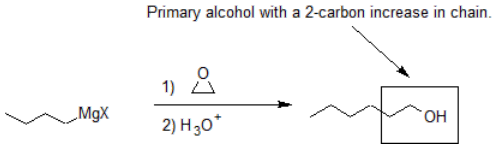


The reaction of benzoyl chloride with a Grignard reagent is shown below as an example.

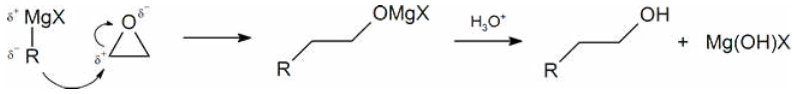


Grignard Reactions with Epoxides

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.

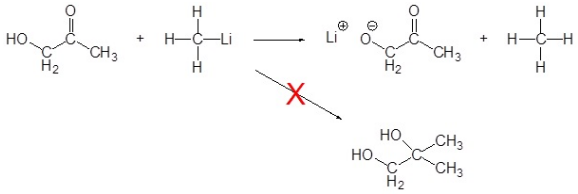


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section.



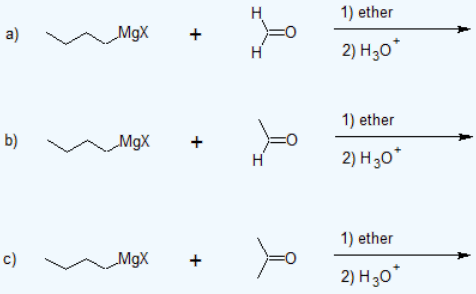
Limitation of Organometallic Reagents

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 are: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

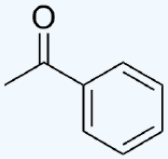


Exercises

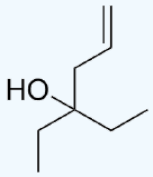
14. Predict the products of the reactions below.

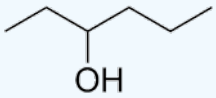


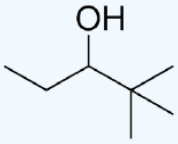
15. If allylmagnesium chloride were added to a solution of the following compound and then worked-up with acid, the product would contain a chiral center. Would the product be a racemic mixture or an enatiomerically pure product? Draw both enantiomers.

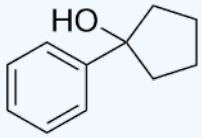


16. What combination of carbonyl compound and grignard (use MgBr) reagent would yield the following alcohols (after workup)?

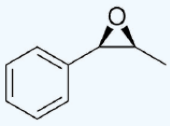
(a) 

(b) 

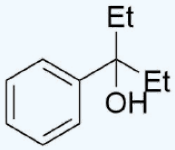
(c) 

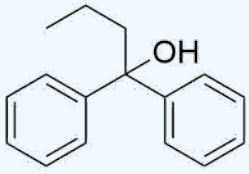
(d) 

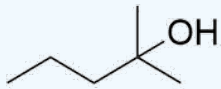
17. The following epoxide can be transformed into an alcohol using a grignard reagent, take for example allylmagnesium chloride. Draw the product of the treatment of this epoxide with this grignard after being worked up with H_2O. Note the stereochemistry and also remember that benzyllic carbons are good Sn2 electrophiles.



18. How might you prepare the following molecules from esters and Grignards?

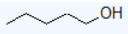
(a) 

(b) 

(c) 

Answer

14.

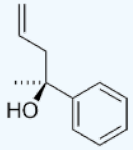
a) 

b)

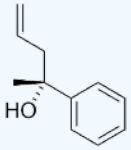
c)

15.

The result would be a racemic mixture of the following.

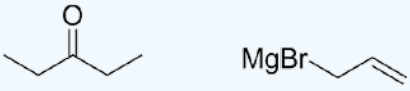


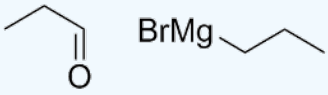
s enantiomer



r enantiomer

16.

(a) 

(b) 

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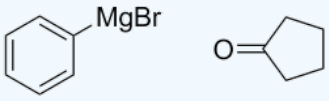
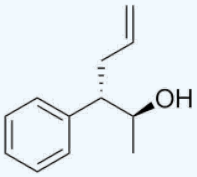
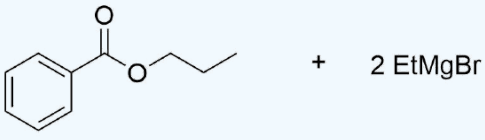
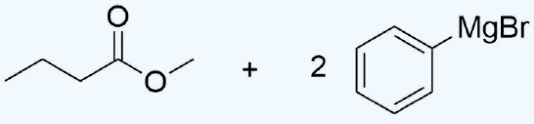
(d) 

17.



18.

(a) 

(b) 

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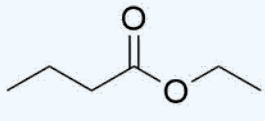
(c)  + 2 CH_3MgBr

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11.10: Thiols (Mercaptans)

Objectives

After completing this section, you should be able to

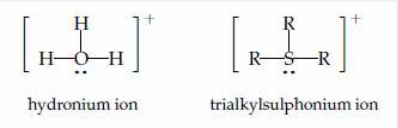
1. Nomenclature and Reactivity
   a. write the IUPAC name of a thiol, given its Kekulé, condensed or shorthand structure.
   b. draw the structure of a thiol, given its IUPAC name.
   c. write an equation to represent the formation of a thiol by the reaction of hydrosulfide anion with an alkyl halide.
   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

- 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 (see Section 11.5, pages 389-394 of the textbook). 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:



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.

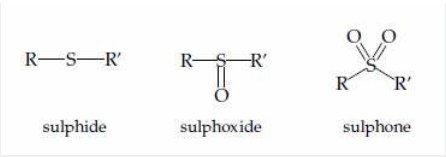


Table 18.1, below, provides a quick comparison of oxygen-containing and sulfur-containing organic compounds.

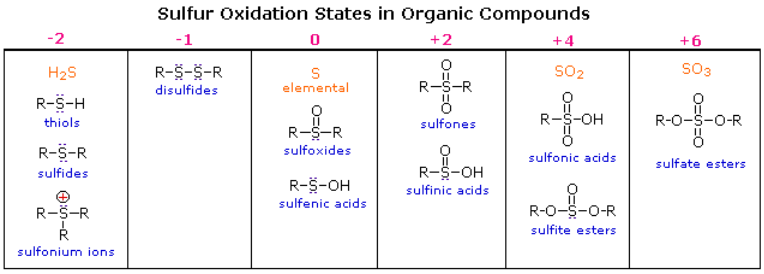
Oxygen-containing Compound	Sulphur Analogue
ether, R—O—R′	sulphide, R—S—R′
R—O—, alkoxy group	R—S—, alkylthio group
R—O⁻, alkoxy anion	R—S⁻, thiolate anion
alcohol, R—OH	thiol, R—SH
—OH, hydroxy group	—SH, mercapto group
R—O—O—R′, peroxide	R—S—S—R′, disulphide

Table 18.1 Comparison of compounds containing oxygen and sulphur

Note that when we name thiols, we include the "e" of the alkane name. Thus, CH_3CH_2SH is called "ethanethiol," not "ethanthiol."

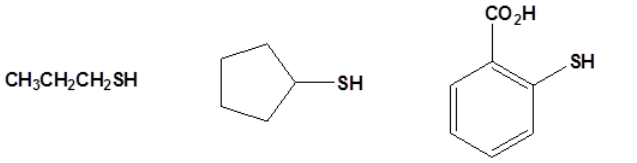
Oxidation States of Sulfur Compounds

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).

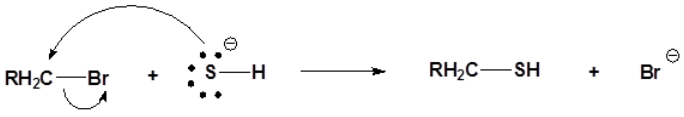


Thiols

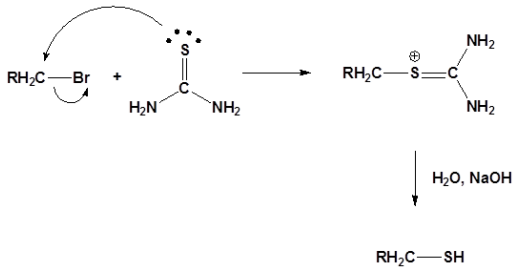
Thiols, which are also called mercaptans, are analogous to alcohols. They are named in a similar fashion as alcohols except the suffix *-thiol* is used in place of *-ol*. By itself the -SH group is called a mercapto group.



Thiols are usually prepared by using the hydrosulfide anion (-SH) as a neucleophile in an S_N2 reaction with alkyl halides.

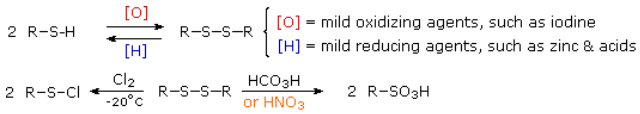


On problem with this reaction is that the thiol product can undergo a second S_N2 reaction with an additional alkyl halide to produce a sulfide side product. This problem can be solved by using thiourea, $(NH_2)_2C{=}S$, as the nucleophile. The reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



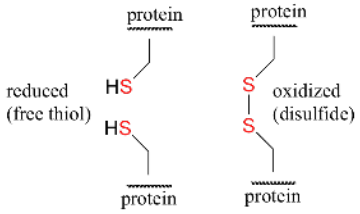
Disulfides

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.



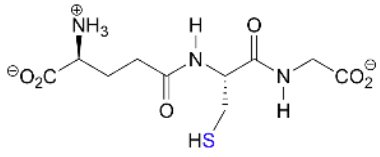
Disulfide bridges in proteins

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.

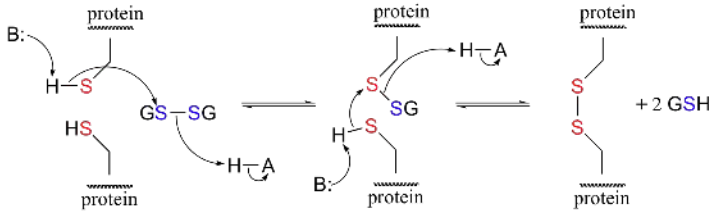
The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). Recall that the important functional group in glutathione is the thiol, highlighted in blue in the figure 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 GSSH, 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.

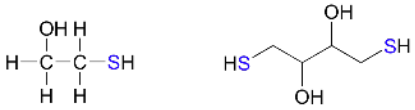


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to $FADH_2$ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.

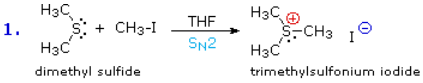


Sulfides

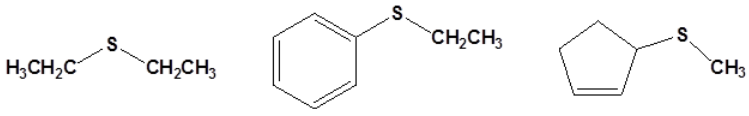
Sulfur analogs of ethers are called **sulfides**. The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

$$R–S^{(-)}\ Na^{(+)} + (CH_3)_2CH–Br \longrightarrow (CH_3)_2CH–S–R + Na^{(+)}\ Br^{(-)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is 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. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3º-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.



sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.

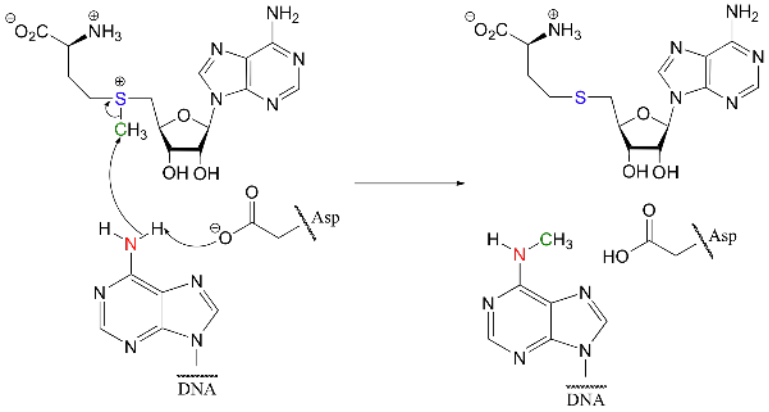


Diethyl sulfide **Ethyl phenyl sulfide** **3-(Methylthio)cyclopentene**

SAM methyltransferases

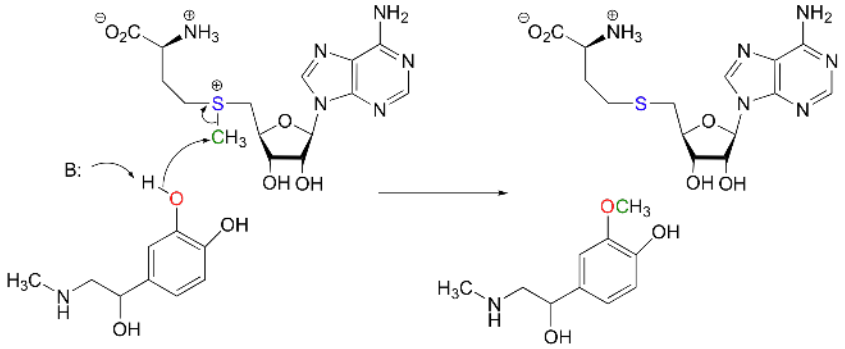
The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. Some of the most important examples of S_N2 reactions in biochemistry are those catalyzed by S-adenosyl methionine (SAM) – dependent

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:



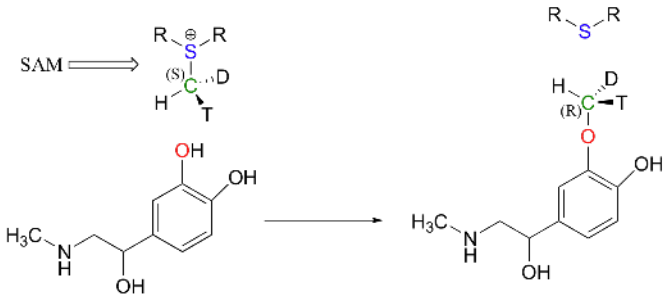
(*Nucleic Acids Res.* **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



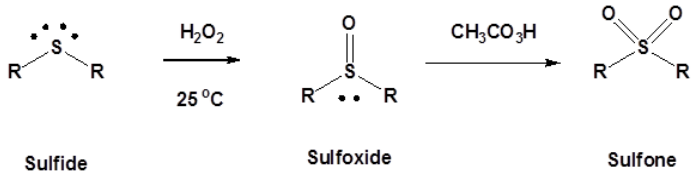
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it 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).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room termpeature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is polar aprotic solvent.

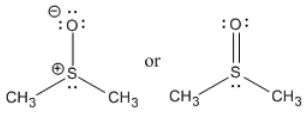


Figure AB16.3. DMSO is a very polar, aprotic solvent.

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- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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11.11: Commercially Important Alcohols

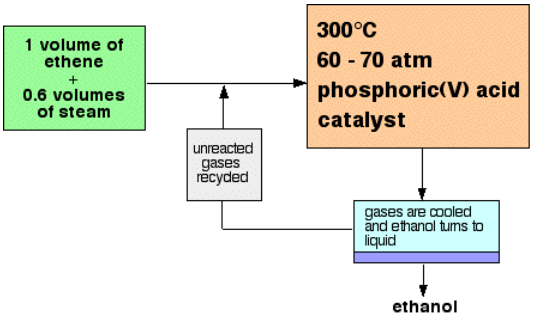
This page looks at the manufacture of alcohols by the direct hydration of alkenes, concentrating mainly on the hydration of ethene to make ethanol. It then compares that method with making ethanol by fermentation.

Manufacturing alcohols from alkenes

Ethanol is manufactured by reacting ethene with steam. The catalyst used is solid silicon dioxide coated with phosphoric(V) acid. The reaction is reversible.

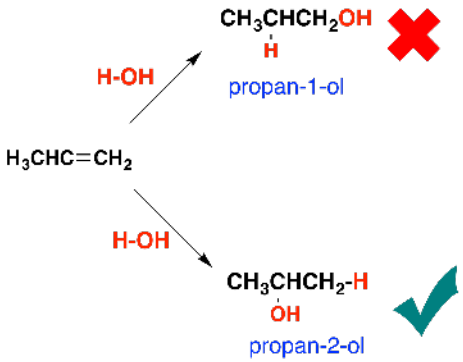
$$H_2C{=}CH_2(g) \;+\; H_2O(g) \underset{}{\overset{H_3PO_4}{\rightleftharpoons}} CH_3CH_2OH(g)$$

Only 5% of the ethene is converted into ethanol at each pass through the reactor. By removing the ethanol from the equilibrium mixture and recycling the ethene, it is possible to achieve an overall 95% conversion. A flow scheme for the reaction looks like this:



The manufacture of other alcohols from alkenes

Some - but not all - other alcohols can be made by similar reactions. The catalyst used and the reaction conditions will vary from alcohol to alcohol. The reason that there is a problem with some alcohols is well illustrated with trying to make an alcohol from propene, $CH_3CH{=}CH_2$. In principle, there are two different alcohols which might be formed:



You might expect to get either propan-1-ol or propan-2-ol depending on which way around the water adds to the double bond. In practice what you get is propan-2-ol. If you add a molecule H-X across a carbon-carbon double bond, the hydrogen nearly always gets attached to the carbon with the most hydrogens on it already - in this case the CH_2 rather than the CH. The effect of this is that there are bound to be some alcohols which it is impossible to make by reacting alkenes with steam because the addition would be the wrong way around.

Making ethanol by fermentation

This method only applies to ethanol and you cannot make any other alcohol this way. The starting material for the process varies widely, but will normally be some form of starchy plant material such as maize (US: corn), wheat, barley or potatoes. Starch is a complex carbohydrate, and other carbohydrates can also be used - for example, in the lab sucrose (sugar) is normally used to

produce ethanol. Industrially, this wouldn't make sense. It would be silly to refine sugar if all you were going to use it for was fermentation. There is no reason why you should not start from the original sugar cane, though.

The first step is to break complex carbohydrates into simpler ones. For example, if you were starting from starch in grains like wheat or barley, the grain is heated with hot water to extract the starch and then warmed with malt. Malt is germinated barley which contains enzymes which break the starch into a simpler carbohydrate called maltose, $C_{12}H_{22}O_{11}$. Maltose has the same molecular formula as sucrose but contains two glucose units joined together, whereas sucrose contains one glucose and one fructose unit.

Yeast is then added and the mixture is kept warm (say 35°C) for perhaps several days until fermentation is complete. Air is kept out of the mixture to prevent oxidation of the ethanol produced to ethanoic acid (vinegar). Enzymes in the yeast first convert carbohydrates like maltose or sucrose into even simpler ones like glucose and fructose, both $C_6H_{12}O_6$, and then convert these in turn into ethanol and carbon dioxide. You can show these changes as simple chemical equations, but the biochemistry of the reactions is much, much more complicated than this suggests.

$$C_{12}H_{22}O_{11} + H_2O \longrightarrow 2C_6H_{12}O_6 \tag{11.11.1}$$

$$C_6H_{12}O_6 \longrightarrow 2CH_3CH_2OH + 2CO2 \tag{11.11.2}$$

Yeast is killed by ethanol concentrations in excess of about 15%, and that limits the purity of the ethanol that can be produced. The ethanol is separated from the mixture by fractional distillation to give 96% pure ethanol. For theoretical reasons (minimum boiling point azeotrope), it is impossible to remove the last 4% of water by fractional distillation.

Table 1.1.1: A comparison of fermentation with the direct hydration of ethene

	Fermentation	Hydration of ethene
Type of process	A batch process. Everything is put into a container and then left until fermentation is complete. That batch is then cleared out and a new reaction set up. This is inefficient.	A continuous flow process. A stream of reactants is passed continuously over a catalyst. This is a more efficient way of doing things.
Rate of reaction	Very slow.	Very rapid.
Quality of product	Produces very impure ethanol which needs further processing	Produces much purer ethanol.
Reaction conditions	Uses gentle temperatures and atmospheric pressure.	Uses high temperatures and pressures, needing lots of energy input.
Use of resources	Uses renewable resources based on plant material.	Uses finite resources based on crude oil.

Contributors

- Jim Clark (Chemguide.co.uk)

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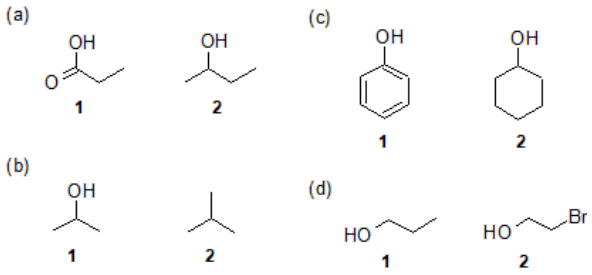
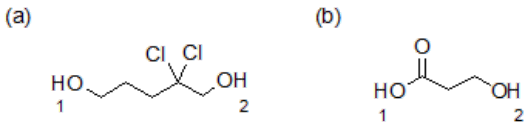
11.12: 13.12 Additional Exercises

Physical Properties of Alcohols

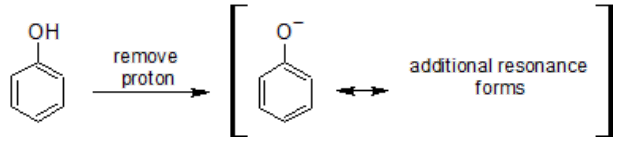
13-1 Identify which compound is more acidic. Explain your reasoning for each choice.



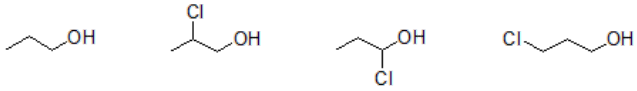
13-2 Identify which is the most acidic proton in the following compounds. Explain your reasoning for each choice.



13-3 Draw all possible resonance forms of the conjugate base of phenol.



13-4 List the following compounds in order from most to least acidic.



13-5 Predict which compound of each pair is more soluble in water and explain your reasoning.

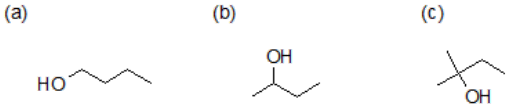
1. butan-1-ol or pentan-1-ol
2. phenol or cyclohexanol
3. octan-1,3-diol or octan-1-ol
4. 1-chlorohexane or hexan-1-ol

13-6 Predict which compound has the higher boiling point and explain your reasoning.

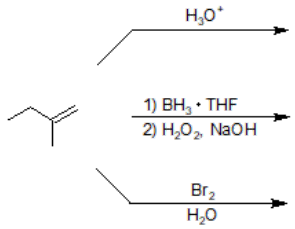
1. water or ethanol
2. butan-1-ol or octan-1-ol
3. hexan-2-ol or hexan-2-one

Synthesis of Alcohols

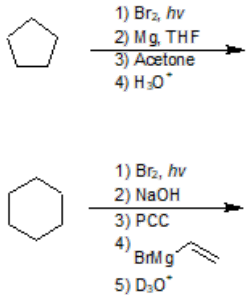
13-7 Show a possible way to synthesize the following alcohols.



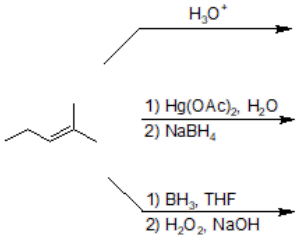
13-8 Give the product of each reaction.



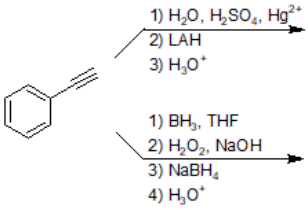
13-9 Give the product of each reaction.



13-10 Give the product of each reaction.

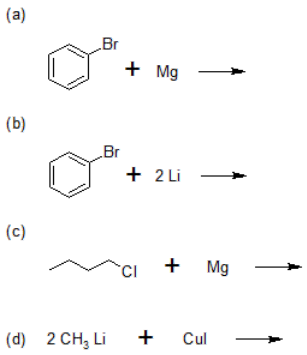


13-11 Give the product of each reaction.

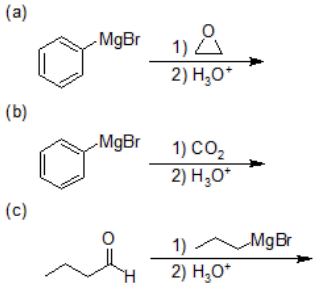


Organometallic Reagents for Alcohol Synthesis

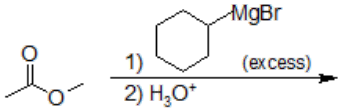
13-12 Draw the products of the following reactions.



13-13 Draw the products of the following reactions.

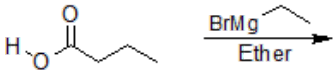


13-14 What is the final product of the following reaction.



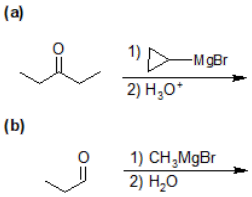
13-15 Draw the mechanism for question **13-14**.

13-16 Identify the product of the following reaction and explain why that is the correct answer.

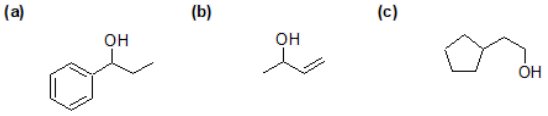


Addition of Organometallic Reagents to Carbonyl Compounds

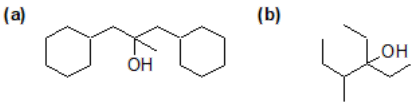
13-17 Give the product(s) of the following reactions. Include stereochemistry when necessary.



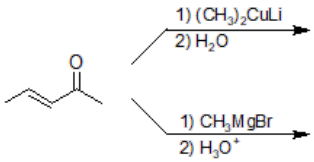
13-18 Show a possible carbonyl compound that was used to make the following alcohols through a Grignard reaction.



13-19 For the following compounds, identify the Grignard reagent used and the initial methyl ester compound.

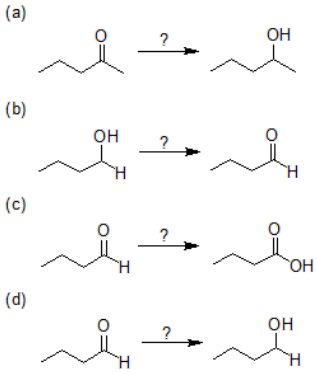


13-20 Give the products of the following reactions.

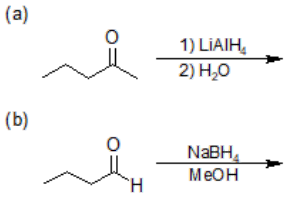


Reduction of the Carbonyl Group

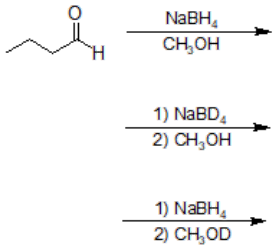
13-21 Identify whether the initial compound is undergoing oxidation or reduction.



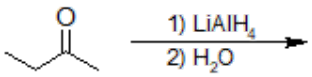
13-22 Give the product of each reaction.



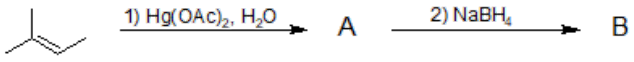
13-23 Give the product of each reaction (same starting molecule), making sure to specify where each proton ends up in the final product.



13-24 Give the mechanism for the following hydride reduction reaction.



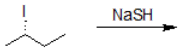
13-25 Draw the structures for A and B.



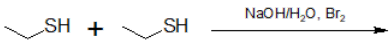
Thiols (Mercaptans)

13-26 Name the following compounds following IUPAC nomenclature.

13-27 Identify the product of the following reaction. Include stereochemistry if appropriate.



13-28 Identify the product of the following reaction.



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11.13: Solutions to Additional Exercises

Physical Properties of Alcohols

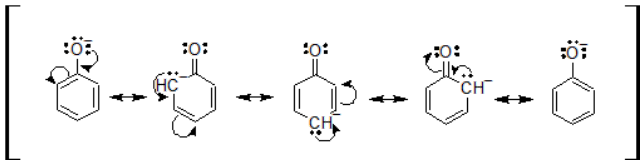
13-1

1. Compound 1 is more acidic than compound 2, since its conjugate base is stabilized by resonance.
2. Compound 1 is more acidic than compound 2 as the proton in question is bonded to a very electronegative atom (oxygen). When comparing the conjugate bases of both compounds, oxygen can stabilize a negative charge far better than the carbon atom of compound 2, allowing it to be a more stable conjugate base and stronger acid.
3. Compound 1 is more acidic than compound 2, since its conjugate base is stabilized by resonance.
4. Compound 2 is more acidic than compound 1. The halogen on compound 2 helps stabilize the negative charge of the conjugate base by withdrawing electron density through induction.

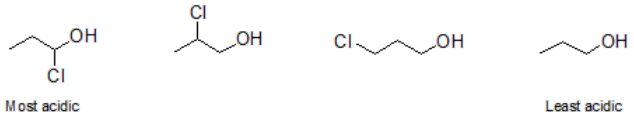
13-2

1. Proton 2 is more acidic than proton 1. The conjugate base formed by removing proton 2 is more stable than the conjugate base formed by removing proton 1, due to the strong induction effects by the halogens which withdraw electron density and stabilize the negative charge.
2. Proton 1 is more acidic than proton 2. The conjugate base formed by removing proton 1 is stabilized by resonance.

13-3 Resonance forms of the phenol conjugate base:



13-4



13-5

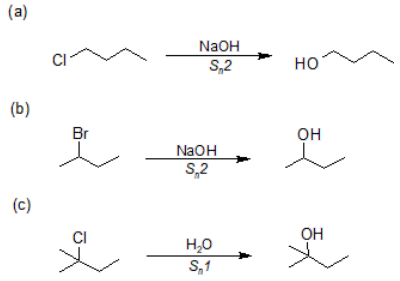
1. butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
2. phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better than cyclohexanol due to the conjugated pi-system of electrons in its ring, which which gives it a more ionic character.
3. 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.
4. 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.

13-6

1. 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.
2. 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.
3. Since hexan-1-ol can H-bond, it has a higher boiling point than hexan-2-one, which cannot H-bond.

Synthesis of Alcohols

13-7



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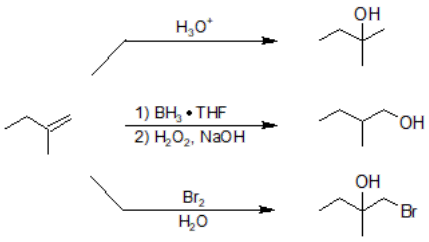

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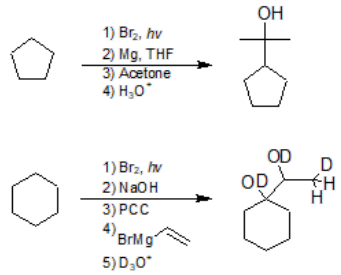

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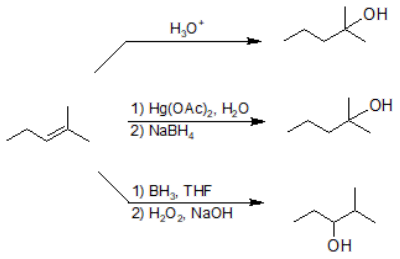
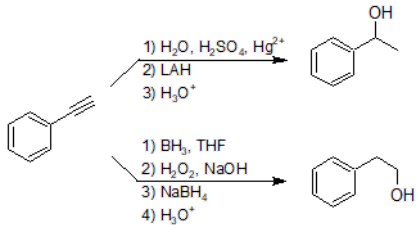
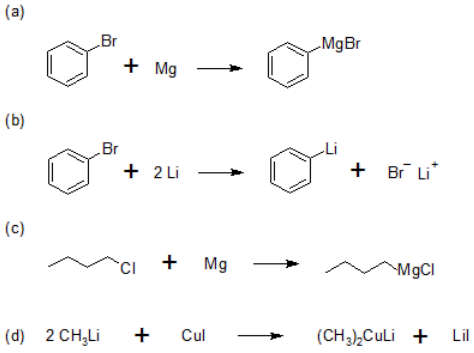


13-11

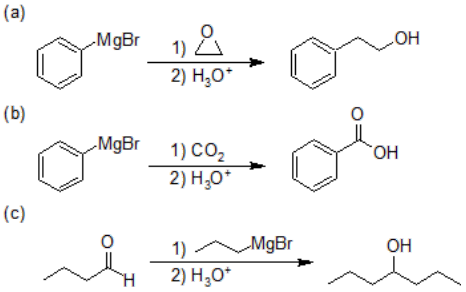


Organometallic Reagents for Alcohol Synthesis

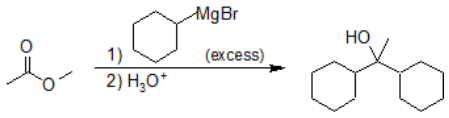
13-12



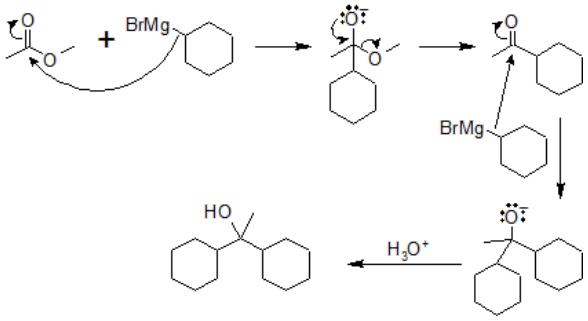
13-13



13-14

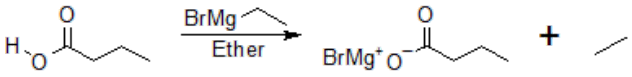


13-15



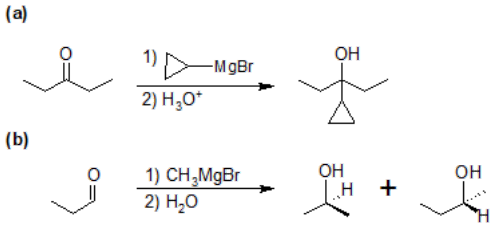
13-16

When you react an acid with an organometallic reagent, you will get a salt since organometallics are strong bases and will deprotonate the acid, before even getting a chance to attack the carbonyl carbon.



Addition of Organometallic Reagents to Carbonyl Compounds

13-17



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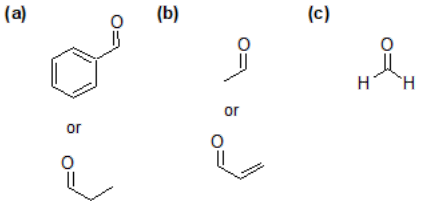

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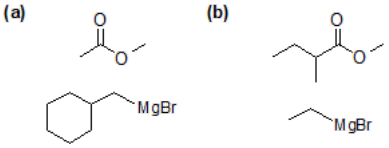

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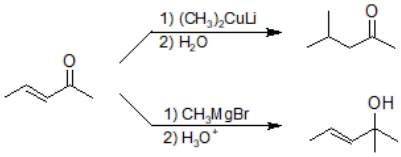
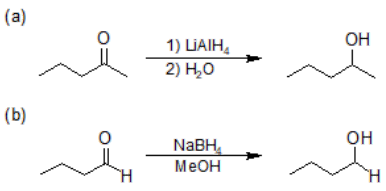


Reduction of the Carbonyl Group

13-21

1. Reduction
2. Oxidation
3. Oxidation
4. Reduction

13-22



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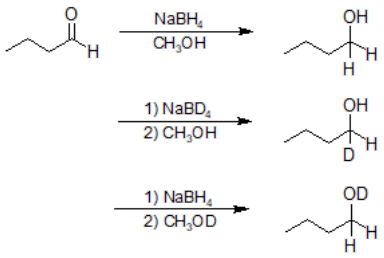

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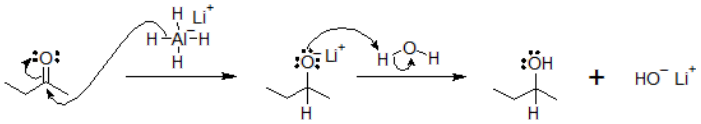

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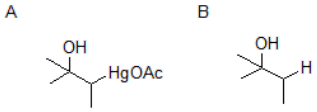
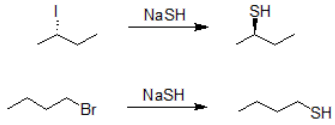


Thiols (Mercaptans)

13-26

13-27



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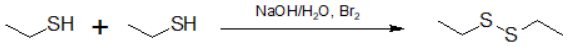

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CHAPTER OVERVIEW

12: Infrared Spectroscopy and Mass Spectrometry

Learning Objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- correlate regions of the electromagnetic spectrum to spectroscopic techniques - refer to section 11.1
- explain how an IR spectrometer works and the IR region interacts with organic compounds - refer to section 11.2
- explain the role of asymmetry in IR absorption - refer to section 11.3
- interpret IR spectra - refer to section 11.4, 11.5, and 11.6
- expalin how a mass spectrometer works - refer to section 11.7
- explain the source of the base peak and molecular ion in a mass spectrum - refer to section 11.7
- correlate bond strength to fragmentation patterns - refer to section 11.8
- use fragmentation patterns to elucidate structural features of organic compounds - refer to section 11.9
- explain how high-resolution mass can be used to determine chemical formulas - refer to section 11.10

12.1: The Electromagnetic Spectrum

12.2: Infrared (IR) Spectroscopy

12.3: IR-Active and IR-Inactive Vibrations

12.4: Interpretting IR Spectra

12.5: Infrared Spectra of Some Common Functional Groups

12.6: Summary and Tips to Distinguish between Carbonyl Functional Groups

12.7: Mass Spectrometry - an introduction

12.8: Fragmentation Patterns in Mass Spectrometry

12.9: Useful Patterns for Structure Elucidation

12.10: Determination of the Molecular Formula by High Resolution Mass Spectrometry

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12.1: 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 $1 \text{ Hz} = \text{s}^{-1}$.

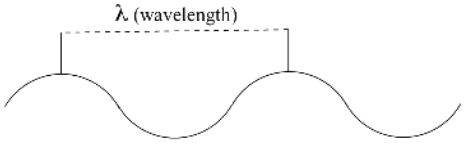
A *quantum* is a small, definite quantity of electromagnetic radiation whose energy is directly proportional to its frequency. (The plural is "quanta.") If you wish, you can read about the properties of electromagnetic radiation and the relationships among wavelength, frequency and energy, or refer to 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:

$$E = \frac{hc}{\lambda} \tag{12.5.1}$$

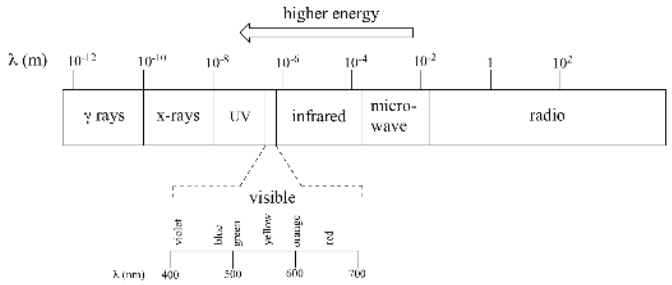
where E is energy in kcal/mol, **λ** (the Greek letter *lambda*) is wavelength in meters, *c* is 3.00 x 10^{8} m/s (the speed of light), and *h* is 9.537 x 10^{-14} kcal•s•mol^{-1}, a number known as Planck's constant.

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 4.29 x 10^{14} Hz, and an energy of 40.9 kcal per mole of photons. 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

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?

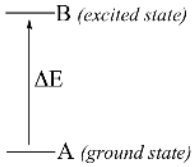
Solution

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.



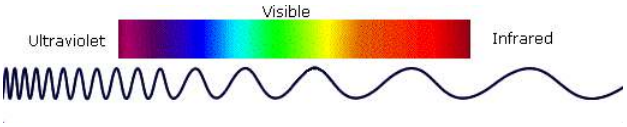
By observing which wavelengths a molecule absorbs, and to what extent it absorbs them, we can gain information about the nature of the energetic transitions that a molecule is able to undergo, and thus information about its structure.

12.1: The Electromagnetic Spectrum is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

12.2: Infrared (IR) Spectroscopy

Introduction

Photon energies associated with the infrared (from 1 to 15 kcal/mole) are not large enough to excite electrons, but may induce vibrational excitation of covalently bonded atoms and groups.

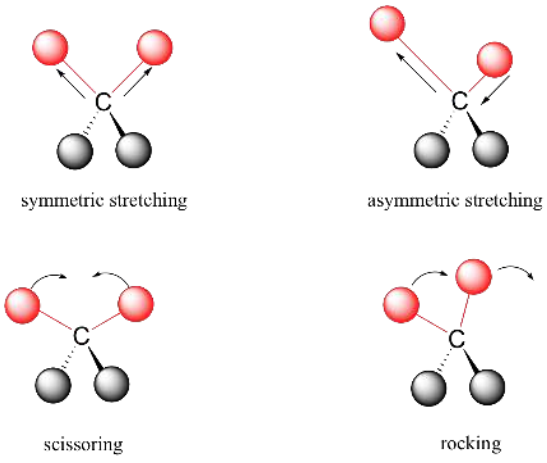


The covalent bonds in molecules are not rigid sticks or rods, such as found in molecular model kits, but are more like stiff springs that can be stretched and bent. The mobile nature of organic molecules was noted in the chapter concerning conformational isomers. We must now recognize that, in addition to the facile rotation of groups about single bonds, molecules experience a wide variety of vibrational motions, characteristic of their component atoms. Consequently, virtually all organic compounds will absorb infrared radiation that corresponds in energy to these vibrations. Infrared spectrometers, similar in principle to the UV-Visible spectrometer described elsewhere, permit chemists to obtain absorption spectra of compounds that are a unique reflection of their molecular structure.

Vibrational Spectroscopy

A molecule composed of n-atoms has 3n degrees of freedom, six of which are translations and rotations of the molecule itself. This leaves 3n-6 degrees of vibrational freedom (3n-5 if the molecule is linear). Vibrational modes are often given descriptive names, such as stretching, bending, scissoring, rocking and twisting. The four-atom molecule of formaldehyde, the gas phase spectrum of which is shown below, provides an example of these terms. If a ball & stick model of formaldehyde is not displayed to the right of the spectrum, press the **view ball&stick model** button on the right. We expect six fundamental vibrations (12 minus 6), and these have been assigned to the spectrum absorptions. To see the formaldehyde molecule display a vibration, click one of the buttons under the spectrum, or click on one of the absorption peaks in the spectrum.

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.

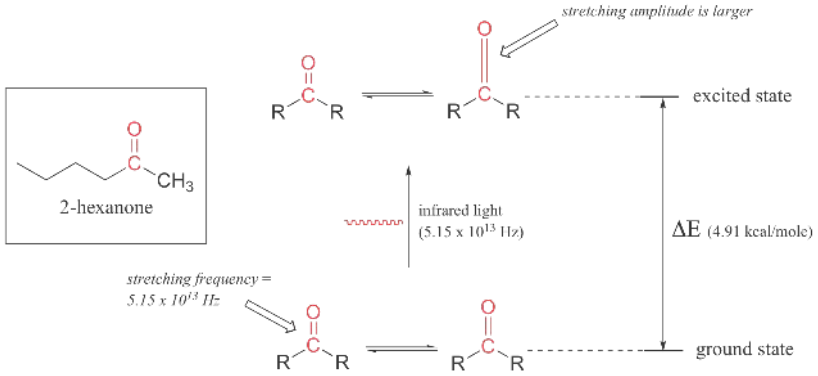


The energy of molecular vibration is *quantized* rather than continuous, meaning that a molecule can only stretch and bend at certain 'allowed' frequencies. If a molecule is exposed to electromagnetic radiation that matches the frequency of one of its vibrational modes, it will in most cases absorb energy 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.

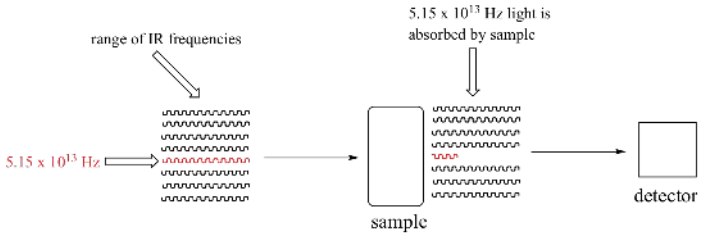
An IR Spectrum

We will use a ketone sample to illustrate this process. The sample is irradiated with infrared light and 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.

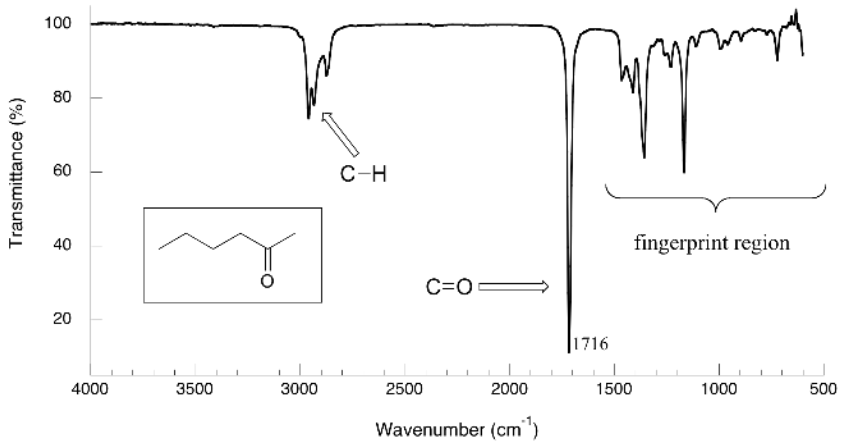


Our 5.15 x 10^{13} Hz carbonyl stretching frequency, however, is absorbed by the 2-hexanone sample, and so the detector records that the intensity of this frequency, after having passed through the sample, is something less than 100% of its initial intensity.

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.

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!

A calculator for interconverting these frequency and wavelength values is provided on the right. Simply enter the value to be converted in the appropriate box, press "Calculate" and the equivalent number will appear in the empty box.
Infrared spectra may be obtained from samples in all phases (liquid, solid and gaseous). Liquids are usually examined as a thin film sandwiched between two polished salt plates (note that glass absorbs infrared radiation, whereas NaCl is transparent). If solvents are used to dissolve solids, care must be taken to avoid obscuring important spectral regions by solvent absorption. Perchlorinated solvents such as carbon tetrachloride, chloroform and tetrachloroethene are commonly used. Alternatively, solids may either be incorporated in a thin KBr disk, prepared under high pressure, or mixed with a little non-volatile liquid and ground to a paste (or mull) that is smeared between salt plates.

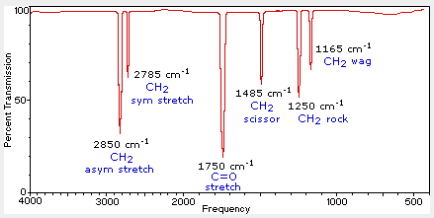
Frequency - Wavelength Converter

Frequency in cm^{-1}

Calculate

Wavelength in μ

Gas Phase Infrared Spectrum of Formaldehyde, $H_2C=O$



1. View CH2 Asymmetric Stretch
   View CH2 Symmetric Stretch
   View C=O Stretch
   View CH2 Scissoring
   View CH2 Rocking
   View CH2 Wagging

- O Ball&Stick Model
- O Spacefill Model
- O Stick Model
- O Motion Off

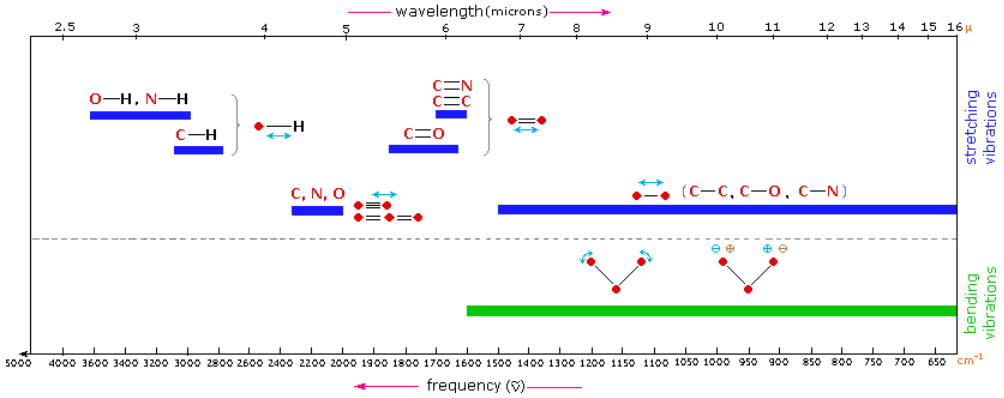
The exact frequency at which a given vibration occurs is determined by the strengths of the bonds involved and the mass of the component atoms. For a more detailed discussion of these factors Click Here. In practice, infrared spectra do not normally display separate absorption signals for each of the 3n-6 fundamental vibrational modes of a molecule. The number of observed absorptions may be increased by additive and subtractive interactions leading to combination tones and overtones of the fundamental vibrations, in much the same way that sound vibrations from a musical instrument interact. Furthermore, the number of observed absorptions may be decreased by molecular symmetry, spectrometer limitations, and spectroscopic selection rules. One selection rule that influences the intensity of infrared absorptions, is that a change in dipole moment should occur for a vibration to absorb infrared energy. Absorption bands associated with C=O bond stretching are usually very strong because a large change in the dipole takes place in that mode.

Some General Trends:

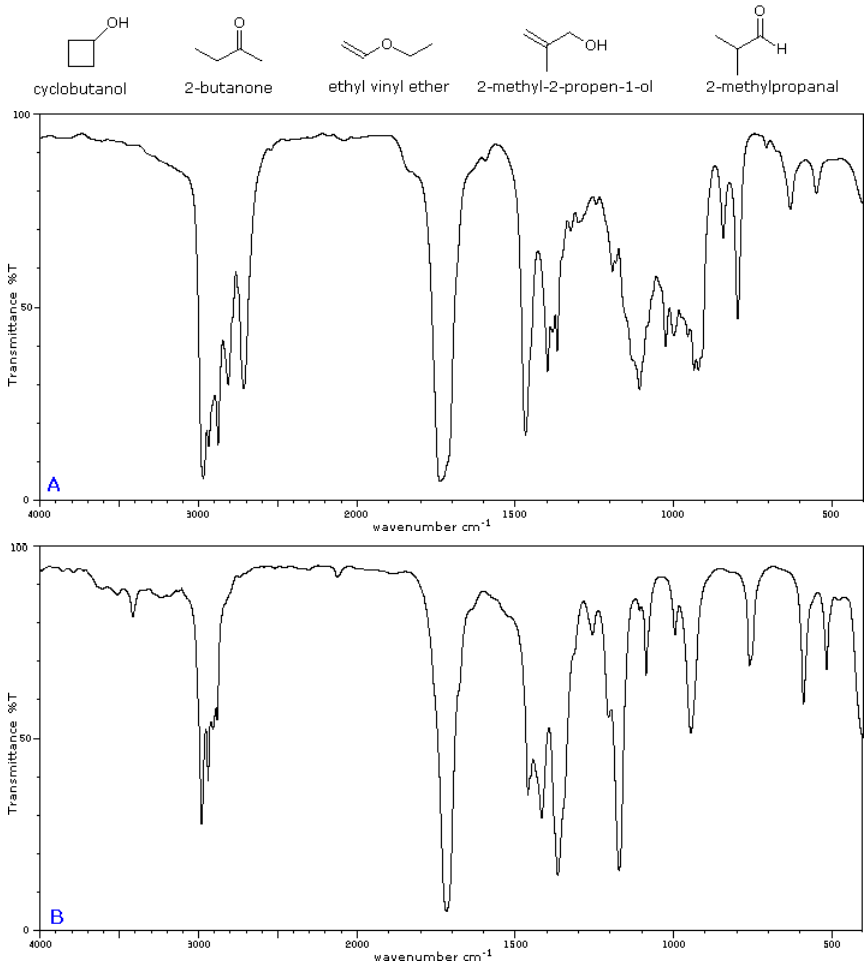
1. Stretching frequencies are higher than corresponding bending frequencies. (It is easier to bend a bond than to stretch or compress it.)
2. Bonds to hydrogen have higher stretching frequencies than those to heavier atoms.
3. Triple bonds have higher stretching frequencies than corresponding double bonds, which in turn have higher frequencies than single bonds.(Except for bonds to hydrogen).

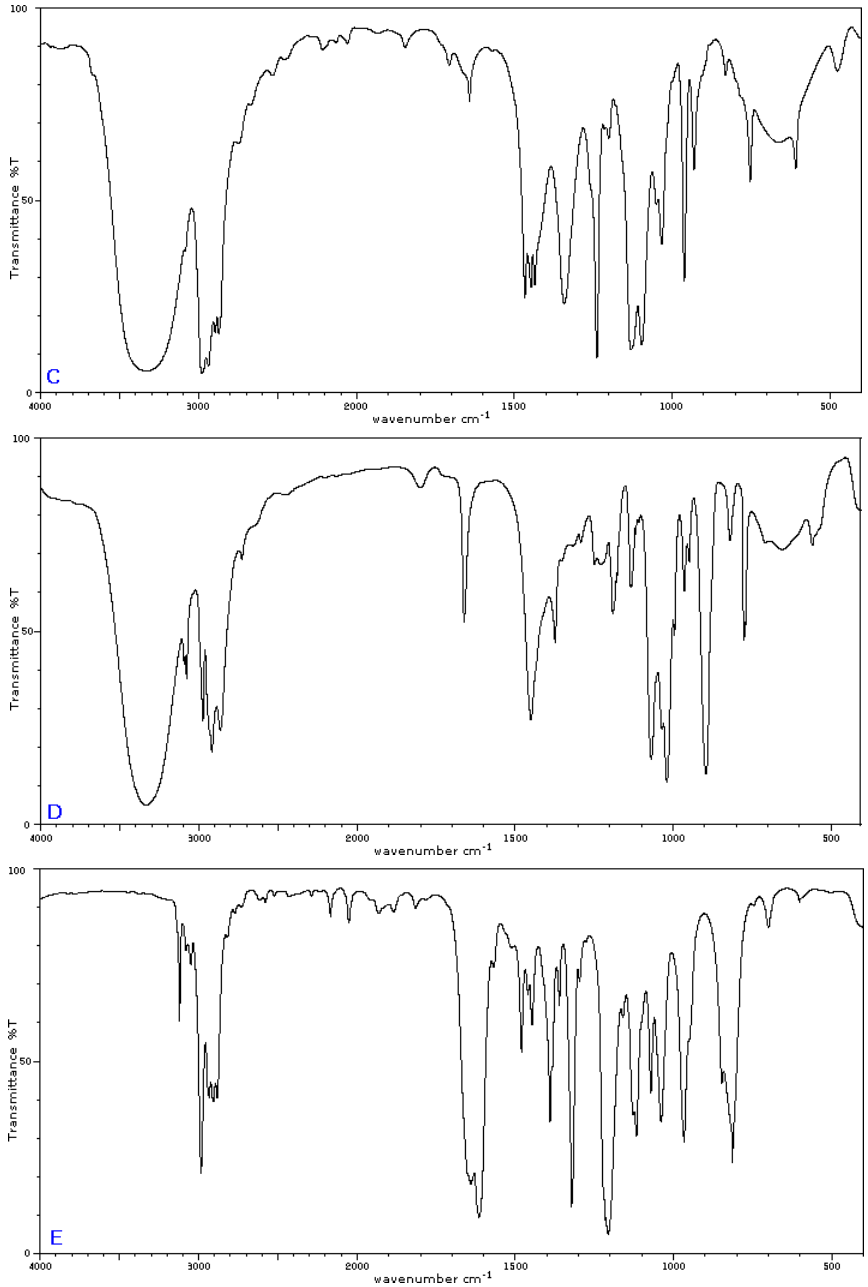
The general regions of the infrared spectrum in which various kinds of vibrational bands are observed are outlined in the following chart. Note that the blue colored sections above the dashed line refer to stretching vibrations, and the green colored band below the

line encompasses bending vibrations. The complexity of infrared spectra in the 1450 to 600 cm^{-1} region makes it difficult to assign all the absorption bands, and because of the unique patterns found there, it is often called the **fingerprint** region. Absorption bands in the 4000 to 1450 cm^{-1} region are usually due to stretching vibrations of diatomic units, and this is sometimes called the **group frequency** region.



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 (A - E) with one of the isomers in the row above it.





Answers

Internal Links

- Organic Chemistry With a Biological Emphasis

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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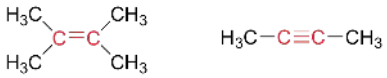
12.3: IR-Active and IR-Inactive Vibrations

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

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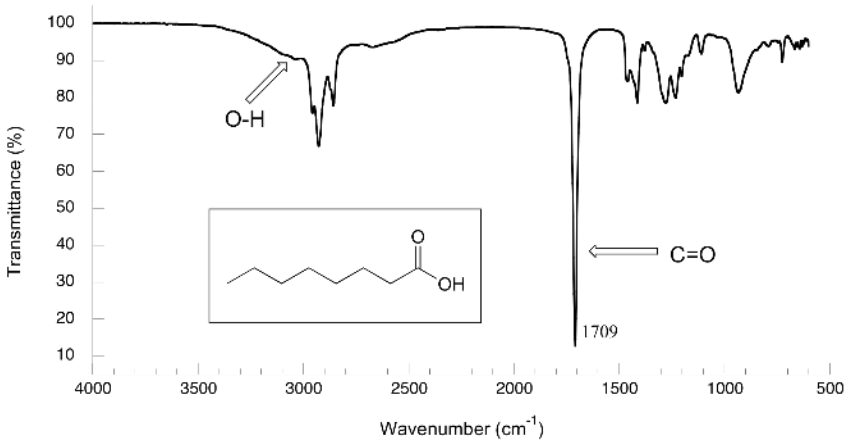
12.4: Interpretting IR Spectra

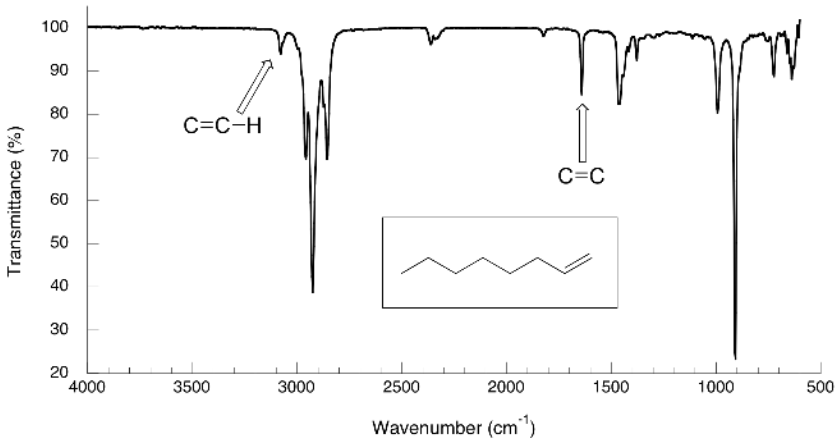
Guided IR Spectrum Interpretation

Now, let's take a look at the IR spectrum for 1-hexanol. There 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-

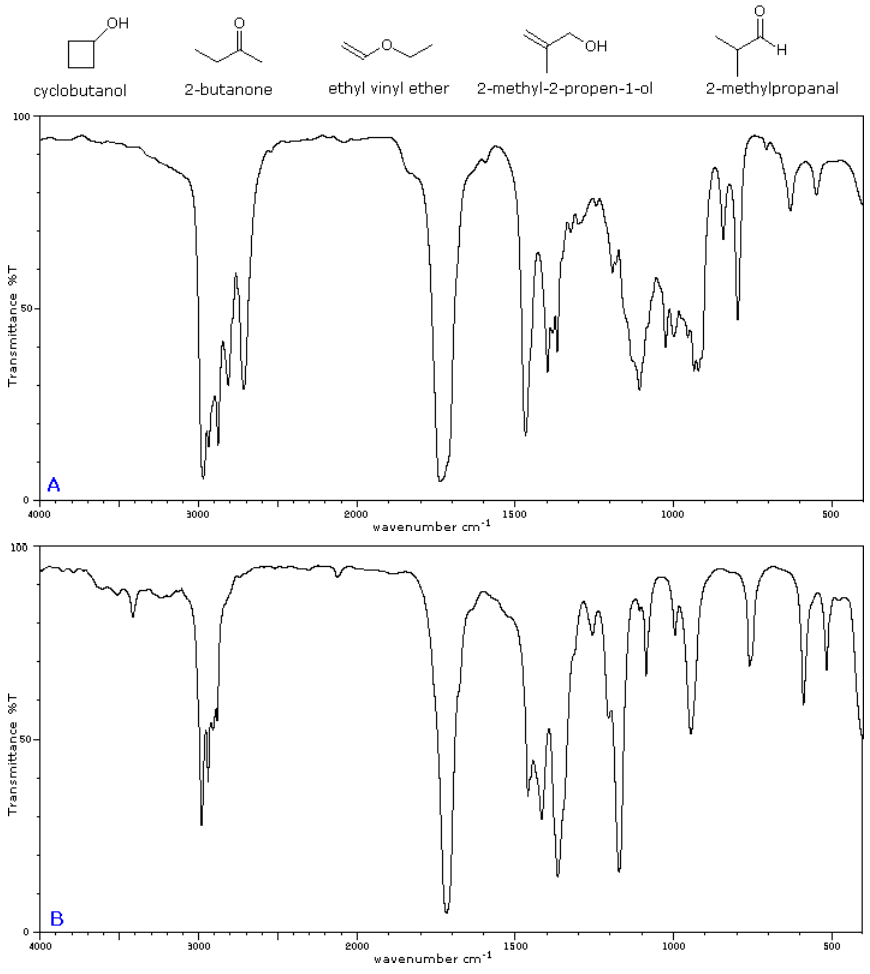
hybridized carbon and the terminal hydrogen.

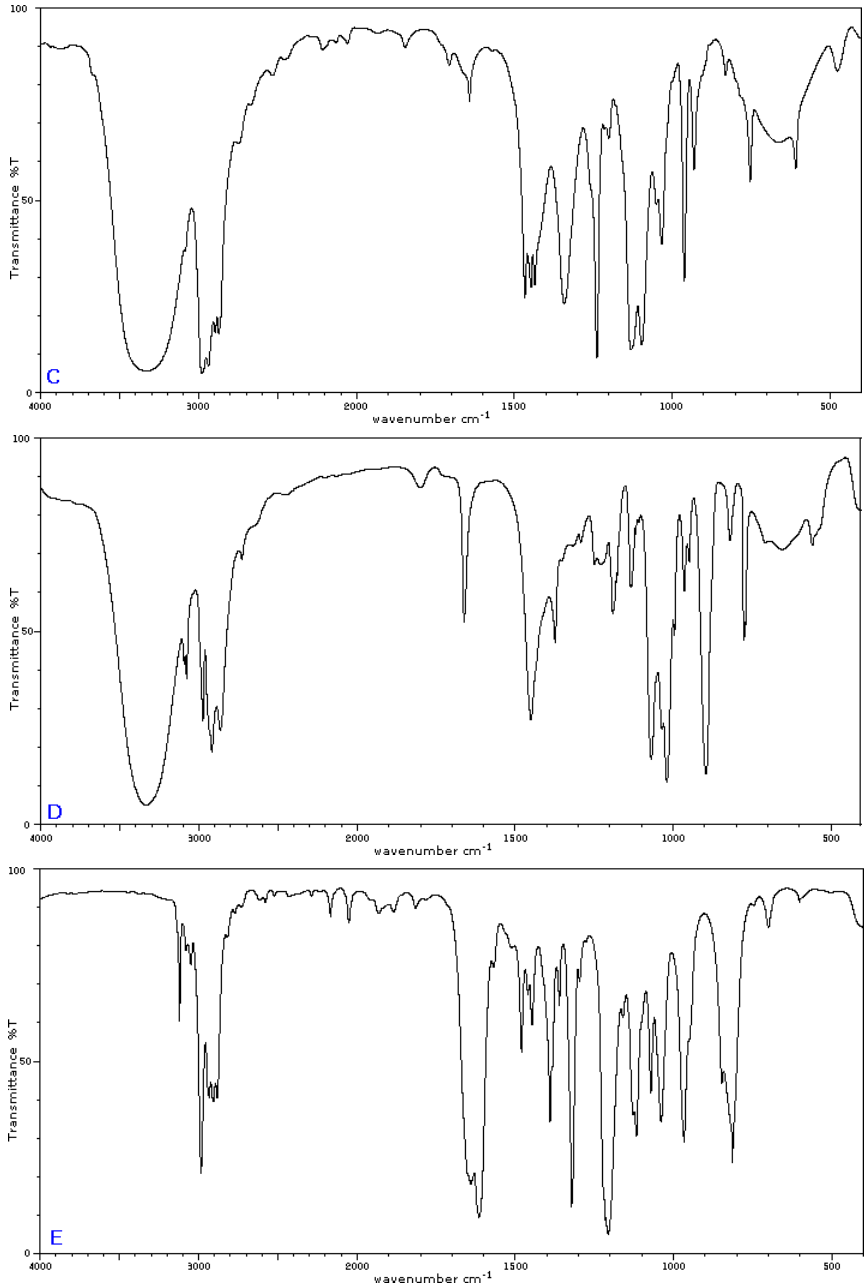
It is possible to identify other functional groups such as amines and ethers, but the characteristic peaks for these groups are considerably more subtle and/or variable, and often are overlapped with peaks from the fingerprint region. For this reason, we will limit our discussion here to the most easily 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.





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}

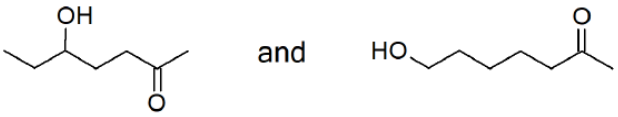
Q12.7.2

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.

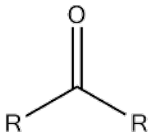
C)

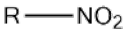


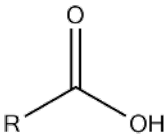
(i) (ii)

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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12.5: Infrared Spectra of Some Common Functional Groups

Common Group Frequencies Summary

When analyzing an IR spectrum, it is helpful to overlay the diagram below onto the spectrum with our mind to help recognize functional groups.

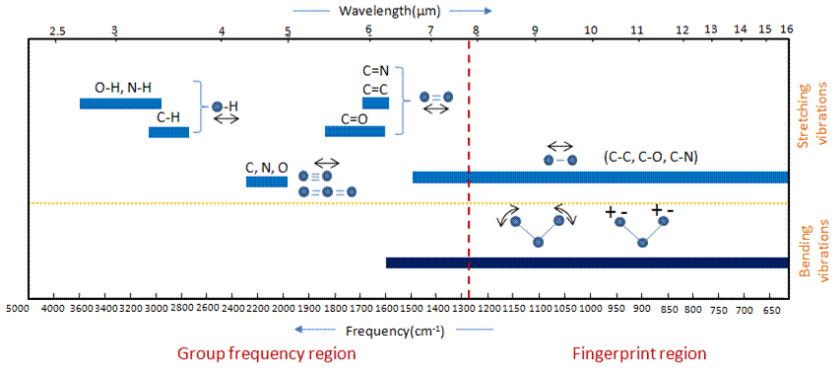


Figure 1. Group frequency and fingerprint regions of the mid-infrared spectrum

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.

Group Frequencies - a closer look

Detailed information about the infrared absorptions observed for various bonded atoms and groups is usually presented in tabular form. The following table provides a collection of such data for the most common functional groups. Following the color scheme of the chart, stretching absorptions are listed in the blue-shaded section and bending absorptions in the green shaded part. **More detailed descriptions for certain groups (e.g. alkenes, arenes, alcohols, amines & carbonyl compounds) may be viewed by clicking on the functional class name**. Since most organic compounds have C-H bonds, a useful rule is that absorption in the 2850 to 3000 cm^{-1} is due to sp^3 C-H stretching; whereas, absorption above 3000 cm^{-1} is from sp^2 C-H stretching or sp C-H stretching if it is near 3300 cm^{-1}.

Stretching Vibrations	Bending Vibrations

Functional Class	Range (cm^{-1})	Intensity	Assignment	Range (cm^{-1})	Intensity	Assignment
Alkanes	2850-3000	str	CH_3, CH_2 & CH 2 or 3 bands	1350-1470 1370-1390 720-725	med med wk	CH_2 & CH_3 deformat CH_3 deformation CH_2 rocking
Alkenes	3020-3100 1630-1680 1900-2000	med var str	=C-H & $=CH_2$ (usually sharp) C=C (symmetry reduces intensity) C=C asymmetric stretch	880-995 780-850 675-730	str med med	=C-H & $=CH_2$ (out-of-plane bending) cis-RCH=CHR
Alkynes	3300 2100-2250	str var	C-H (usually sharp) C≡C (symmetry reduces intensity)	600-700	str	C-H deformation
Arenes	3030 1600 & 1500	var med-wk	C-H (may be several bands) C=C (in ring) (2 bands) (3 if conjugated)	690-900	str-med	C-H bending & ring puckering
Alcohols & Phenols	3580-3650 3200-3550 970-1250	var str str	O-H (free), usually sharp O-H (H-bonded), usually broad C-O	1330-1430 650-770	med var-wk	O-H bending (in-plane) O-H bend (out-of-plane)
Amines	3400-3500 (dil. soln.) 3300-3400 (dil. soln.) 1000-1250	wk wk med	N-H (1°-amines), 2 bands N-H (2°-amines) C-N	1550-1650 660-900	med-str var	NH_2 scissoring (1°-amines) NH_2 & N-H wagging (shifts on H-bonding)
Aldehydes & Ketones	2690-2840(2 bands) 1720-1740 1710-1720					
med str str str str str str	C-H (aldehyde C-H) C=O (saturated aldehyde) C=O (saturated ketone) aryl ketone α, β-unsaturation cyclopentanone cyclobutanone	1350-1360 1400-1450 1100	str str med	α-CH_3 bending α-CH_2 bending C-C-C bending		
Carboxylic Acids & Derivatives	2500-3300 (acids) 1705-1720 (acids) 1210-1320 (acids)	overlap C-H				
str str med-str str	O-H (very broad) C=O (H-bonded) O-C (sometimes 2-peaks)	1395-1440	med	C-O-H bending		

str str str str str	C=O C=O (2-bands) O-C C=O O-C (2-bands) C=O (amide I band)	 1590-1650 1500-1560	 med med	 N-H (1°-amide) II band N-H (2°-amide) II band
Nitriles **Isocyanates,Isothiocyanates, Diimides, Azides & Ketenes**	2240-2260 2100-2270	med med	C≡N (sharp) -N=C=O, -N=C=S -N=C=N-, $-N_3$, C=C=O	

Recognizing Group Frequencies in IR Spectra - a very close look

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 3. 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.

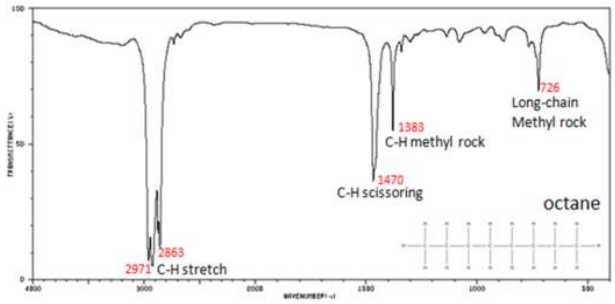


Figure 3. Infrared Spectrum of Octane

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 4. 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.

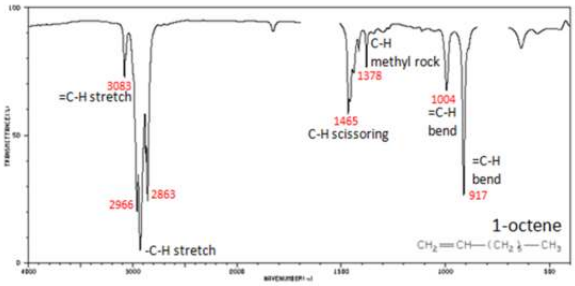


Figure 4. Infrared Spectrum of 1-Octene

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.

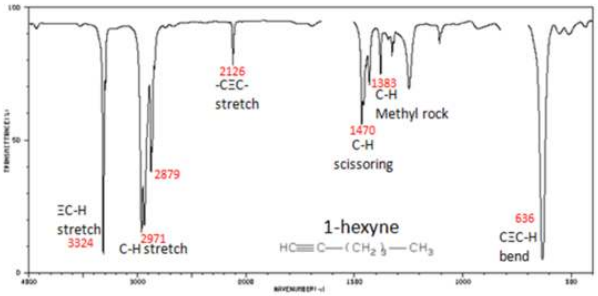


Figure 5. Infrared Spectrum of 1-Hexyne

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 6. shows the spectrum of toluene.

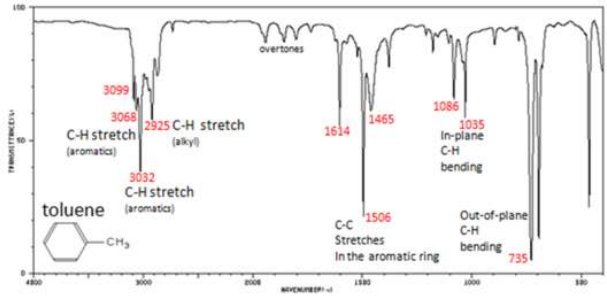


Figure 6. Infrared Spectrum of Toluene

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 7. shows the spectrum of ethanol. Note the very broad, strong band of the O–H stretch.

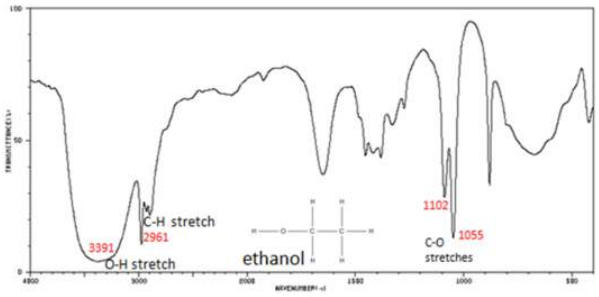


Figure 7. Infrared Spectrum of Ethanol

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

- C=O stretch - aliphatic ketones 1715 cm^{-1}

- ?, ?-unsaturated ketones 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.

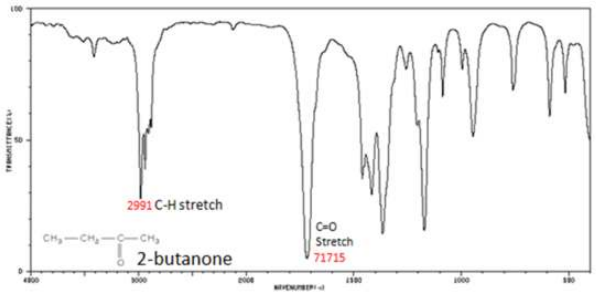


Figure 8. Infrared Spectrum of 2-Butanone

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}
  - alpha, beta-unsaturated aldehydes 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

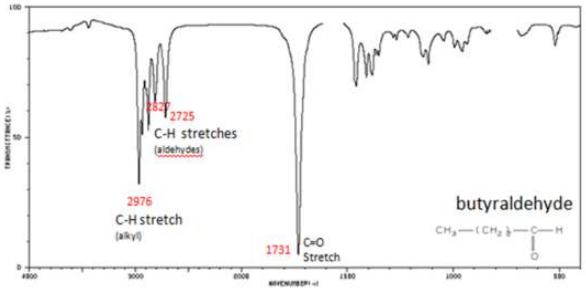


Figure 9. Infrared Spectrum of Butyraldehyde

The carbonyl stretch C=O of esters appears:

- C=O stretch
  - aliphatic from 1750-1735 cm^{-1}
  - ?, ?-unsaturated from 1730-1715 cm^{-1}

- C–O stretch from 1300-1000 cm^{-1}

Figure 10. shows the spectrum of ethyl benzoate.

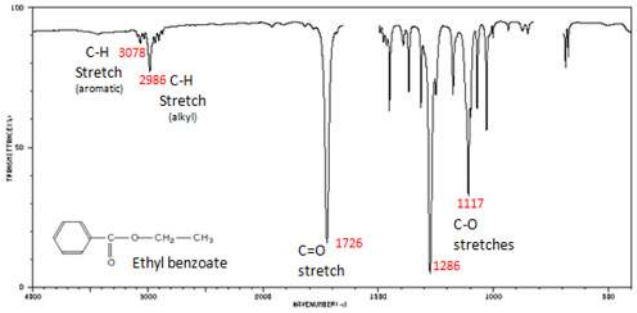


Figure 10. Infrared Spectrum of Ethyl benzoate

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 11. shows the spectrum of hexanoic acid.

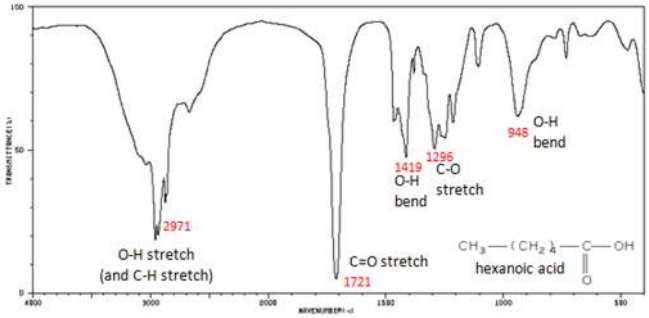


Figure 11. Infrared Spectrum of Hexanoic acid

Organic Nitrogen Compounds

- N–O asymmetric stretch from 1550-1475 cm^{-1}
- N–O symmetric stretch from 1360-1290 cm^{-1}

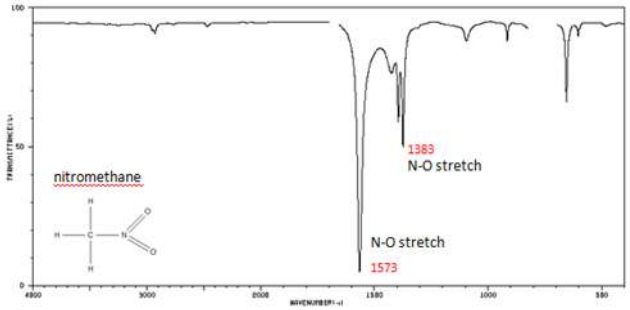


Figure 12. Infrared Spectrum of Nitomethane

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.

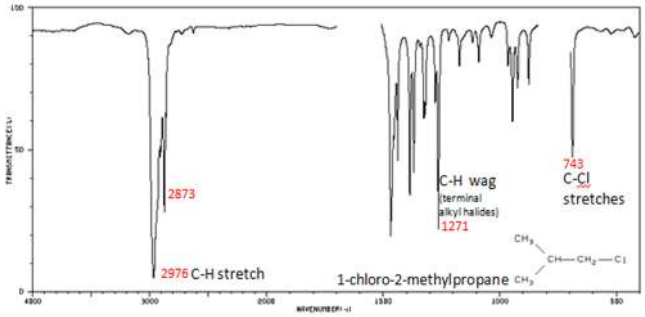


Figure 13. Infrared Spectrum of 1-chloro-2-methylpropane

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

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}

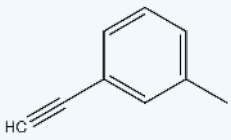
2. How can you distinguish the following pairs of compounds through IR analysis?

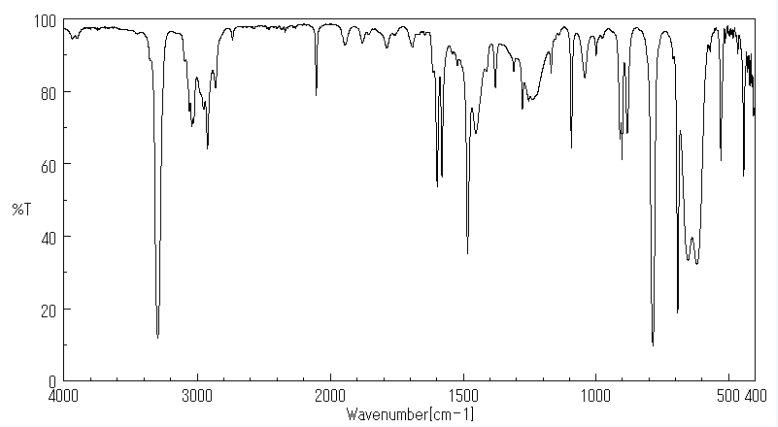
A) CH_3OH (Methanol) and $CH_3CH_2OCH_2CH_3$ (Diethylether)

B) Cyclopentane and 1-pentene.

C)

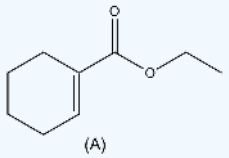
3. The following spectra is for the accompanying compound. What are the peaks that you can I identify in the spectrum?



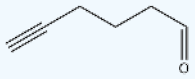


Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 2 December 2016)

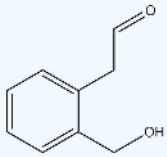
4. What absorptions would the following compounds have in an IR spectra?



(A)



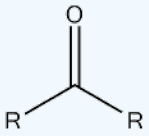
(B)



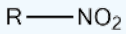
(C)

Answer

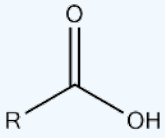
1.

A) 

Carbonyl

B) 

Nitro

C) 

Carboxylic Acid

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.

3.

Frequency (cm-1) Functional Group

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.)

4.

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

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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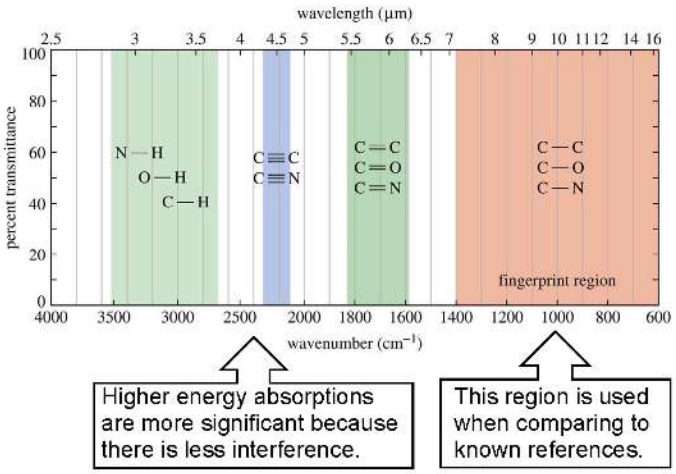
12.6: Summary and Tips to Distinguish between Carbonyl Functional Groups

Summary for Interpreting IR Spectra



IR Absorption Bands to Memorize

- ≈ 3400 cm^{-1}: O-H and N-H stretch
- ≈ 3100 cm^{-1}: sp and sp^2 C-H stretch
- ≈ 2900 cm^{-1}: sp^3 C-H stretch
- ≈ 2700 cm^{-1}: aldehyde C-H stretch (fangs)
- ≈ 2200 cm^{-1}: C≡C & C≡N stretch
  (primarily for terminal C≡C & C≡N)
- ≈ 1700 cm^{-1}: C=O stretch
- ≈ 1600 cm^{-1}: C=C stretch (primarily for terminal C=C)
- ≈ 1200 cm^{-1}: C-O stretch

Distinguishing between Functional Groups with Carbonyls C=O's

While there may subtle differences in the wavenumbers of the carbonyl stretch between some of the functional groups, it is the secondary features of the IR spectrum that help with discernment.

Functional Grp	Carbonyl Stretch	Secondary IR Spectral Feature
Aldehyde	1710 cm^{-1}	fangs at 2700 & 2800 cm^{-1}
Ketone	1710 cm^{-1}	
Acid	1710 cm^{-1}	broad O-H stretch between 3500-2500 cm^{-1}
Ester	1735 cm^{-1}	C-O stretch ≈ 1200 cm^{-1}
Amide	1660 cm^{-1} (doublet)	N-H stretch ≈ 3300 cm^{-1} 2 peaks for $RCONH_2$ 1 peak for RCONHR'
Acid Chloride	1800 cm^{-1}	energy of carbonyl stretch
Anhydride	1800 & 1750 cm^{-1}	energy of carbonyl doublet

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12.7: Mass Spectrometry - an introduction

Learning Objectives

After completing this section, you should be able to

1. sketch a simple diagram to show the essential features of a mass spectrometer.
2. 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.

- parent peak (molecular ion peak)
- relative abundance
- mass spectroscopy
- 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.

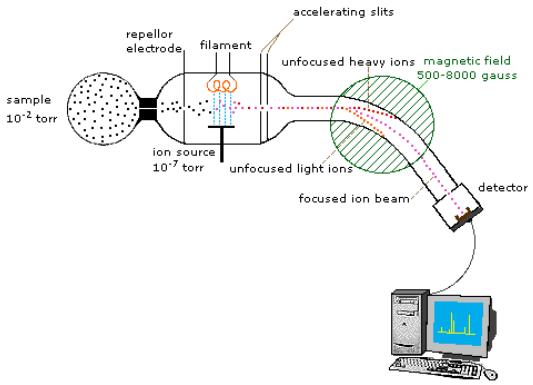
Mass spectrometers are large and expensive, and usually operated only by fully trained personnel, so you will not have the opportunity to use such an instrument as part of this course. Research chemists often rely quite heavily on mass spectra to assist them in the identification of compounds, and you 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

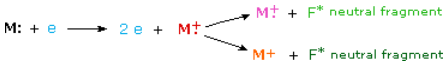
In order to measure the characteristics of individual molecules, a mass spectrometer converts them to ions so that they can be moved about and manipulated by external electric and magnetic fields. The three essential functions of a mass spectrometer, and the associated components, are:

1. The ions are sorted and separated according to their mass and charge. **The Mass Analyzer**
2. The separated ions are then measured, and the results displayed on a chart. **The Detector**

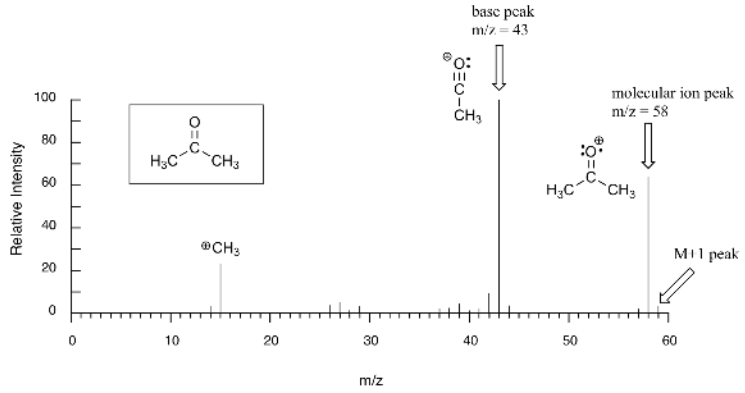
Because ions are very reactive and short-lived, their formation and manipulation must be conducted in a vacuum. Atmospheric pressure is around 760 torr (mm of mercury). The pressure under which ions may be handled is roughly 10^{-5} to 10^{-8} torr (less than a billionth of an atmosphere). Each of the 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-impact) 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 (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.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.8: Fragmentation Patterns in Mass Spectrometry

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 $M^{+\cdot}$, $(M + 1)^{+\cdot}$, 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

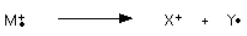
When interpreting fragmentation patterns, you may find it helpful to know that, as you might expect, the weakest carbon-carbon bonds are the ones most likely to break. You might wish to refer to the table of bond dissociation energies when attempting problems involving the interpretation of mass spectra.

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

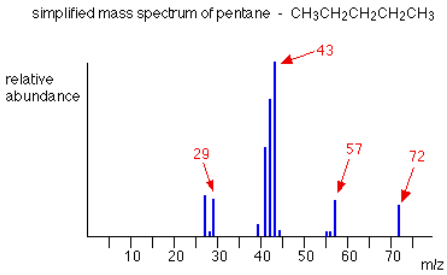
When the vaporized organic sample passes into the ionization chamber of a mass spectrometer, it is bombarded by a stream of electrons. These electrons have a high enough energy to knock an electron off an organic molecule to form a positive ion. This ion is called the **molecular ion - or sometimes the parent ion** and is often given the symbol M^+ or $M^{+\cdot}$. 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:



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.

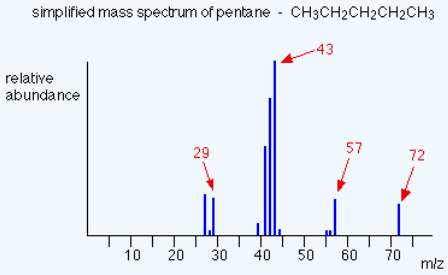
In the stick diagram showing the mass spectrum of pentane, the line produced by the heaviest ion passing through the machine (at m/z = 72) is due to the molecular ion. The tallest line in the stick diagram (in this case at m/z = 43) is called the **base peak**. This is usually given an arbitrary height 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: Pentane

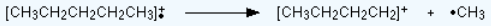
Let's have another look at the mass spectrum for pentane:



What causes the line at m/z = 57?

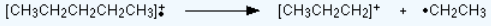
How many carbon atoms are there in this ion? There cannot be 5 because 5 x 12 = 60. What about 4? 4 x 12 = 48. That leaves 9 to make up a total of 57. How about $C_4H_9^+$ then?

$C_4H_9^+$ would be $[CH_3CH_2CH_2CH_2]^+$, and this would be produced by the following fragmentation:



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:

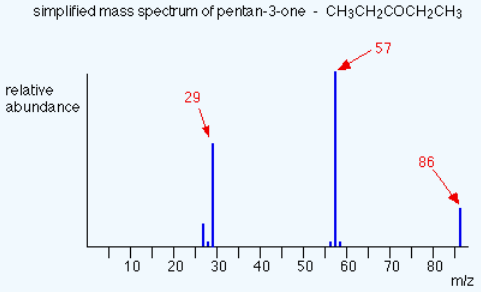


The line at m/z = 29 is typical of an ethyl ion, $[CH_3CH_2]^+$:

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: 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:

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.

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.

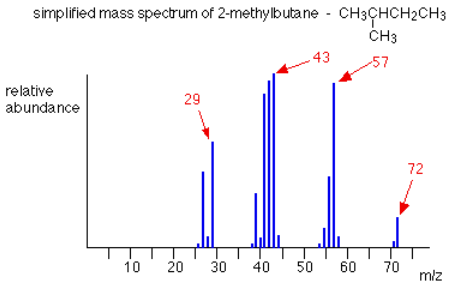
Carbocations (carbonium ions)

Summarizing the most important conclusion from the page on carbocations:

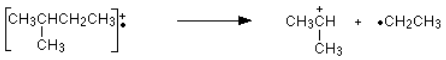
Order of stability of carbocations

primary < secondary < tertiary

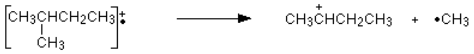
Applying the logic of this to fragmentation patterns, it means that a split which produces a secondary carbocation is going to be more successful than one producing a primary one. A split producing a tertiary carbocation will be more successful still. Let's look at the mass spectrum of 2-methylbutane. 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:



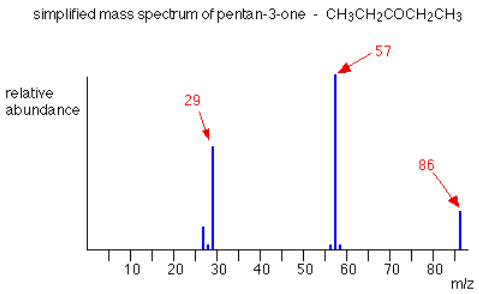
The ion formed is a secondary carbocation - it has two alkyl groups attached to the carbon with the positive charge. As such, it is relatively stable. The peak at m/z = 57 is much taller than the corresponding line in pentane. Again a secondary carbocation is formed - this time, by:



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:

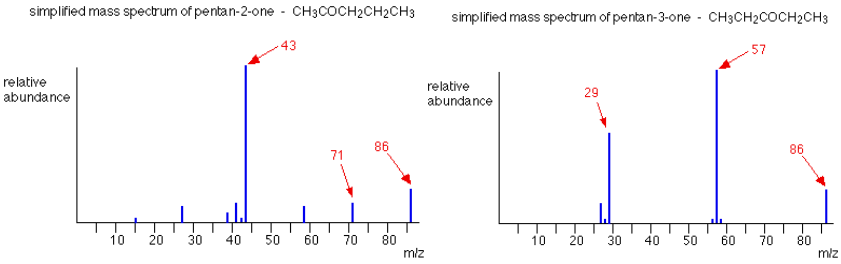
- $[CH_3CO]^+$
- $[COCH_2CH_2CH_3]^+$

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:



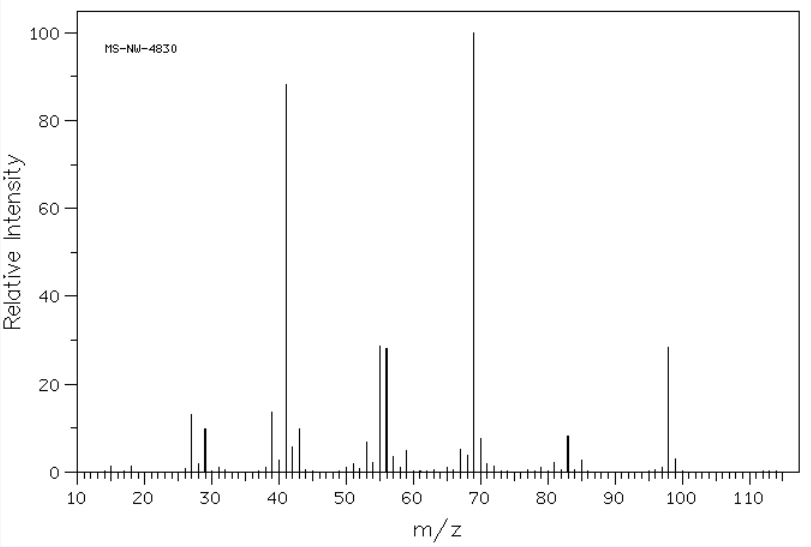
As you've seen, the mass spectrum of even very similar organic compounds will be quite different because of the different fragmentation patterns that can occur. Provided you have a computer data base of mass spectra, any unknown spectrum can be computer analyzed and simply matched against the data base.

Exercise

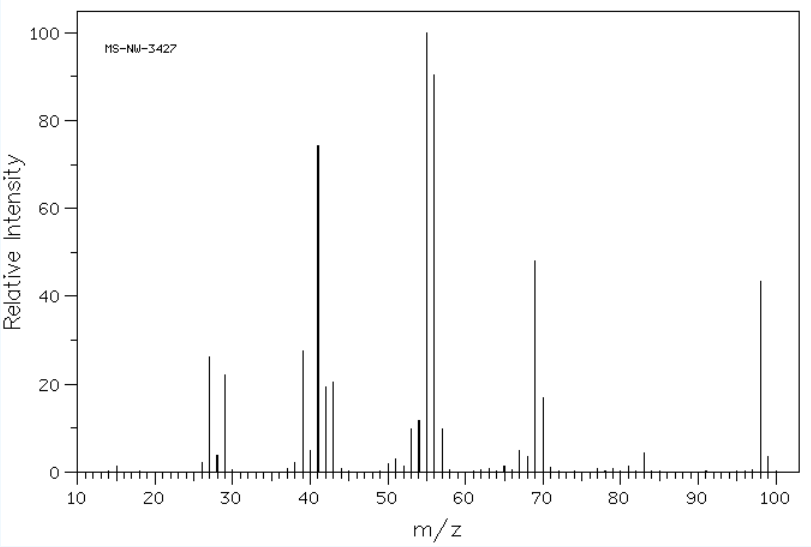
5. Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

6. 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

5. $C_8H_{10}N_4O_2$

C = 12 × 8 = 96

N = 14 × 4 = 56

H = 1 × 10 = 10

O = 2 × 16 = 32

96+56+10+32 = 194 g/mol

6. 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.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Jim Clark (Chemguide.co.uk)

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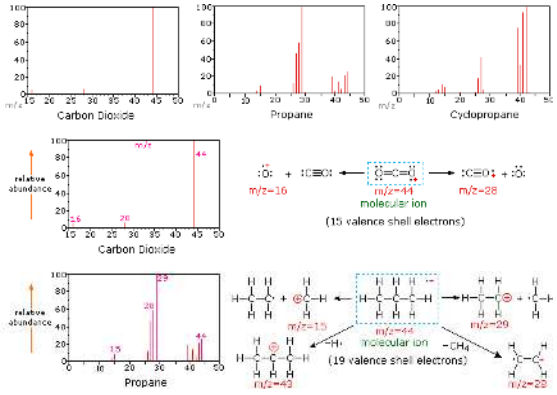
12.9: Useful Patterns for Structure Elucidation

The Nature of Mass Spectra

A mass spectrum will usually be presented as a vertical bar graph, in which each bar represents an ion having a specific mass-to-charge ratio (m/z) and the length of the bar indicates the relative abundance of the ion. The most intense ion is assigned an abundance of 100, and it is referred to as the **base peak**. Most of the ions formed in a mass spectrometer have a single charge, so the m/z value is equivalent to mass itself. Modern mass spectrometers easily distinguish (resolve) ions differing by only a single atomic mass unit, and thus provide completely accurate values for the molecular mass of a compound. The highest-mass ion in a spectrum is normally considered to be the molecular ion, and lower-mass ions are fragments from the molecular ion, assuming the sample is a single pure compound.

Atomic mass is given in terms of the **unified atomic mass unit** (symbol: μ) or **dalton** (symbol: Da). In recent years there has been a gradual change towards using the dalton in preference to the unified atomic mass unit. The dalton is classified as a "non-SI unit whose values in SI units must be obtained experimentally". It is defined as one twelfth of the rest mass of an unbound atom of carbon-12 in its nuclear and electronic ground state, and has a value of $1.660538782(83)\times10^{-27}$ kg.

The following diagram displays the mass spectra of three simple gaseous compounds, carbon dioxide, propane and cyclopropane. The molecules of these compounds are similar in size, CO_2 and C_3H_8 both have a nominal mass of 44 Da, and C_3H_6 has a mass of 42 Da. The molecular ion is the strongest ion in the spectra of CO_2 and C_3H_6, and it is moderately strong in propane. The unit mass resolution is readily apparent in these spectra (note the separation of ions having m/z=39, 40, 41 and 42 in the cyclopropane spectrum). Even though these compounds are very similar in size, it is a simple matter to identify them from their individual mass spectra. By clicking on each spectrum in turn, a partial fragmentation analysis and peak assignment will be displayed. Even with simple compounds like these, it should be noted that it is rarely possible to explain the origin of all the fragment ions in a spectrum. Also, the structure of most fragment ions is seldom known with certainty.

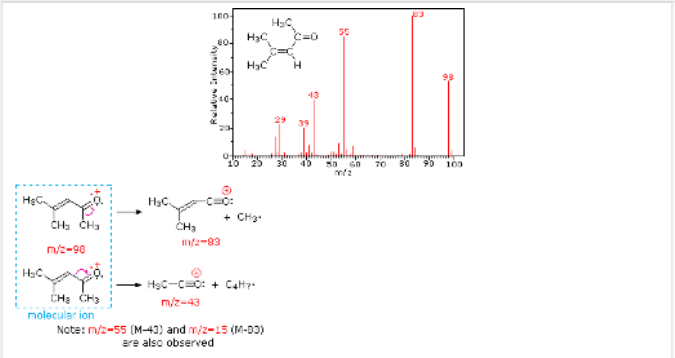


Since a molecule of carbon dioxide is composed of only three atoms, its mass spectrum is very simple. The molecular ion is also the base peak, and the only fragment ions are CO (m/z=28) and O (m/z=16). The molecular ion of propane also has m/z=44, but it is not the most abundant ion in the spectrum. Cleavage of a carbon-carbon bond gives methyl and ethyl fragments, one of which is a carbocation and the other a radical. Both distributions are observed, but the larger ethyl cation (m/z=29) is the most abundant, possibly because its size affords greater charge dispersal. A similar bond cleavage in cyclopropane does not give two fragments, so the molecular ion is stronger than in propane, and is in fact responsible for the the base peak. Loss of a hydrogen atom, either before or after ring opening, produces the stable allyl cation (m/z=41). The third strongest ion in the spectrum has m/z=39 (C_3H_3). Its structure is uncertain, but two possibilities are shown in the diagram. The small m/z=39 ion in propane and the absence of a m/z=29 ion in cyclopropane are particularly significant in distinguishing these hydrocarbons.

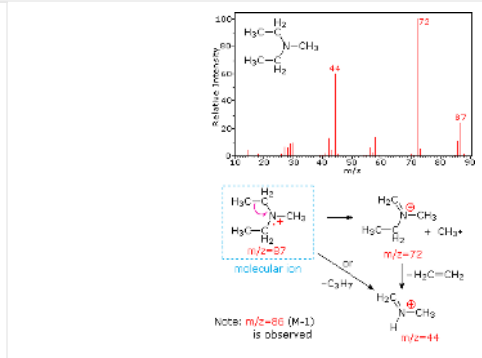
Most stable organic compounds have an even number of total electrons, reflecting the fact that electrons occupy atomic and molecular orbitals in pairs. When a single electron is removed from a molecule to give an ion, the total electron count becomes an odd number, and we refer to such ions as **radical cations**. The molecular ion in a mass spectrum is always a radical cation, but the fragment ions may either be even-electron cations or odd-electron radical cations, depending on the neutral fragment lost. The simplest and most common fragmentations are bond cleavages producing a neutral radical (odd number of electrons) and a cation having an even number of electrons. A less common fragmentation, in which an even-electron neutral fragment is lost, produces an odd-electron radical cation fragment ion. Fragment ions themselves may fragment further. As a rule, odd-electron ions may fragment either to odd or even-electron ions, but even-electron ions fragment only to other even-electron ions. The masses of molecular and fragment ions also reflect the electron count, depending on the number of nitrogen atoms in the species.

Ions with no nitrogen or an even # N atoms	odd-electron ions even-number mass	even-electron ions odd-number mass
Ions having an odd # N atoms	odd-electron ions odd-number mass	even-electron ions even-number mass

This distinction is illustrated nicely by the follwing two examples. The unsaturated ketone, 4-methyl-3-pentene-2-one, on the left has no nitrogen so the mass of the molecular ion (m/z = 98) is an even number. Most of the fragment ions have odd-numbered masses, and therefore are even-electron cations. Diethylmethylamine, on the other hand, has one nitrogen and its molecular mass (m/z = 87) is an odd number. A majority of the fragment ions have even-numbered masses (ions at m/z = 30, 42, 56 & 58 are not labeled), and are even-electron nitrogen cations. The weak even -electron ions at m/z=15 and 29 are due to methyl and ethyl cations (no nitrogen atoms). The fragmentations leading to the chief fragment ions will be displayed by clicking on the appropriate spectrum. Repeated clicks will cycle the display.



4-methyl-3-pentene-2-one

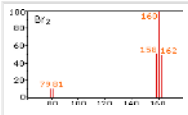


N,N-diethylmethylamine

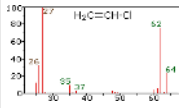
When non-bonded electron pairs are present in a molecule (e.g. on N or O), fragmentation pathways may sometimes be explained by assuming the missing electron is partially localized on that atom. A few such mechanisms are shown above. Bond cleavage generates a radical and a cation, and both fragments often share these roles, albeit unequally.

Isotopes

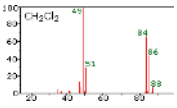
Since a mass spectrometer separates and detects ions of slightly different masses, it easily distinguishes different isotopes of a given element. This is manifested most dramatically for compounds containing bromine and chlorine, as illustrated by the following examples. Since molecules of bromine have only two atoms, the spectrum on the left will come as a surprise if a single atomic mass of 80 Da is assumed for Br. The five peaks in this spectrum demonstrate clearly that natural bromine consists of a nearly 50:50 mixture of isotopes having atomic masses of 79 and 81 Da respectively. Thus, the bromine molecule may be composed of two ^{79}Br atoms (mass 158 Da), two ^{81}Br atoms (mass 162 Da) or the more probable combination of ^{79}Br-^{81}Br (mass 160 Da). Fragmentation of Br_2 to a bromine cation then gives rise to equal sized ion peaks at 79 and 81 Da.



bromine



vinyl chloride



methylene chloride

The center and right hand spectra show that chlorine is also composed of two isotopes, the more abundant having a mass of 35 Da, and the minor isotope a mass 37 Da. The precise isotopic composition of chlorine and bromine is:

- **Chlorine:** 75.77% ^{35}Cl and 24.23% ^{37}Cl
- **Bromine:** 50.50% ^{79}Br and 49.50% ^{81}Br

The presence of chlorine or bromine in a molecule or ion is easily detected by noticing the intensity ratios of ions differing by 2 Da. In the case of methylene chloride, the molecular ion consists of three peaks at m/z=84, 86 & 88 Da, and their diminishing intensities may be calculated from the natural abundances given above. Loss of a chlorine atom gives two isotopic fragment ions at m/z=49 & 51 Da, clearly incorporating a single chlorine atom. Fluorine and iodine, by contrast, are monoisotopic, having masses of 19 Da and 127 Da respectively. It should be noted that the presence of halogen atoms in a molecule or fragment ion does not change the odd-even mass rules given above.

To make use of a calculator that predicts the isotope clusters for different combinations of chlorine, bromine and other elements Click Here. This application was developed at Colby College.

Isotopic Abundance Calculator

C H .

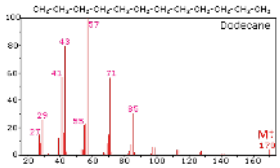
Molecular Ion 100%	M + 1	M + 2

Two other common elements having useful isotope signatures are carbon, ^{13}C is 1.1% natural abundance, and sulfur, ^{33}S and ^{34}S are 0.76% and 4.22% natural abundance respectively. For example, the small m/z=99 Da peak in the spectrum of 4-methyl-3-pentene-2-one (above) is due to the presence of a single ^{13}C atom in the molecular ion. Although less important in this respect, ^{15}N and ^{18}O also make small contributions to higher mass satellites of molecular ions incorporating these elements.

The calculator on the right may be used to calculate the isotope contributions to ion abundances 1 and 2 Da greater than the molecular ion (M). Simply enter an appropriate subscript number to the right of each symbol, leaving those elements not present blank, and press the "Calculate" button. The numbers displayed in the M+1 and M+2 boxes are relative to M being set at 100%.

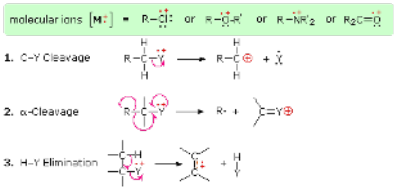
Fragmentation Patterns

The fragmentation of molecular ions into an assortment of fragment ions is a mixed blessing. The nature of the fragments often provides a clue to the molecular structure, but if the molecular ion has a lifetime of less than a few microseconds it will not survive long enough to be observed. Without a molecular ion peak as a reference, the difficulty of interpreting a mass spectrum increases markedly. Fortunately, most organic compounds give mass spectra that include a molecular ion, and those that do not often respond successfully to the use of milder ionization conditions. Among simple organic compounds, the most stable molecular ions are those from aromatic rings, other conjugated pi-electron systems and cycloalkanes. Alcohols, ethers and highly branched alkanes generally show the greatest tendency toward fragmentation.



The mass spectrum of dodecane on the right illustrates the behavior of an unbranched alkane. Since there are no heteroatoms in this molecule, there are no non-bonding valence shell electrons. Consequently, the radical cation character of the molecular ion (m/z = 170) is delocalized over all the covalent bonds. Fragmentation of C-C bonds occurs because they are usually weaker than C-H bonds, and this produces a mixture of alkyl radicals and alkyl carbocations. The positive charge commonly resides on the smaller fragment, so we see a homologous series of hexyl (m/z = 85), pentyl (m/z = 71), butyl (m/z = 57), propyl (m/z = 43), ethyl (m/z = 29) and methyl (m/z = 15) cations. These are accompanied by a set of corresponding alkenyl carbocations (e.g. m/z = 55, 41 &27) formed by loss of 2 H. All of the significant fragment ions in this spectrum are even-electron ions. In most alkane spectra the propyl and butyl ions are the most abundant.

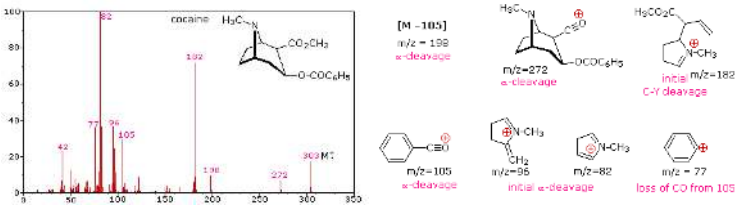
The presence of a functional group, particularly one having a heteroatom Y with non-bonding valence electrons (Y = N, O, S, X etc.), can dramatically alter the fragmentation pattern of a compound. This influence is thought to occur because of a "localization" of the radical cation component of the molecular ion on the heteroatom. After all, it is easier to remove (ionize) a non-bonding electron than one that is part of a covalent bond. By localizing the reactive moiety, certain fragmentation processes will be favored. These are summarized in the following diagram, where the green shaded box at the top displays examples of such "localized" molecular ions. The first two fragmentation paths lead to even-electron ions, and the elimination (path #3) gives an odd-electron ion. Note the use of different curved arrows to show single electron shifts compared with electron pair shifts.



The charge distributions shown above are common, but for each cleavage process the charge may sometimes be carried by the other (neutral) species, and both fragment ions are observed. Of the three cleavage reactions described here, the alpha-cleavage is generally favored for nitrogen, oxygen and sulfur compounds. Indeed, in the previously displayed spectra of 4-methyl-3-pentene-2-one and N,N-diethylmethylamine the major fragment ions come from alpha-cleavages. Further examples of functional group influence on fragmentation are provided by a selection of compounds that may be examined by clicking the left button below. Useful tables of common fragment ions and neutral species may be viewed by clicking the right button.

Assorted Mass Spectra	View Fragment Tables

The complexity of fragmentation patterns has led to mass spectra being used as "fingerprints" for identifying compounds. Environmental pollutants, pesticide residues on food, and controlled substance identification are but a few examples of this application. Extremely small samples of an unknown substance (a microgram or less) are sufficient for such analysis. The following mass spectrum of cocaine demonstrates how a forensic laboratory might determine the nature of an unknown street drug. Even though extensive fragmentation has occurred, many of the more abundant ions (identified by magenta numbers) can be rationalized by the three mechanisms shown above. Plausible assignments may be seen by clicking on the spectrum, and it should be noted that all are even-electron ions. The m/z = 42 ion might be any or all of the following: C_3H_6, C_2H_2O or C_2H_4N. A precise assignment could be made from a high-resolution m/z value (next section).

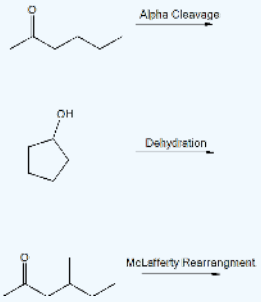


Odd-electron fragment ions are often formed by characteristic rearrangements in which stable neutral fragments are lost. Mechanisms for some of these rearrangements have been identified by following the course of isotopically labeled molecular ions. A few examples of these rearrangement mechanisms may be seen by clicking the following button.

Assorted Rearrangement Fragmentations

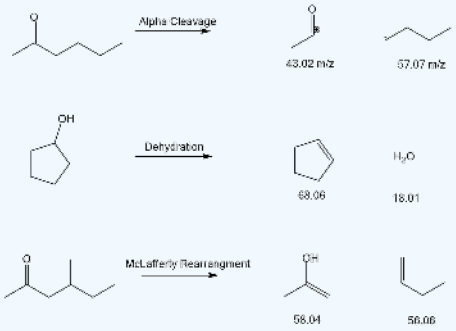
Exercise

7. What are the masses of all the components in the following fragmentations?



Answer

7.



Contributors and Attributions

Contributors

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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12.10: Determination of the Molecular Formula by High Resolution Mass Spectrometry

High Resolution Mass Spectrometry

In assigning mass values to atoms and molecules, we have assumed integral values for isotopic masses. However, accurate measurements show that this is not strictly true. Because the strong nuclear forces that bind the components of an atomic nucleus together vary, the actual mass of a given isotope deviates from its nominal integer by a small but characteristic amount (remember $E = mc^2$). Thus, relative to ^{12}C at 12.0000, the isotopic mass of ^{16}O is 15.9949 Da (not 16) and ^{14}N is 14.0031 Da (not 14).

Formula	C_6H_{12}	C_5H_8O	$C_4H_8N_2$
Mass	84.0939	84.0575	84.0688

By designing mass spectrometers that can determine m/z values accurately to four decimal places, it is possible to distinguish different formulas having the same nominal mass. The table on the right illustrates this important feature, and a double-focusing high-resolution mass spectrometer easily distinguishes ions having these compositions. Mass spectrometry therefore not only provides a specific molecular mass value, but it may also establish the molecular formula of an unknown compound.

Tables of precise mass values for any molecule or ion are available in libraries; however, the mass calculator provided below serves the same purpose. Since a given nominal mass may correspond to several molecular formulas, lists of such possibilities are especially useful when evaluating the spectrum of an unknown compound. Composition tables are available for this purpose, and a particularly useful program for calculating all possible combinations of H, C, N & O that give a specific nominal mass has been written by Jef Rozenski. To use this calculator Click Here.

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CHAPTER OVERVIEW

13: Nuclear Magnetic Resonance Spectroscopy

Learning Objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- explain how ^{1}H NMR spectrometers work - refer to section 12.1
- interpret chemical shifts of ^{1}H NMR spectra as they relate to shielding and deshielding - refer to section 12.2 and 12.14
- explain the delta scale of ^{1}H NMR spectra - refer to section 12.3
- recognize equivalent protons within an organic compound - refer to section 12.4
- correlate functional group structural features with chemical shifts - refer to section 12.5
- determine the proton ratio from ^{1}H NMR spectra peak integration data - refer to section 12.6
- explain and interpret spin-spin splitting patterns in ^{1}H NMR spectra - refer to section 12.7
- explain and interpret spin-spin splitting patterns in ^{1}H NMR spectra - refer to section 12.8
- describes examples of some uses of ^{1}H NMR spectroscopy - refer to section 12.9
- explain how ^{13}C NMR spectrometers work - refer to section 12.10
- interpret the chemical shifts of ^{13}C NMR spectra to determine the structural features of organic compounds - refer to section 12.11 and 12.14
- explain how DEPT (distortionless enhancement by polarization transfer) is used to determine the number of hydrogens bonded to each carbon - refer to section 12.12
- describes some uses of ^{13}C NMR spectroscopy - refer to section 12.13

Topic hierarchy

13.1: Theory of Nuclear Magnetic Resonance (NMR)
13.2: NMR Spectra - an introduction
13.3: Chemical Shifts and Shielding
13.4: ^{1}H NMR Spectroscopy and Proton Equivalence
13.5: Functional Groups and Chemical Shifts in ^{1}H NMR Spectroscopy
13.6: Integration of ^{1}H NMR Absorptions: Proton Counting
13.7: Spin-Spin Splitting in ^{1}H NMR Spectra
13.8: More Complex Spin-Spin Splitting Patterns
13.9: Uses of ^{1}H NMR Spectroscopy
13.10: ^{13}C NMR Spectroscopy
13.11: Chemical Shifts and Interpreting ^{13}C NMR Spectra
13.12: ^{13}C NMR Spectroscopy
13.13: Uses of ^{13}C NMR Spectroscopy
13.14: More NMR Examples
13.15: Sample NMR Spectra

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13.1: Theory of Nuclear Magnetic Resonance (NMR)

Nuclear precession, spin states, and the resonance condition

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 below right.

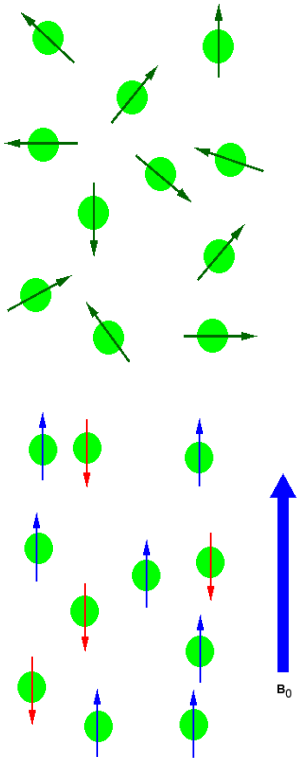
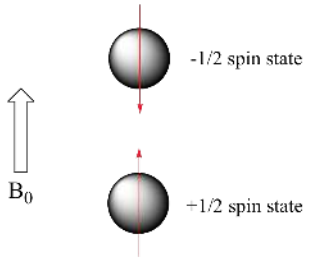


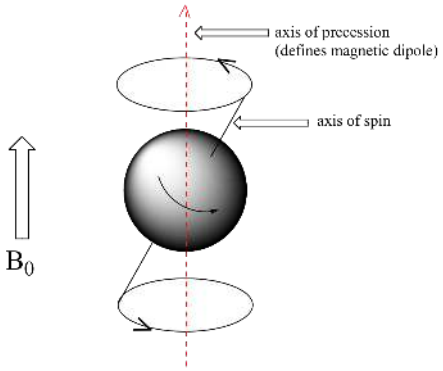
Figure 1: (Left) Random nuclear spin without an external magnetic field. (Right)Ordered nuclear spin in an external magnetic field

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.



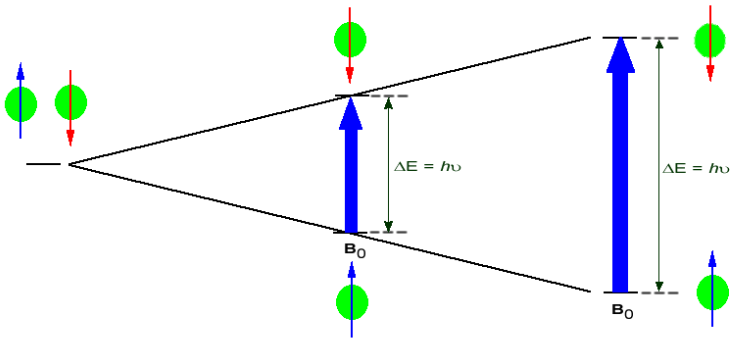
The **frequency of precession** (also called the **Larmour frequency,** abbreviated $\boldsymbol{\omega_L}$) is simply the number of times per second that the proton precesses in a complete circle. A proton`s precessional frequency increases with the strength of B_0.

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.

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

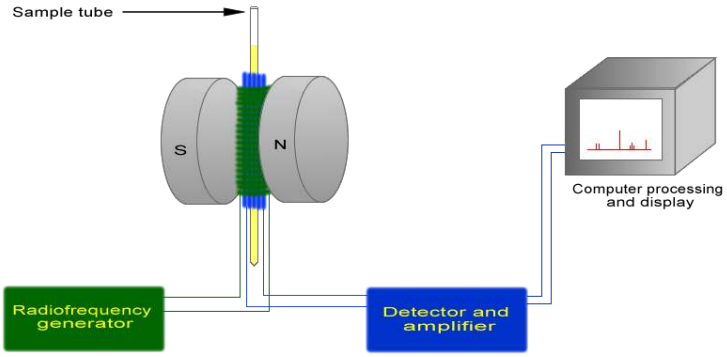
energy difference between the two spin states increases and a higher frequency (more energy) EM radiation needs to be applied to achieve a spin-flip (see image below).



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.

The basic arrangement of an NMR spectrometer is displayed below. A sample (in a small glass tube) is placed between the poles of a strong magnetic. 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.



Exercise

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?

2. 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

1.

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(150\ \text{MHz})$

$E = 9.93 \times 10^{-26}$ 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).

2.

$E = h\upsilon$

$E = (6.62 \times 10^{-34})(400 \text{ MHz})$

$E = 2.648 \times 10^{-25}$ J

The energy would increase if the frequency would increase to 500 MHz, and decrease if the frequency would decrease to 300 MHz.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
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13.2: NMR Spectra - an introduction

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.

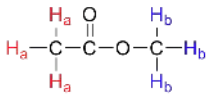
Study Notes

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.

The basics of an NMR experiment

Given that chemically nonequivalent protons have different resonance frequencies in the same applied magnetic field, we can see how NMR spectroscopy can 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 in very simple terms, here is what happens. First, a sample compound (we'll use methyl acetate) is placed inside a very strong applied magnetic field (B_0).

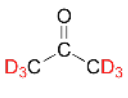


methyl acetate

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 are aligned against B_0. Then, the sample is hit with electromagnetic radiation in the radio frequency range. The two specific frequencies which match $\omega_a$andω_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 use 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, so 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.

deuterated chloroform ($CDCl_3$)

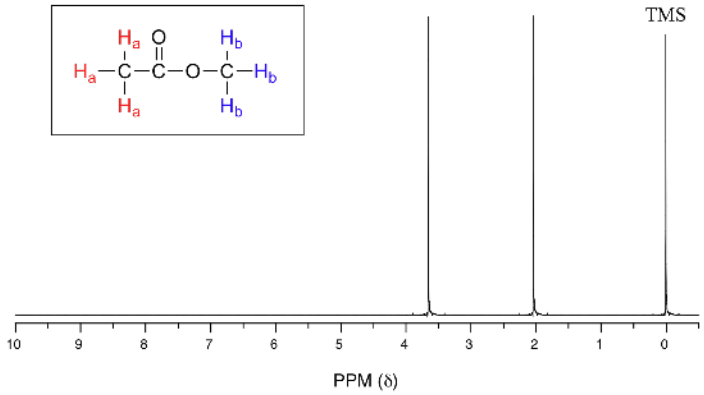


d_6-acetone

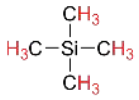
D_2O

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.

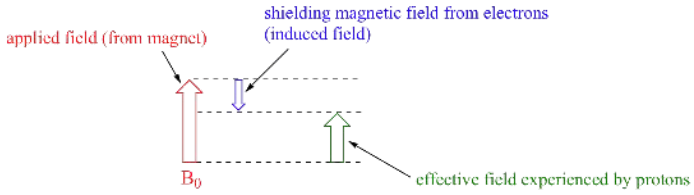
a. a) What is its chemical shift, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?
b. b) What is its resonance frequency, expressed in Hz, in a 300 MHz instrument? On a 200 MHz instrument?

(Assume that in these instruments, the TMS protons resonate at exactly 300 or 200 MHz, respectively)

Solution

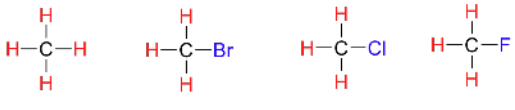
Diamagnetic shielding and deshielding

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.



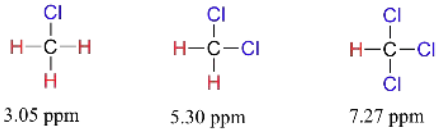
Therefore, their resonance frequency is slightly lower than what it would be if they did not have electrons nearby to shield them.

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).

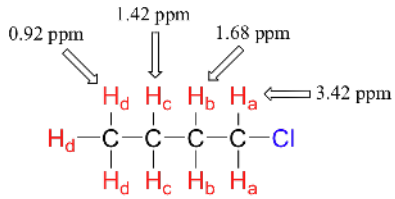


To a large extent, then, we can predict trends in chemical shift by considering how much deshielding is taking place near a proton. The chemical shift of trichloromethane is, as expected, higher than that of dichloromethane, which is in turn higher than that of

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:

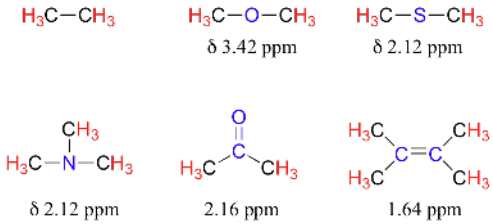
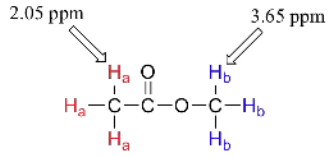
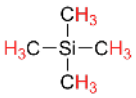


Table 2 lists typical chemical shift values for protons in different chemical environments.

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.

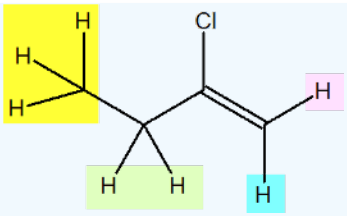


Exercise

3. 2-cholorobutene shows 4 different hydrogen signals. Explain why this is.

Answer

3. The same colors represent the same signal. 4 different colors for 4 different signals. The hydrogen on the alkene would give two different signals.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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13.3: Chemical Shifts and Shielding

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

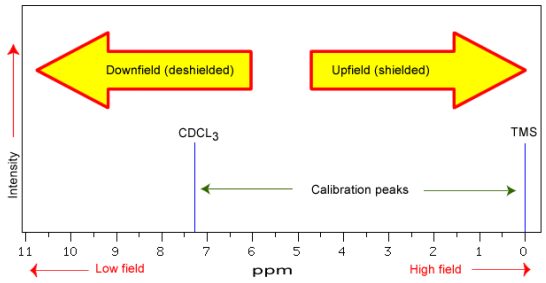
Study Notes

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 increases 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**.

$$\delta = \frac{\text{frequency of signal} - \text{frequency of standard}}{\text{spectrometer frequency}} \times 10^{6}$$

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.*

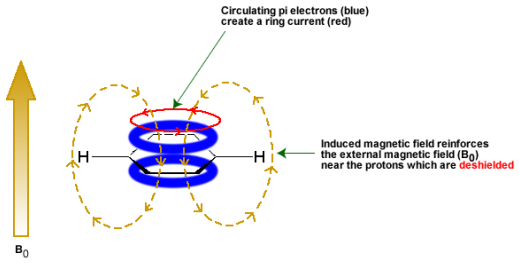
Compound	CH_4	CH_3Cl	CH_2Cl_2	$CHCl_3$
δ (ppm)	0.23	3.05	5.30	7.27

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: Pi 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).

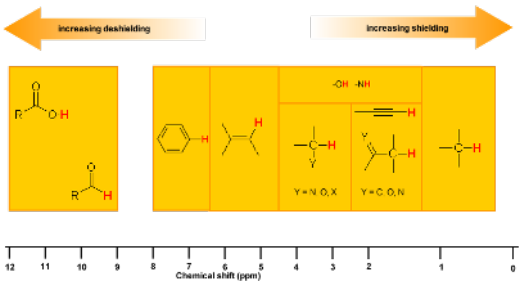


This effect is common for any atoms near a π bond, *i.e.*

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		

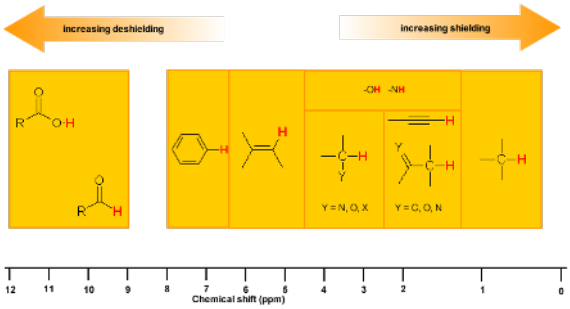
Hydrogen Bonding

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

4. 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

5. 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

4.

A. 3.627 ppm

B. 1.525 ppm

C. 1.732 ppm

D. 2.65 ppm

5.

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

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Dr. Richard Spinney (The Ohio State University)

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13.4: ^{1}H NMR Spectroscopy and Proton Equivalence

Objectives

After completing this section, you should be able to

1. identify those protons which are equivalent in a given chemical structure.
2. use the ^{1}H NMR spectrum of a simple organic compound to determine the number of equivalent sets of protons present.

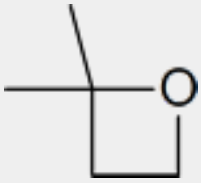
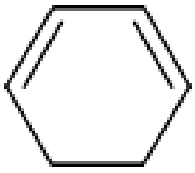
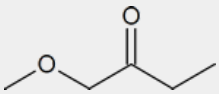
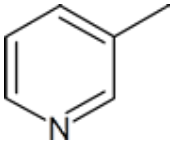
Key Terms

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

- diastereotopic
- enantiotopic
- homotopic

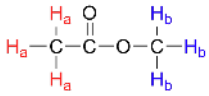
Study Notes

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	
$CH_3OCH_2CH_2Br$	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

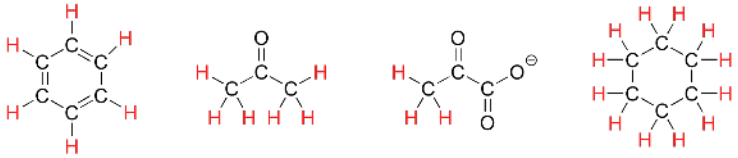
If all protons in all organic molecules had the same resonance frequency in an external magnetic field of a given strength, the information in the previous paragraph would be interesting from a theoretical standpoint, but would not be terribly useful to organic chemists. Fortunately for us, however, 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.

The ability to recognize chemical equivalancy 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.



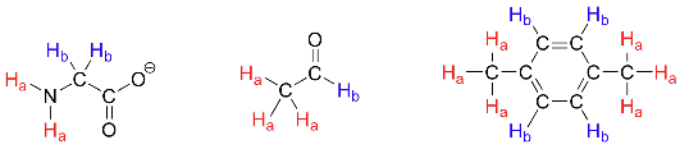
benzene acetone pyruvate cyclohexane

You might expect that the equitorial 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 equitorial 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 equitorial 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.

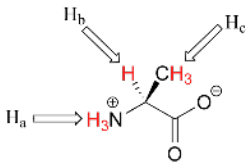
Each the molecules in the next figure contains *two* sets of protons, just like our previous example of methyl acetate, and again in each case the resonance frequency of the H_a protons will be different from that of the H_b protons.



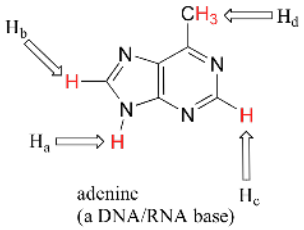
glycine acetaldehyde *para*-xylene

Notice how the symmetry of *para*-xylene results in there being only two different sets of protons.

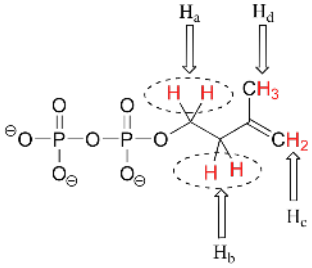
Most organic molecules have several sets of protons in different chemical environments, and each set, in theory, will have a different resonance frequency in ^{1}H-NMR spectroscopy.



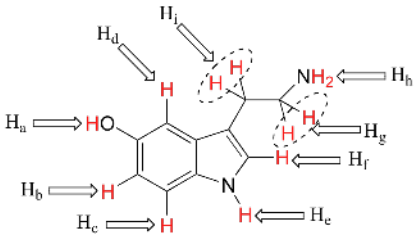
alanine
(an amino acid)



adenine
(a DNA/RNA base)

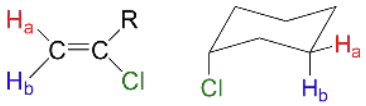


isopentenyl diphosphate
(a lipid building block)

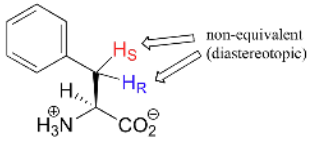


seratonin (a neurotransmitter)

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.

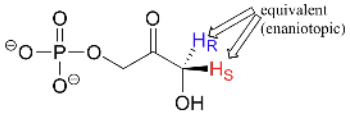


What is not so intuitive is that diastereotopic hydrogens (section 3.10) on chiral molecules are also non-equivalent:

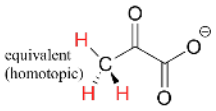


phenylalanine

However, enantiotopic and homotopic hydrogens are chemically equivalent.



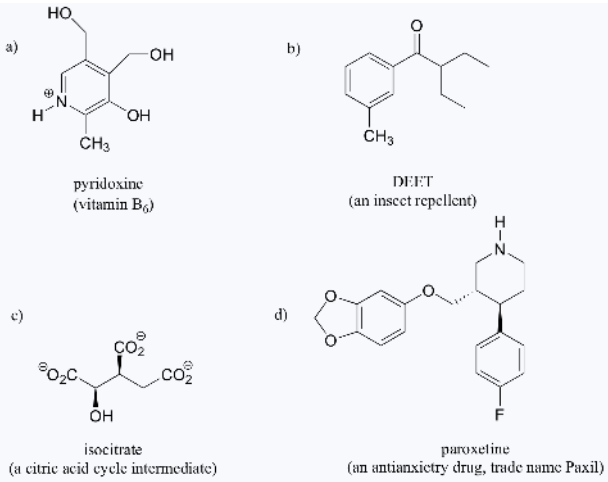
dihydroxyacetone
phosphate



pyruvate

Example

How many different sets of protons do the following molecules contain? (count diastereotopic protons as non-equivalent).



Solution

Exercise

6. 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

6. A. 3; B. 3; C. 5; D. 7

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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13.5: Functional Groups and 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:
    1. aromatic.
    2. vinylic.
    3. those bonded to carbon atoms which are in turn bonded to a highly electronegative element.
    4. those bonded to carbons which are next to unsaturated centres.
    5. 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 fulfil 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 phenonomena 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 shift is associated with the Larmor frequency of a nuclear spin to its chemical environment. Tetramethylsilan[TMS; $(CH_3)_4Si$] is generally used for standard to determine chemical shift of compounds: δ_{TMS}=0ppm. In other words, frequencies for chemicals are measured for a ^{1}H or ^{13}C nucleus of a sample from the ^{1}H or ^{13}C 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.

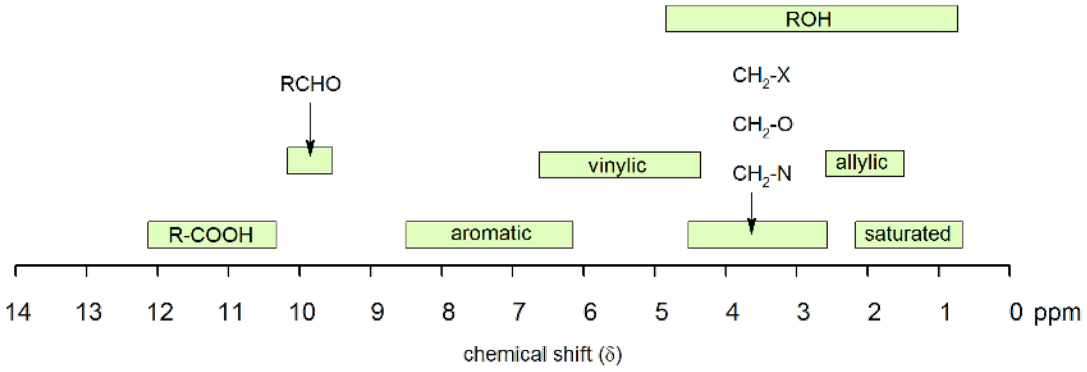
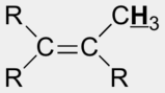
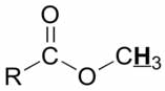
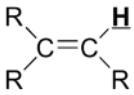
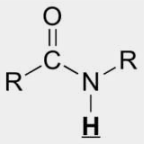
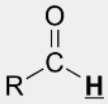
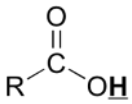


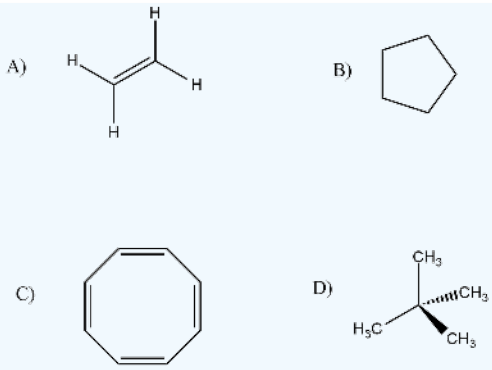
Figure 1. 1H chemical shift ranges for organic compounds

Chemical shift values are in parts per million (ppm) relative to tetramethylsilane.

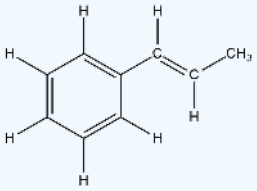
Hydrogen type	Chemical shift (ppm)
$RC\underline{H}_3$	0.9 - 1.0
$RC\underline{H}_2R$	1.2 - 1.7
$R_3C\underline{H}$	1.5 – 2.0
	2.0 – 2.3
	1.5 – 1.8
$RN\underline{H}_2$	1 - 3
$ArC\underline{H}_3$	2.2 – 2.4
$R-C\equiv C-\underline{H}$	2.3 – 3.0
$ROC\underline{H}_3$	3.7 – 3.9
	3.7 – 3.9
$RO\underline{H}$	1 - 5
	3.7 – 6.5
	5 - 9
$Ar\underline{H}$	6.0 – 8.7
	9.5 – 10.0
	10 - 13

Exercise

7. The following have one H^1 NMR peak. In each case predict approximately where this peak would be in a spectra.



8. Identify the different equivalent protons in the following molecule and predict their expected chemical shift.

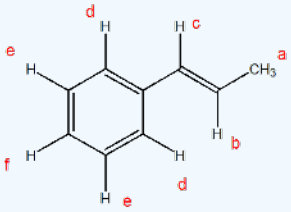


Answer

7. A. 5.20 δ; B. 1.50 δ; C. 6.40 δ; D. 1.00 δ

8. 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



Contributors and Attributions

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13.6: Integration of ^{1}H NMR Absorptions: Proton Counting

Objectives

After completing this section, you should be able to

1. explain what information can be obtained from an integrated ^{1}H NMR spectrum, and use this information in the interpretation of such a spectrum.
2. 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 1H 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.

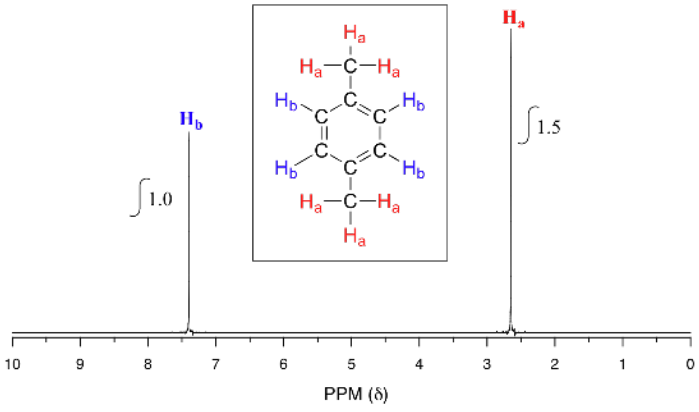
In practice, we do not have to measure these areas ourselves: it is all done electronically by the spectrometer, and an integration curve is superimposed on the rest of the spectrum. The integration curve appears as a series of steps, with the height of each step being proportional to the area of the 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

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*. The two signals in the methyl acetate spectrum, for example, integrate to approximately the same area, because they both correspond to a set of three equivalent protons.

Take a look next at the spectrum of *para*-xylene (IUPAC name 1,4-dimethylbenzene):



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. 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 13.6.1

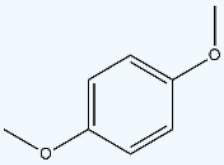
You take a ^{1}H-NMR spectrum of a mixed sample of acetone ($CH_3(CO)CH_3$) and dichloromethane (CH_2Cl_2). The integral ratio of the two signals (acetone : dichloromethane) is 2.3 to 1. What is the molar ratio of the two compounds in the sample?

Example 13.6.2

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)

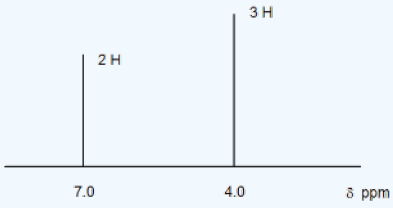
Exercise

9. Predict how many signals the following molecule would have? Sketch the spectra and estimate the integration of the peaks.



Answer

9. There will be two peaks. Ideal general spectrum shown with integration.



Contributors and Attributions

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13.7: 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

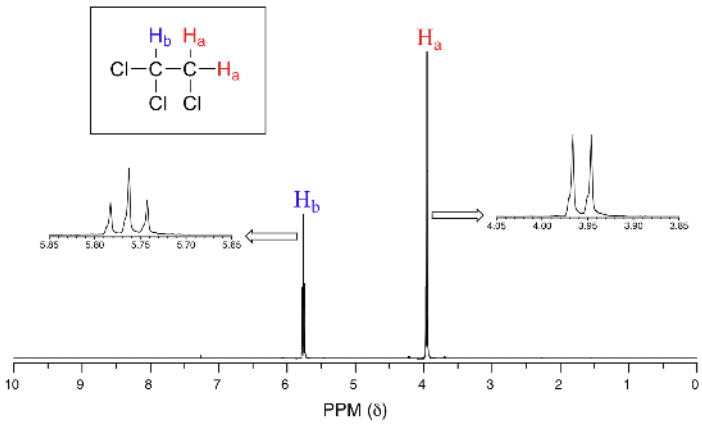
From what we have learned about ^{1}H NMR spectra so far, we might predict that the spectrum of 1,1,2-trichloroethane, $CHCl_2CH_2Cl$, would consist of two peaks—one, at about 2.5-4.0 δ, expected for CH_2-halogen compounds and one shifted downfield because of the presence of an additional electronegative 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

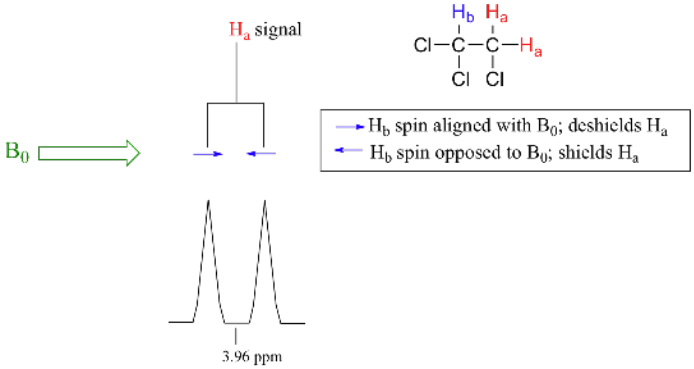
The ^{1}H-NMR spectra that we have seen so far (of methyl acetate and *para*-xylene) are somewhat unusual in the sense that in both of these molecules, each set of protons generates a single NMR signal. In fact, the ^{1}H-NMR spectra of most organic molecules contain proton signals that are 'split' into 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.

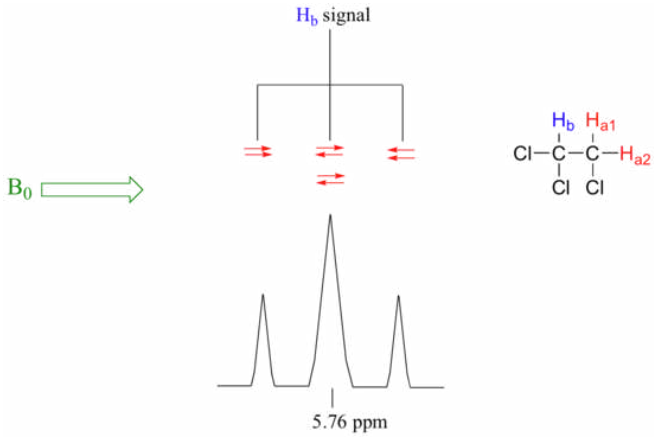


The signal at 3.96 ppm, corresponding to the two H_a protons, is split into two subpeaks of equal height (and area) – this is referred to as a **doublet**. The H_b signal at 5.76 ppm, on the other hand, is split into three sub-peaks, with the middle peak higher than the two outside peaks - if we were 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.

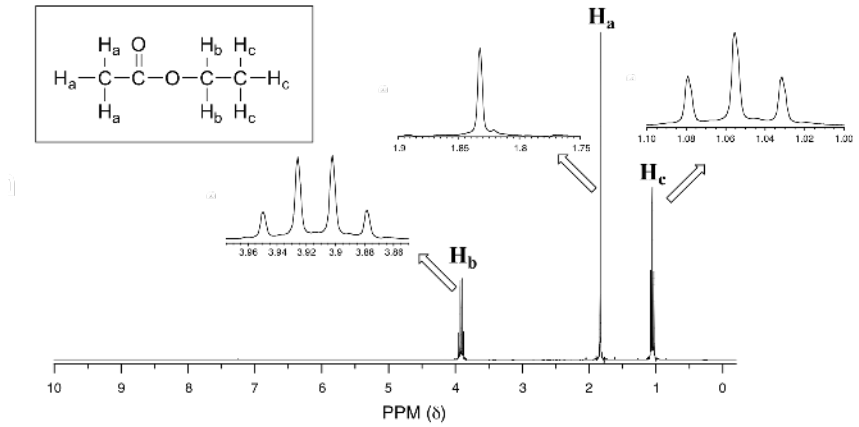


Now, let's think about the $H_b$signal. The magnetic environment experienced by H_b is influenced by the fields of both neighboring H_a protons, which we will call H_{a1} and H_{a2}. There are four possibilities here, each of which is equally probable. First, the magnetic fields of both H_{a1} and H_{a2} 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

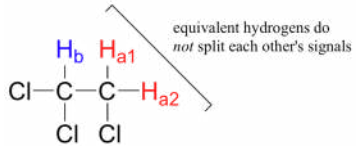
a. Explain, using left and right arrows to illustrate the possible combinations of nuclear spin states for the H_c hydrogens, why the H_b signal in ethyl acetate is split into a quartet.
b. The integration ratio of doublets is 1:1, and of triplets is 1:2:1. What is the integration ratio of the H_b quartet in ethyl acetate? (Hint – use the illustration that you drew in part a to answer this question.)

Solution

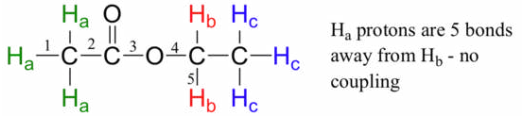
By now, you probably have recognized the pattern which is usually referred to as the ***n* + 1 rule**: if a set of hydrogens has *n* neighboring, non-equivalent hydrogens, it will be split into *n* + 1 subpeaks. Thus the two H_b hydrogens in ethyl acetate split the H_c signal into a triplet, and the 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.

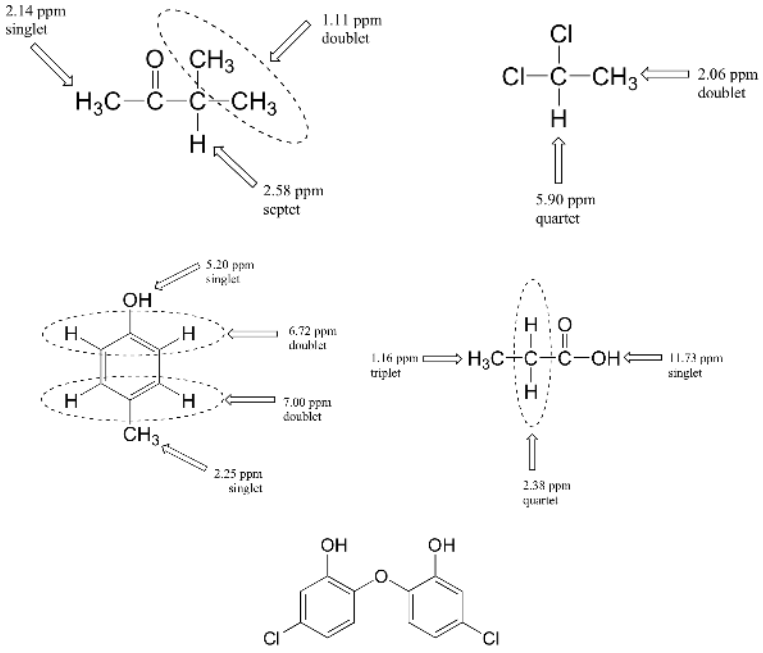


Second, splitting occurs primarily between hydrogens that are separated by three bonds. This is why the H_a hydrogens in ethyl acetate form a singlet– the nearest hydrogen neighbors are five bonds away, too far for coupling to occur.



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

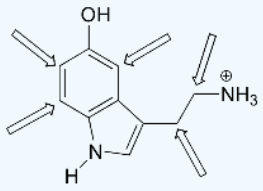
Example

How many proton signals would you expect to see in the ^{1}H-NMR spectrum of triclosan (a common antimicrobial agent found in detergents)? For each of the proton signals, predict the splitting pattern. Assume that you see only 3-bond coupling.

Solutions

Example

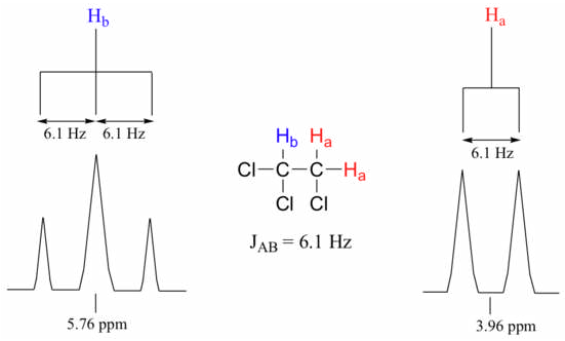
Predict the splitting pattern for the ^{1}H-NMR signals corresponding to the protons at the locations indicated by arrows (the structure is that of the neurotransmitter serotonin).



Solutions

Coupling constants

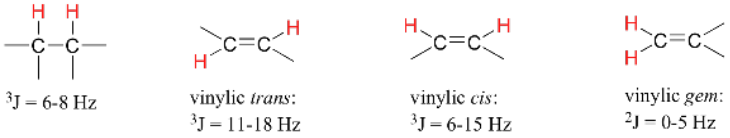
Chemists quantify the spin-spin coupling effect using something called the **coupling constant**, which is abbreviated with the capital letter *J*. The coupling constant is simply the difference, expressed in Hz, between two adjacent sub-peaks in a split signal. For our doublet in the 1,1,2-trichloroethane spectrum, for example, the two subpeaks are separated by 6.1 Hz, and thus we write $^3J_{a\text{-}b}$ = 6.1 Hz.



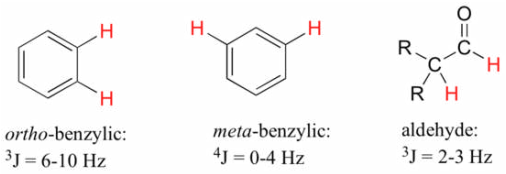
The superscript 3 tells us that this is a three-bond coupling interaction, and the a-b subscript tells us that we are talking about coupling between H_a and H_b. Unlike the chemical shift value, *the coupling constant, expressed in Hz, is the same regardless of the applied field strength of the NMR magnet*. 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.



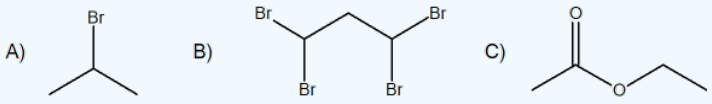
For vinylic hydrogens in a *trans* configuration, we see coupling constants in the range of ^3J = 11-18 Hz, while *cis* hydrogens couple in the ^3J = 6-15 Hz range. The 2-bond coupling between hydrogens bound to the same alkene carbon (referred to as geminal hydrogens) is very fine, generally 5 Hz or 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.

Exercise

10. Predict the splitting patterns of the following molecules:



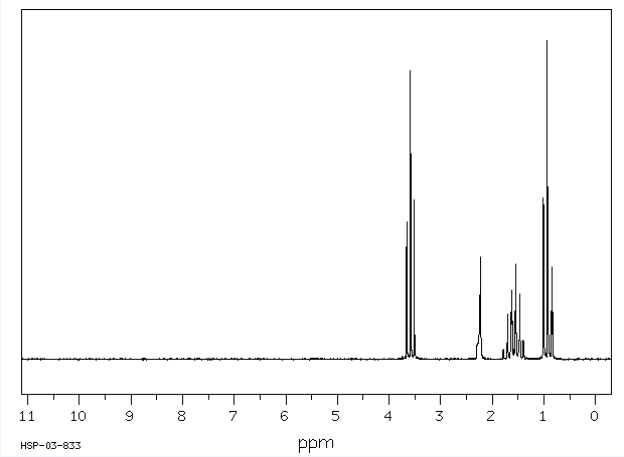
11. Draw the following according to the criteria given.

A. C_3H_5O; two triplet, 1 doublet

B. $C_4H_8O_2$; three singlets

C. C_5H_{12}; one singlet

12. 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)

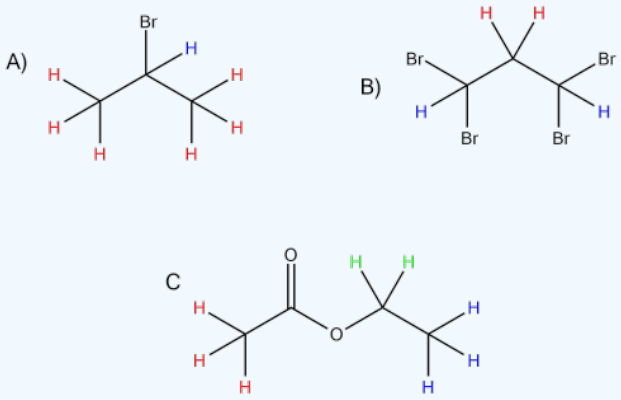
Answer

10.

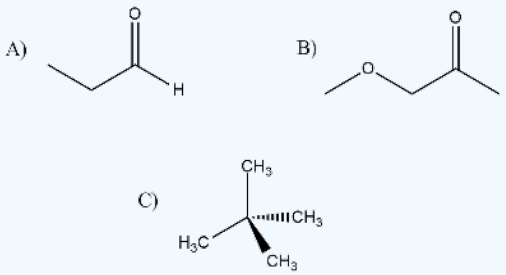
A. H: Doublet. H: Septet

B. H: Doublet, H: Triplet

C. H: Singlet, H: Quartet, H: Triplet

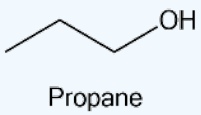


11.



These are just some drawings, more may be possible.

12.



Propane

Note: Remember, chemically equivalent protons do not couple with one another to give spin-spin splitting.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)

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13.8: More Complex Spin-Spin Splitting Patterns

Objectives

After completing this section, you should be able to

1. explain how multiple coupling can give rise to complex-looking ^{1}H NMR spectra.
2. predict the splitting pattern expected in the ^{1}H NMR spectrum of an organic compound in which multiple coupling is possible.
3. 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.

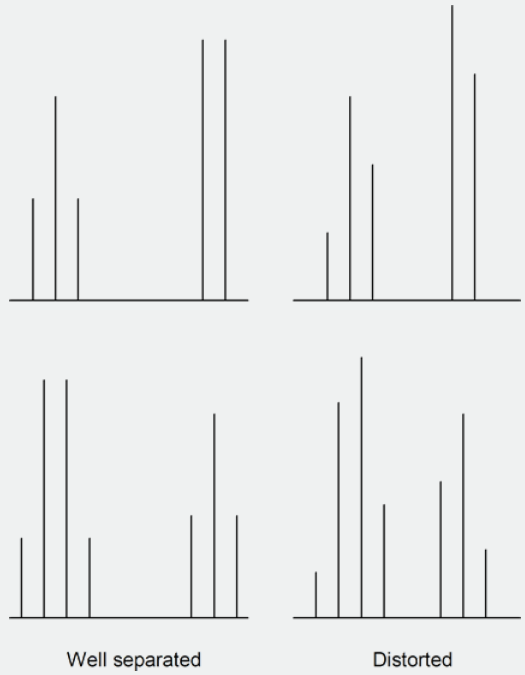
- tree diagram

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 neighbouring 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.

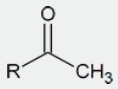
It is much easier to rationalize the observed ^{1}H NMR spectrum of a known compound than it is to determine the structure of an unknown compound from its ^{1}H NMR spectrum. However, rationalizations can be a useful learning technique as you try to improve your proficiency in spectral interpretation. 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

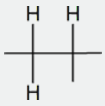
^{1}H NMR	δ (ppm)	Protons	Multiplicity
	0.87	6	doublet
	1.72	1	broad multiplet
	2.00	3	singlet
	2.18	2	doublet

To answer this question, you note that the infrared spectrum of $C_6H_{12}O$ shows $\ce{\sf{C-H}}$ stretching (3000 cm^{-1}) and $\ce{\sf{C-O}}$ 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.

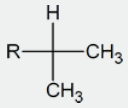


The signal at 1.72 ppm is a broad multiplet, suggesting that a carbon with a single proton is beside carbons with several different protons.

The doublet signal at 2.18 ppm implies that a $\ce{\sf{-CH2-}}$ group is attached to a carbon having only one proton.

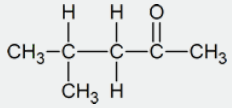


The six protons showing a doublet at 0.87 ppm indicate two equivalent methyl groups attached to a carbon with one proton.



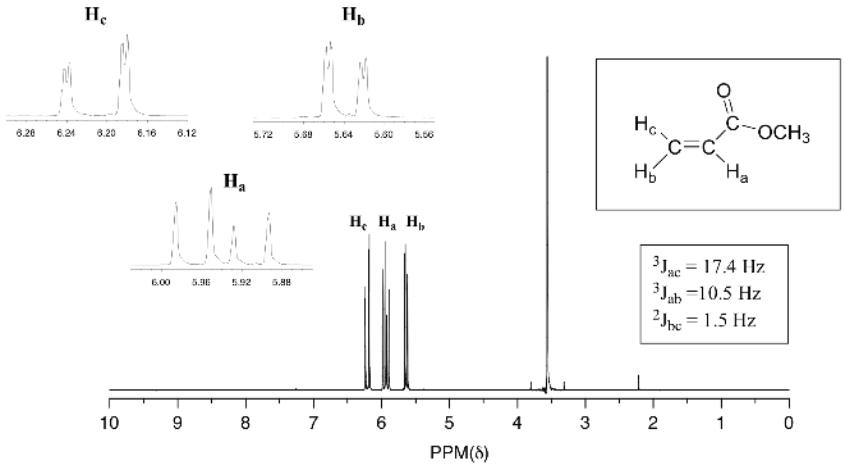
Whenever you see a signal in the 0.7-1.3 ppm range that is a multiplet of three protons (3, 6, 9) it is most likely caused by equivalent methyl groups.

Using trial and error, and with the above observations, you should come up with the correct structure.

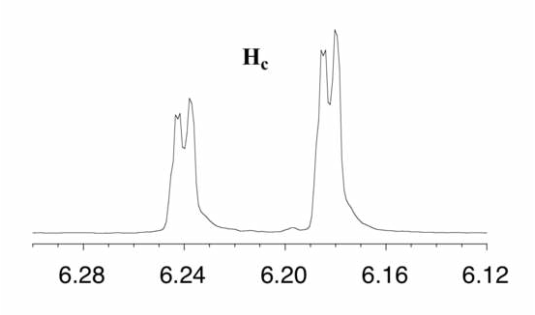


Complex coupling

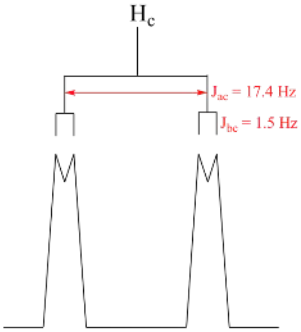
In all of the examples of spin-spin coupling that we have seen so far, the observed splitting has resulted from the coupling of one set of hydrogens to *just one* neighboring set of hydrogens. When a set of hydrogens is coupled to *two or more* sets of nonequivalent neighbors, the result is a phenomenon 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:

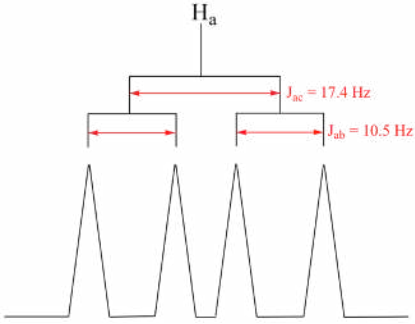


With this enlargement, it becomes evident that the Hc signal is actually composed of four sub-peaks. Why is this? H_c is coupled to both H_a and H_b , but with *two different coupling constants*. Once again, a splitting diagram (or tree diagram) can help us to understand what we are seeing. H_a is *trans* 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.

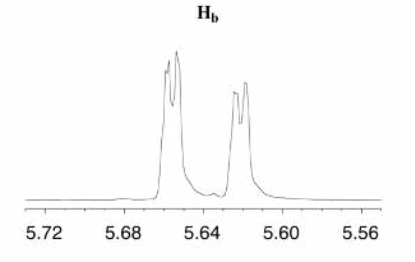


The result of this `double splitting` is a pattern referred to as a **doublet of doublets**, abbreviated `**dd**`.

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:



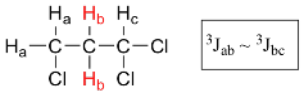
Example

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).

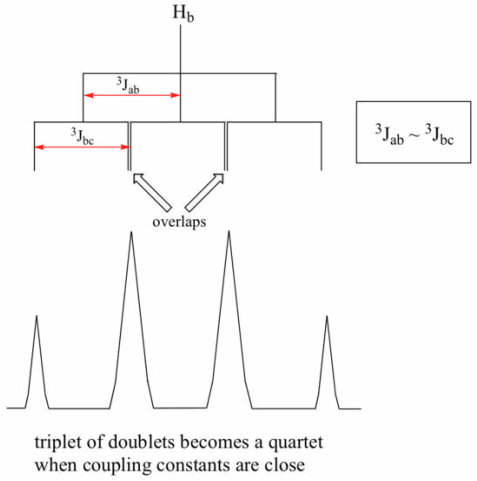
Solution

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).

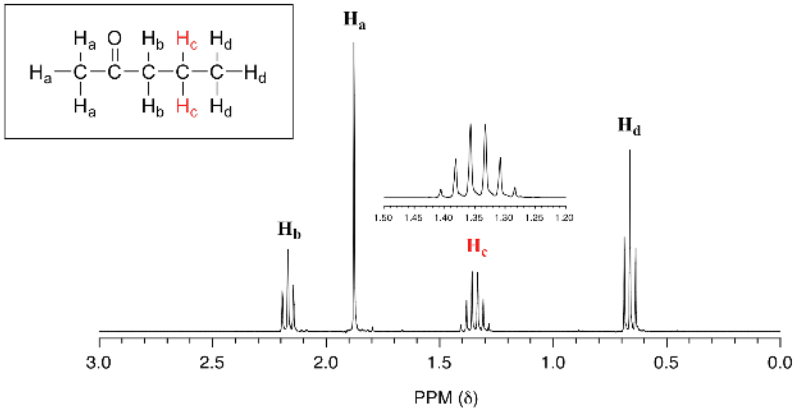
When a proton is coupled to two different neighboring proton sets with identical or very close coupling constants, the splitting pattern that emerges often appears to follow the simple `*n* + 1 rule` of non-complex splitting. In the spectrum of 1,1,3-trichloropropane, for example, we would expect the 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.

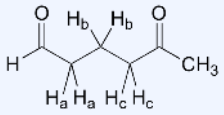


For similar reasons, the H_c peak in the spectrum of 2-pentanone appears as a sextet, split by the five combined H_b and H_d protons. Technically, this 'sextet' could be considered to be a 'triplet of quartets' with overlapping sub-peaks.



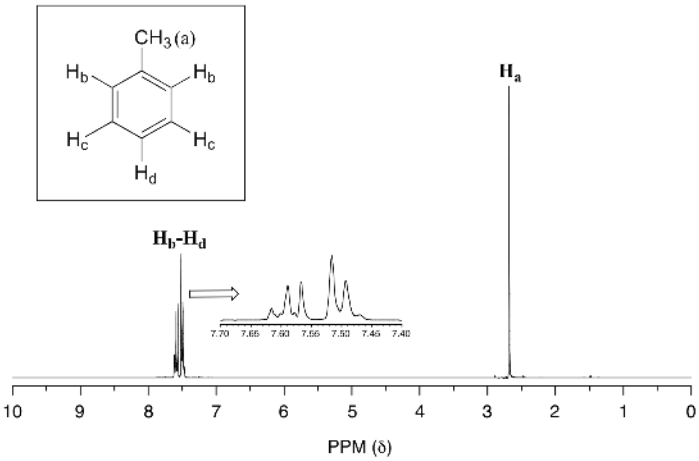
Example

What splitting pattern would you expect for the signal coresponding 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.

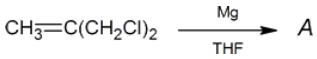


In practice, however, all three aromatic proton groups have very similar chemical shifts and their signals overlap substantially, making such detailed analysis difficult. In this case, we would refer to the aromatic part of the spectrum as a **multiplet**.

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!)

Practice Unknowns

1. Given the information below, draw the structures of compounds *A* through *D*.
   a. 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

   b. 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.

c. 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!

d. Unknown compound *D* ($C_{15}H_{14}O$) has the following spectral properties.

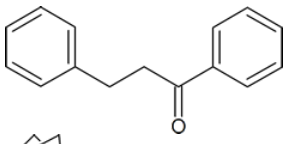
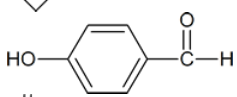
Infrared spectrum:

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

Answers

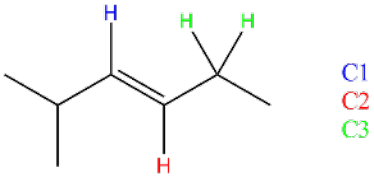
1. 
2.
3. 

4.

Questions

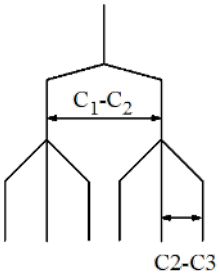
Q13.12.1

In the following molecule, the C2 is coupled with both the vinyl, C1, and the alkyl C3. Draw the splitting tree diagram.



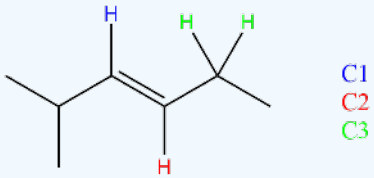
Solutions

S13.12.1



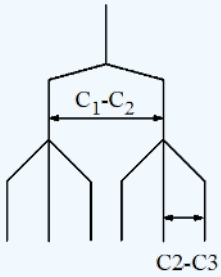
Exercise

13. In the following molecule, the C2 is coupled with both the vinyl, C1, and the alkyl C3. Draw the splitting tree diagram.



Answer

13.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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13.9: Uses of ^{1}H NMR Spectroscopy

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.

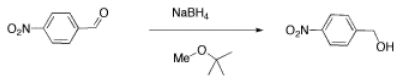
Remember that integration ratios are really only meaningful within a single compound. If your NMR sample contains some benzene (C_6H_6) and some acetone (CH_3COCH_3), and there is a peak at 7.15 that integrates to 1 proton and a peak at 2.10 ppm integrating to 6 protons, it might mean there are 6 protons 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.

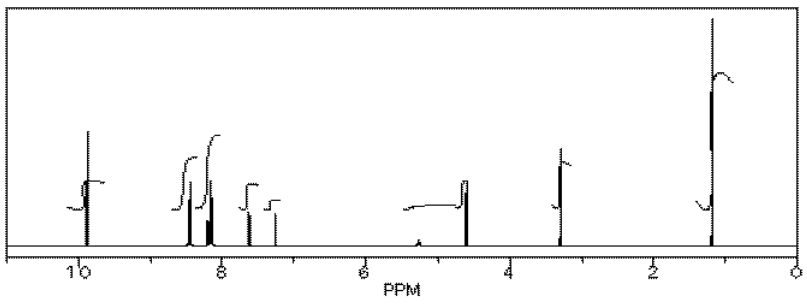
Similarly, if you have decided that you can identify two sets of peaks in the ^{1}H spectrum, analysing them in different tables makes it easy to keep the integration analysis completely separate too ; 1 H in one table will not be the same size integral as 1 H in the other table unless the concentrations 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.

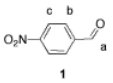
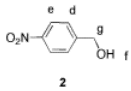


Her reaction produced the following spectrum.



(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		
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		
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.

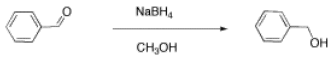
So there is twice as much aldehyde as alcohol in the mixture. In terms of these two compounds alone, she has 33% alcohol and 66% aldehyde. That's (1/(1+2)) x100% for the alcohol, and (2/(1+2)) x100% for the aldehyde. That calculation just represents the amount of individual component divided by the total of the components she wants to compare.

There are a number of things to take note of here.

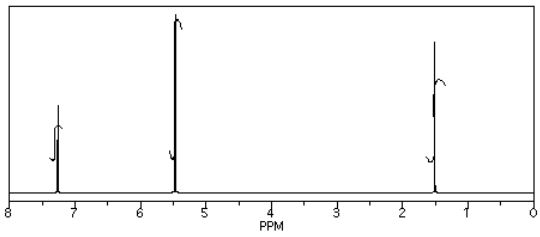
- Her reaction really didn't work very well. She still has majority starting material, not product.
- She will get a good grade on this lab. Although the experiment didn't work well, she has good data, and she has analyzed it very clearly.
- She has separated her data table into different sections for 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.

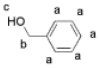
Another student carried out a similar reaction, shown below. He also finished the reaction by washing with water, but because methanol is soluble in water, he had to extract his product out of the water. He chose to use dichloromethane for that purpose.



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

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).

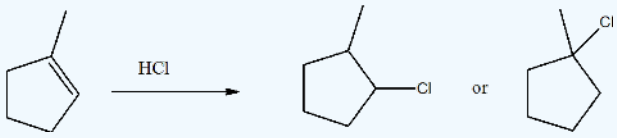
- See the first student's spectrum.
- See the second student's spectrum.
- See the third student's spectrum.

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

Exercise

14. How can H^1 NMR determine products? For example, how can you tell the difference between the products of this reaction?



Answer

14. Yes, you are able to determine the difference in the spectra. For the 2-chloro compound will have multiple quartets while the 1-chloro compound will only have a quintet and a triplet for the signals in the ring.

Contributors and Attributions

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13.10: ^{13}C NMR Spectroscopy

The basics of ^{13}C-NMR spectroscopy

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: more sample is required, and often the data from hundreds of scans must be averaged in order to bring the signal-to-noise ratio down to acceptable levels. 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 (see section 5.6B).

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. 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

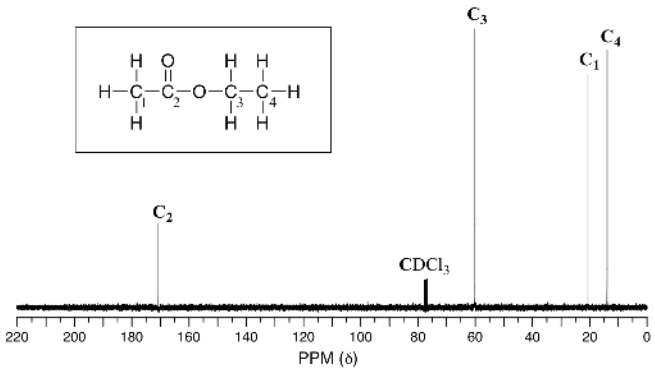
How many sets of non-equivalent carbons are there in each of the molecules shown in exercise 5.1?

Example 13.10.2

How many sets of non-equivalent carbons are there in:

a. toluene
b. 2-pentanone
c. para-xylene
d. triclosan

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.



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.

Contributors and Attributions

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13.11: Chemical Shifts and Interpreting ^{13}C NMR Spectra

^{13}C NMR Chemical Shifts

The Carbon NMR is used for determining functional groups using characteristic shift values. ^{13}C chemical shift is affect by electronegative effect and steric effect. If an H atoms in an alkane is replace by substituent X, electronegative atoms (O, N, halogen), ?-carbon and ?-carbon shift to downfield (left; increase in ppm) while ?-carbon shifts to upfield. The steric effect is observed in acyclic and clyclic system, which leads to downshifted chemical shifts. Figure 9 shows typical ^{13}C chemical shift regions of the major chemical class.

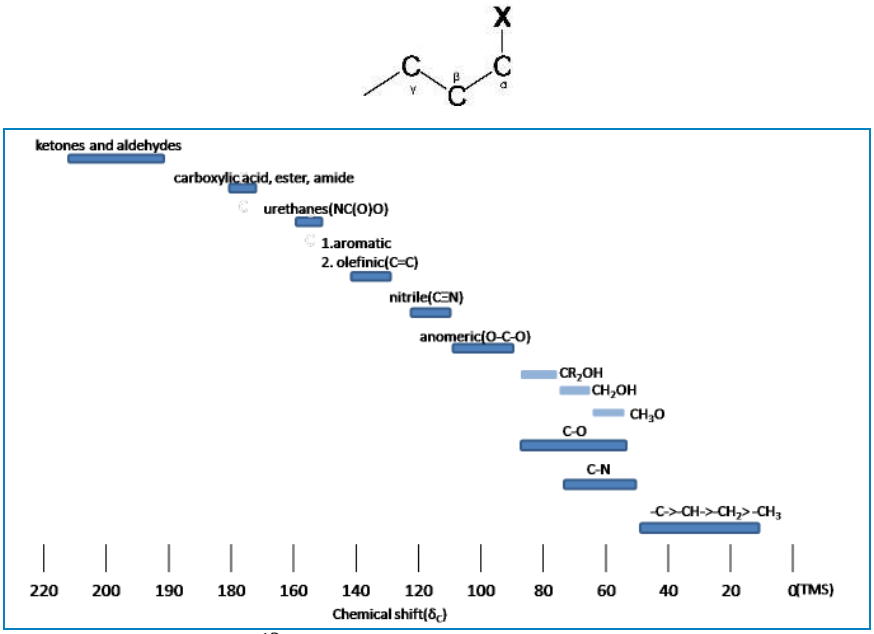

Figure 9: ^{13}C Chemical shift range for organic compound

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 10.). Decoupling is performed by irradiating at the frequency of one proton with continuous low-power RF.

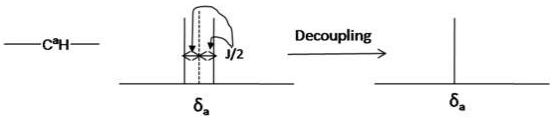

Fig 10. Decoupling in the ^{13}C NMR

Contributors and Attributions

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13.12: ^{13}C NMR Spectroscopy

Distortions Enhancement by Polarization Transfer (DEPT)

DEPT is used for distinguishing between a CH_3 group, a CH_2 group, and a CH group. 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. Fig 11. is an example about DEPT spectrum.

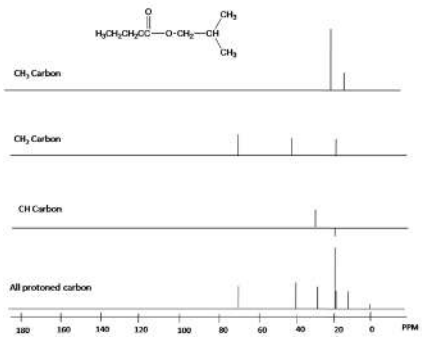
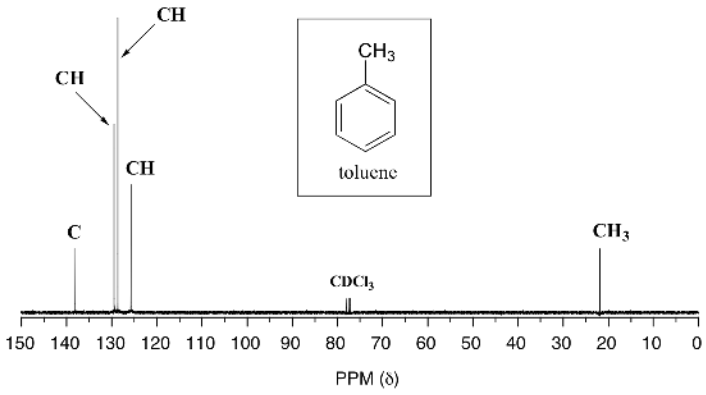
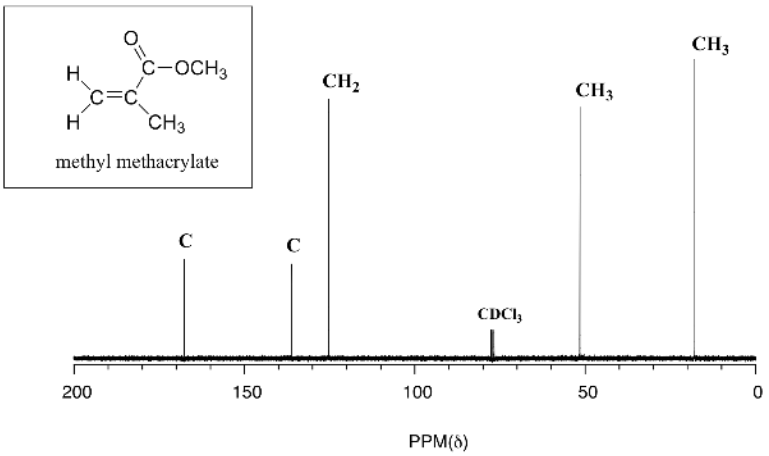


Fig 11. *DEPT spectrum of n-isobutlybutrate*

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 DEPT information.



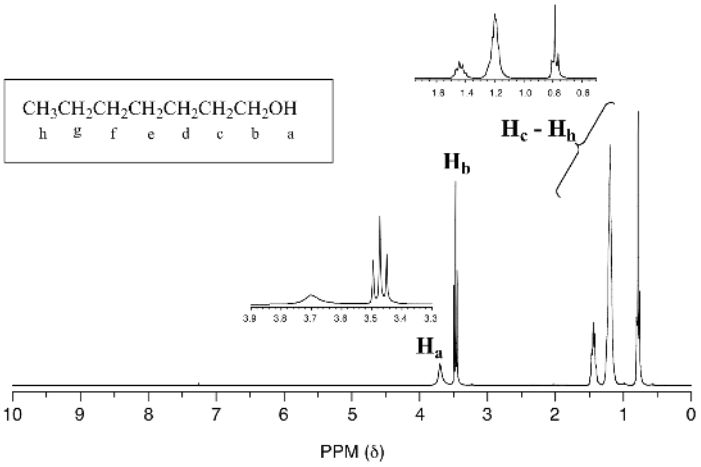


Example 13.5.2

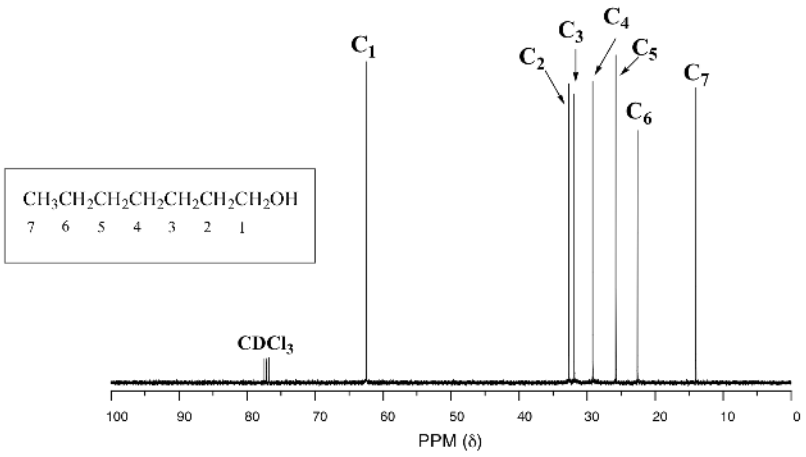
Give peak assignments for the ^{13}C-NMR spectrum of methyl methacrylate, shown above.

Solution

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.)

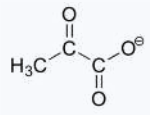


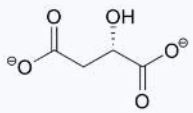
This property of ^{13}C-NMR makes it very helpful in the elucidation of larger, more complex structures.

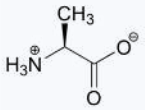
Example 13.5.3

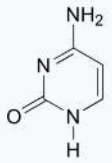
^{13}C-NMR (and DEPT) data for some common biomolecules are shown below (data is from the Aldrich Library of ^{1}H and ^{13}C NMR). Match the NMR data to the correct structure, and make complete peak assignments.

- 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)


pyruvate


(S)-malate

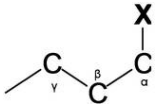

alanine


cytosine

Solution

^{13}C NMR Chemical Shifts

The Carbon NMR is used for determining functional groups using characteristic shift values. ^{13}C chemical shift is affect by electronegative effect and steric effect. If an H atoms in an alkane is replace by substituent X, electronegative atoms (O, N, halogen), ?-carbon and ?-carbon shift to downfield (left; increase in ppm) while ?-carbon shifts to upfield. The steric effect is observed in acyclic and clyclic system, which leads to downshifted chemical shifts. Figure 9 shows typical ^{13}C chemical shift regions of the major chemical class.



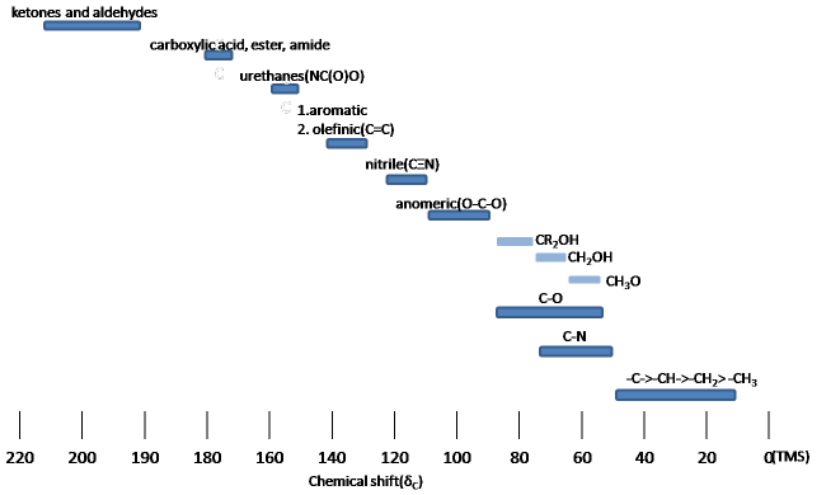


Figure 9: ^{13}C Chemical shift range for organic compound

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 10.). Decoupling is performed by irradiating at the frequency of one proton with continuous low-power RF.

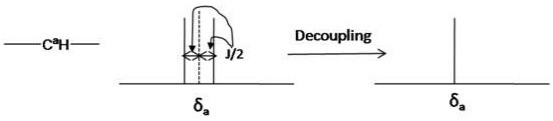


Fig 10. Decoupling in the ^{13}C NMR

Contributors

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13.13: Uses of ^{13}C NMR Spectroscopy

The interpretation of ^{13}C NMR spectra does not form a part of Chemistry 350; hence, you may omit Section 13.7. Interested students may wish to read this section for enrichment purposes.

Features of a C-13 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.

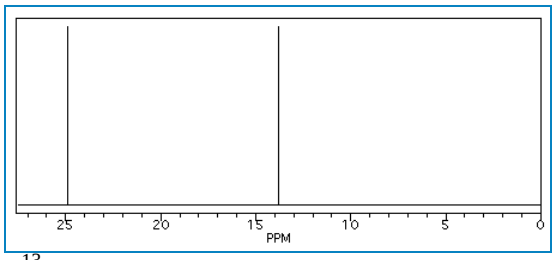


Figure NMR2. Simulated ^{13}C NMR spectrum of butane (showing only the upfield portion of the spectrum).

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.

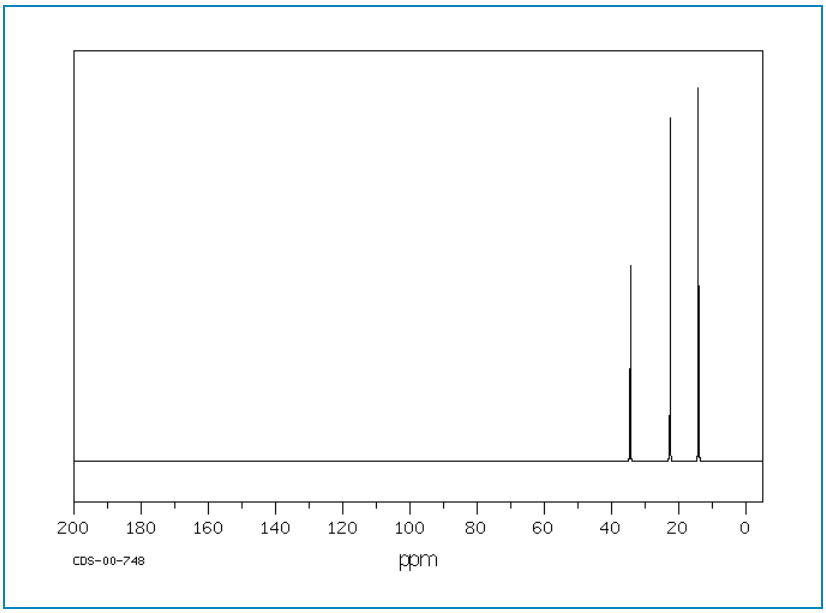


Figure NMR3.^{13}C NMR spectrum of pentane. Source: SDBSWeb : http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 15 August 2008)

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".

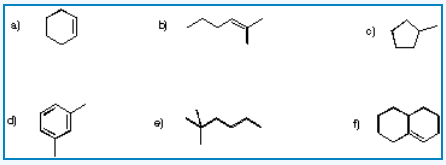
- choose one of the methyl carbons to focus on.
- rotate the model 180 degrees so that you are looking at the same "W" but from the other side.
- note that the methyl you were focusing on has simply switched places with the other methyl group. These two carbons are symmetry-equivalent via two-fold rotation.

Animation NMR1. A three-dimensional model of pentane. Grab the model with the mouse and rotate it so that you are convinced that the second and fourth carbons are symmetry-equivalent, but the third carbon is not.

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 13.13.1

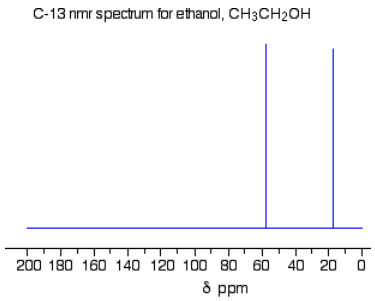
Determine how many inequivalent carbons there are in each of the following compounds. How many peaks do you expect in each ^{13}C NMR spectrum?



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.

The C-13 NMR spectrum for ethanol

This is a simple example of a C-13 NMR spectrum. Don't worry about the scale for now - we'll look at that in a minute.



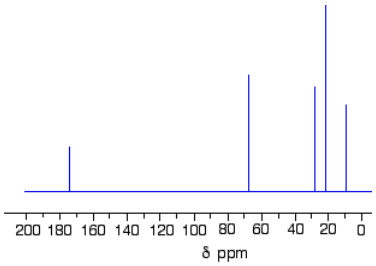
Note

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.

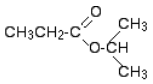
There are two peaks because there are two different environments for the carbons. The carbon in the CH_3 group is attached to 3 hydrogens and a carbon. The carbon in the CH_2 group is attached to 2 hydrogens, a carbon and an oxygen. The two lines are in different places in the NMR spectrum because they need different external magnetic fields to bring them in to resonance at a particular radio frequency.

The C-13 NMR spectrum for a more complicated compound

This is the C-13 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?



Well - 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 C-13 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 C-13. 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 C-13 atom in it, and only about 1 in 10,000 of both being C-13.

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 C-13 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.

Contributors and Attributions

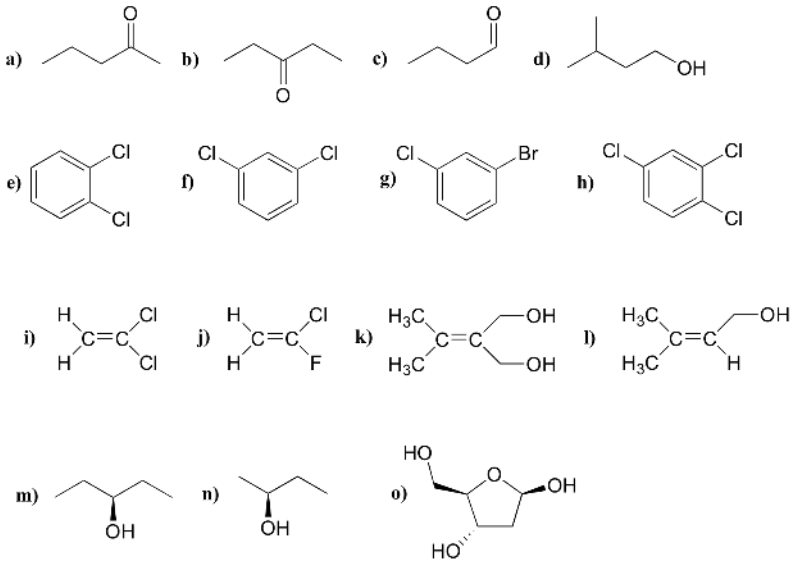
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

13.13: Uses of ^{13}C NMR Spectroscopy is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

13.14: More NMR Examples

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.

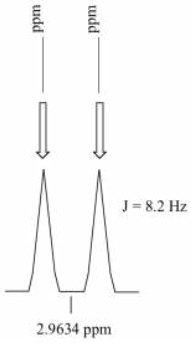


P5.2: For each of the 20 common amino acids, predict the number of signals in the proton-decoupled ^{13}C-NMR spectrum.

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

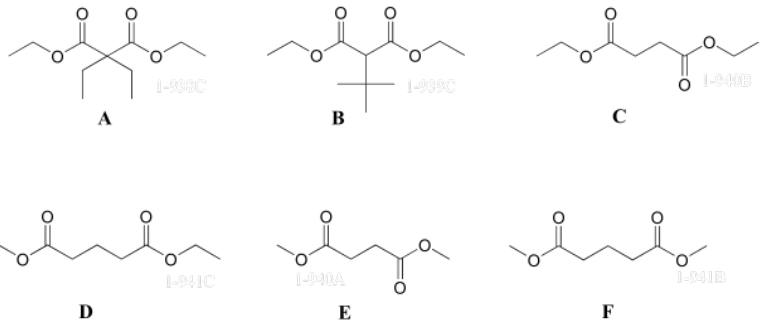


P5.4: Consider a quartet signal in an ^{1}H-NMR spectrum obtained on a 300 MHz instrument. The chemical shift is recorded as 1.7562 ppm, and the coupling constant is J = 7.6 Hz. What is the chemical shift, expressed to the nearest 0.1 Hz, of the furthest downfield sub-peak in the quartet? What is the 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:



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

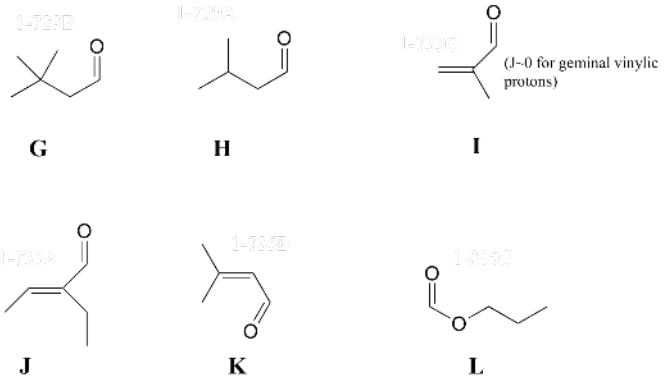
δ	splitting	integration
4.18	q	1
1.92	q	1
1.23	t	1.5
0.81	t	1.5

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:

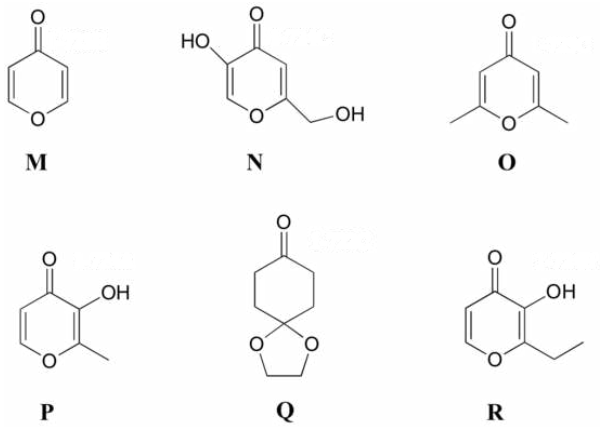
δ	splitting	integration
9.75	t	1
2.30	dd	2
2.21	m	1
0.98	d	6

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:

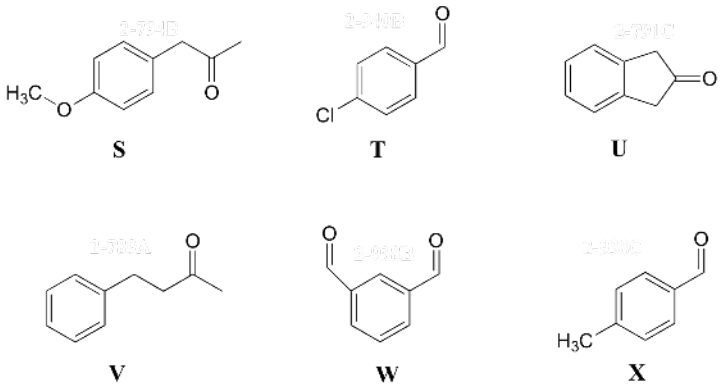
δ	splitting	integration
7.76	d	1
7.57	s (b)	1
6.44	d	1
2.78	q	2
1.25	t	3

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:

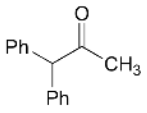
δ	splitting	integration
7.10	d	1
6.86	d	1
3.78	s	1.5
3.61	s	1
2.12	s	1.5

Spectrum 24:

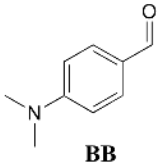
δ	splitting	integration
7.23-7.30	m	1
3.53	s	1

P5.10: Match the ^{1}H-NMR spectra 25-30 below to their corresponding structures AA-FF.

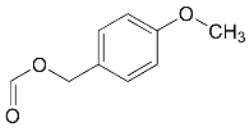
Structures:



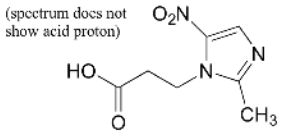
AA



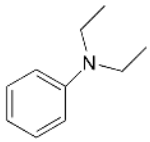
BB



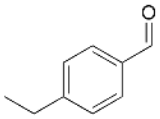
CC



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:

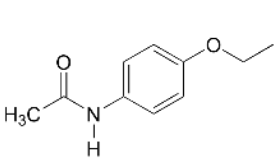
δ	splitting	integration
7.18	d	1
6.65	m	1.5
3.2	q	2
1.13	t	3

Spectrum 30:

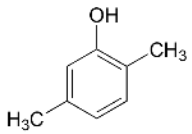
δ	splitting	integration
8.32	s	1
4.19	t	2
2.83	t	2
2.40	s	3

P5.11: Match the ^{1}H-NMR spectra 31-36 below to their corresponding structures GG-LL

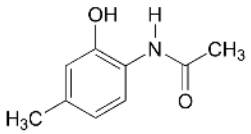
Structures:



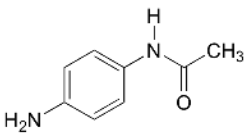
GG



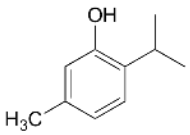
HH



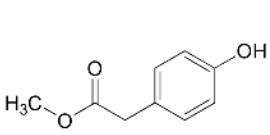
II



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

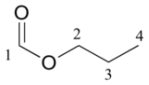
^{13}C-NMR

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:

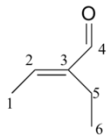
^{13}C-NMR data is given for the molecules shown below. Complete the peak assignment column of each NMR data table.

a)



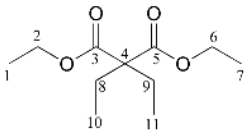
δ	DEPT	carbon #
161.12	CH	
65.54	CH_2	
21.98	CH_2	
10.31	CH_3	

b)



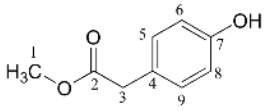
δ	DEPT	carbon #
194.72	C	
149.10	C	
146.33	CH	
16.93	CH_2	
14.47	CH_3	
12.93	CH_3	

c)



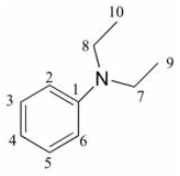
δ	DEPT	carbon #
171.76	C	
60.87	CH_2	
58.36	C	
24.66	CH_2	
14.14	CH_3	
8.35	CH_3	

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	

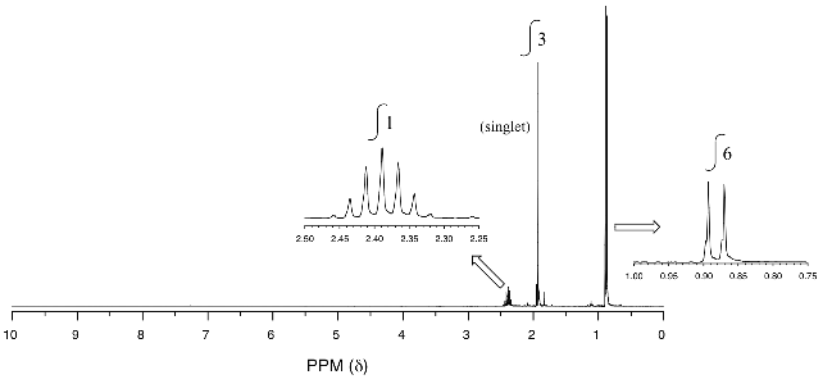
e)



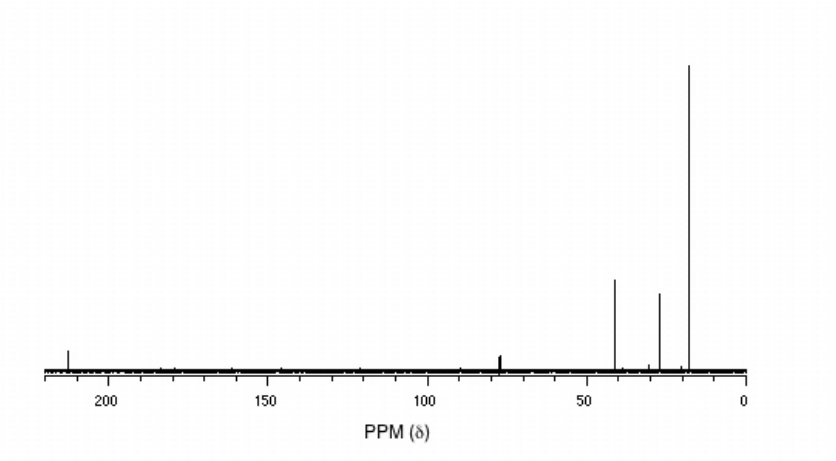
δ	DEPT	carbon #
147.79	C	
129.18	CH	
115.36	CH	
111.89	CH	
44.29	CH_2	
12.57	CH_3	

P5.14: You obtain the following data for an unknown sample. Deduce its structure.

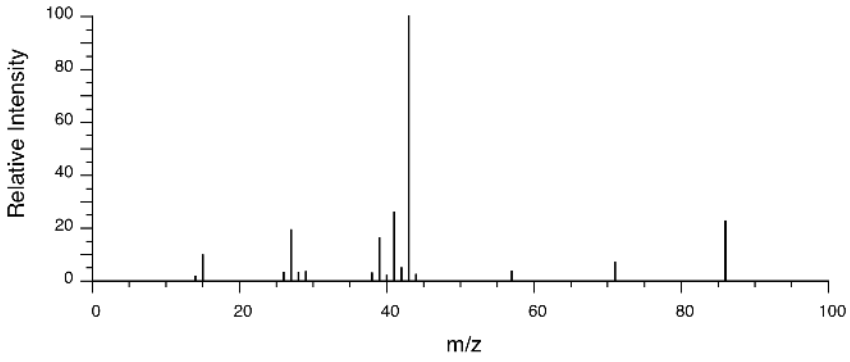
^{1}H-NMR:



^{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:

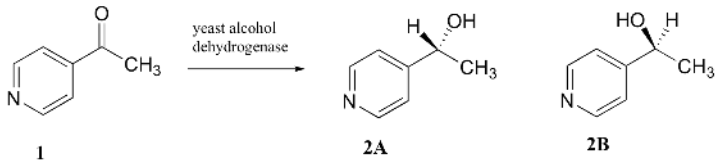
δ	splitting	integration
4.3	septet	0.0735
3.4	triplet	0.661
1.9	sextet	0.665
1.7	doublet	0.441
1.0	triplet	1.00

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).

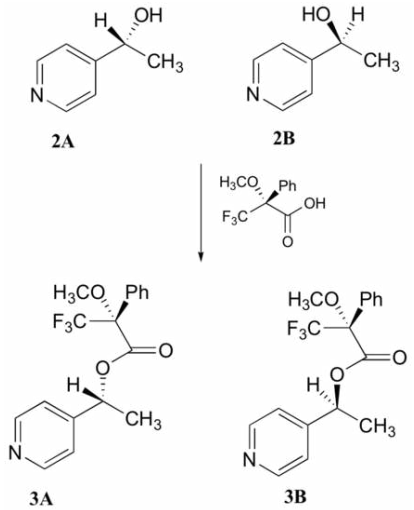


1 2A 2B

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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13.15: Sample NMR Spectra

Sample ^{1}H-NMR Spectra

List of Animated ^{1}H-NMR Spectra				
Bromoethane	**1-bromopropane**	**2-propanol**	**3-bromopropene**	**propanal**
Phenol	**acetone**	**propanoic acid**	**ethyl acetate**	**2-propenamide**
For all spectra click on a peak to highlight the protons responsible for the peak.				
More spectra can be found at Animated Spectra				

To see the integratals, right click on the spectra to open the menu, go to "view" and check the integrate" box.

Contributors and Attributions

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CHAPTER OVERVIEW

14: Ethers, Epoxides and Thioethers

After reading this chapter and completing ALL the exercises, a student can be able to

- predict relative boiling points and solubilities of ethers (refer to section 15.1)
- explain how ether solvents stabilize electrophilic reagents (refer to section 15.1)
- determine the structures of ethers from their spectra, and explain their characteristic absorptions and fragmentations (refer to section 15.2)
- devise efficient laboratory synthesis of ethers and epoxides, including:
  a) Williamson ether synthesis (refer to section 15.3)
  b) alkoximercuration-demercuration (refer to section 15.4)
  c) peroxyacid epoxidation (refer to Chapter 9 section 12)
  d) base-promoted cyclization of halohydrins (refer to section 15.7)
- predict the products or reactions of ethers and epoxides, including:
  a) acidic cleavage of ethers (refer to section 15.5)
  b) opening of epoxides (refer to section 15.8)
  c) reactions of epoxides with organometallic reagents (refer to section 15.10)
- explain how Crown ethers solvate metal cations (refer to section 15.10)
- explain the reaction of epoxy monomers to form the adhesive resin (refer to section 15.11)
- describe the structure and reactive of sulfides (refer to section 15.12)
- use your knowledge of chemical reactivity to propose mechanisms and products for similar reactions you have never seen before (chapters to date)
- propose multiple-step syntheses using all of the reactions studied through this chapter (chapters to date)

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

Topic hierarchy

14.1: Physical Properties of Ethers
14.2: Spectroscopy of Ethers
14.3: The Williamson Ether Synthesis
14.4: Alkoxymercuration-Demercuration Synthesis of Ethers
14.5: Acidic Cleavage of Ethers
14.6: Autoxidation of Ethers
14.7: Synthesis of Epoxides
14.8: Opening of Epoxides
14.9: Reactions of Epoxides with Grignard and Organolithium Reagents
14.10: Crown Ethers
14.11: Epoxy Resins: The Advent of Modern Glues
14.12: Thioethers (Sulfides) and Silyl Ethers
14.13: Additional Exercises

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14.1: Physical Properties of Ethers

Comparisons of Physical Properties of Alcohols and Ethers

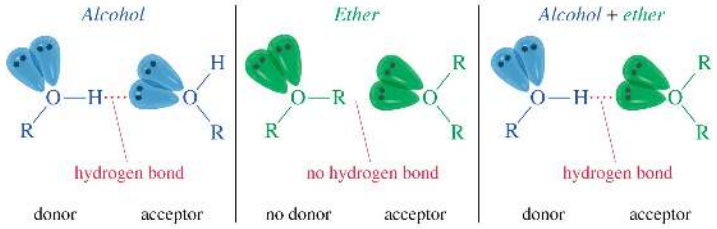
Ether molecules have no hydrogen atom on the oxygen atom (that is, no OH group). Therefore there is no intermolecular hydrogen bonding between ether molecules, and ethers therefore have quite low boiling points for a given molar mass. Ether molecules do have an oxygen atom, however, and engage in hydrogen 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). Indeed, ethers have boiling points about the same as those of alkanes of comparable molar mass and much lower than those of the corresponding alcohols as shown in the table below.

Table. 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

Ethers are Good Solvents for Many Organic Reactions

Ethers can only accept H-bonds, while alcohols are both H-bond donors and acceptors. The ability of ethers to accept H-bonds combined with the London forces of the alkyl groups bonded to the oxygen allows ethers to be excellent solvents for a wide range of organic compounds. The low chemical reactivity of ethers also makes ethers a preferred solvent for many organic reactions. Additionally, the high volatility of ethers allows for their evaporation when isolating reaction products.



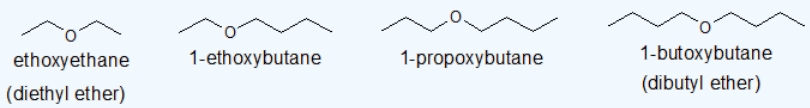
Exercise

1. Draw the bond-line structures and arrange the following ethers in order of increasing boiling point: 1-propoxybutane, diethyl ether, 1-ethoxybutane, dibutyl ether.

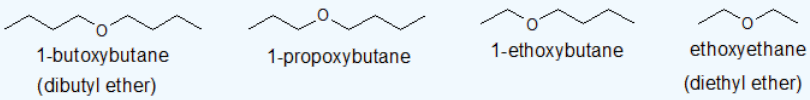
2. Arrange the following ethers in order of increasing water solubility: 1-propoxybutane, diethyl ether, 1-ethoxybutane, dibutyl ether.

Answer

1.



2.



Contributors and Attributions

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- Jim Clark (Chemguide.co.uk)

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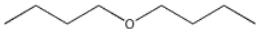
14.2: Spectroscopy of Ethers

Infrared Spectroscopy

Oxygen forms two bonds. An oxygen atom could be found in between two carbons, as in dibutyl ether.



dibutyl ether or butyl ether

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 1000 cm^{-1}. This peak is due to the C-O stretching vibration.

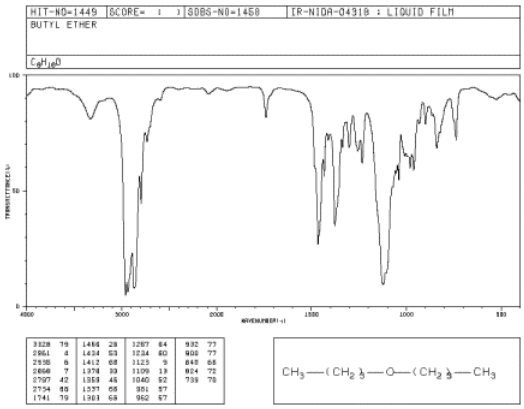
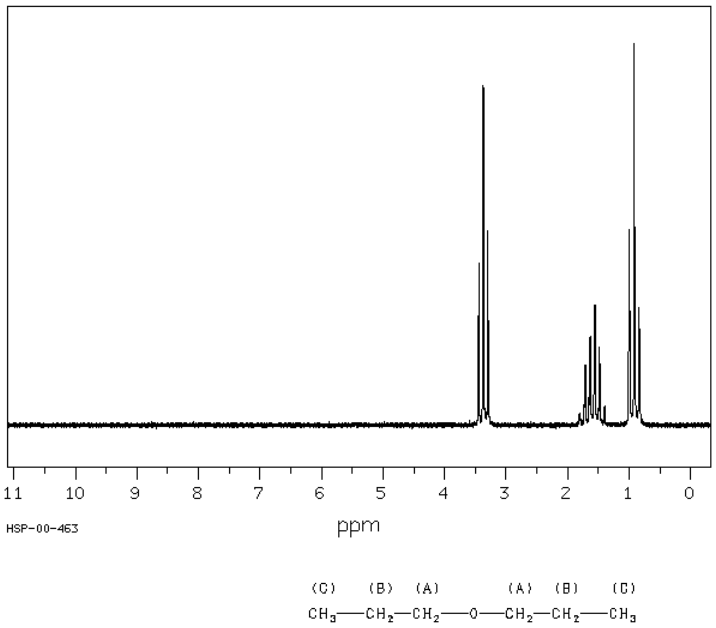


Figure IR. IR spectrum of dibutyl ether. Source: SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology of Japan, 14 July 2008)

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 show up at 2.5 to 3.5 ppm.

The 1H 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 you would therefore formally expect a quartet of triplets. However, because the coupling constants are very similar, the signal appears as a sextet. Source: SDBSWeb : http://sdbs.db.aist.go.jp (National Institute of Advanced Industrial Science and Technology, 28 June 2017)



Exercise

2. A mixture of ethers was separated into two fractions: A and B. Elemental analysis reveals that the fractions are structural isomers: 72% C, 12% H, and 16% O. The IR spectra for both fractions show a couple weak bands near 3050 cm^{-1}, several stronger bands around 2950 cm^{-1}, and a strong, sharp band near 1204 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.

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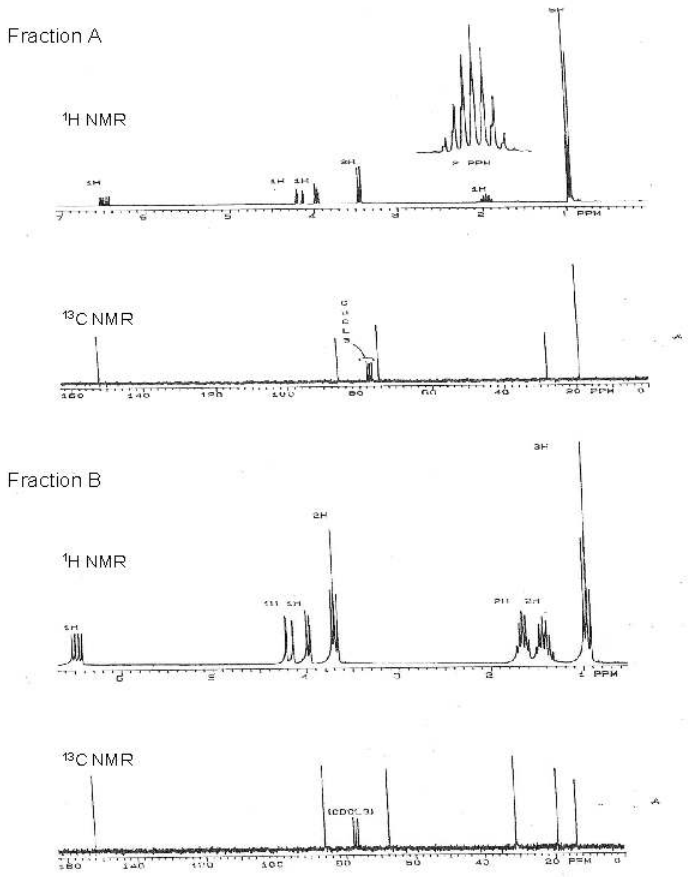
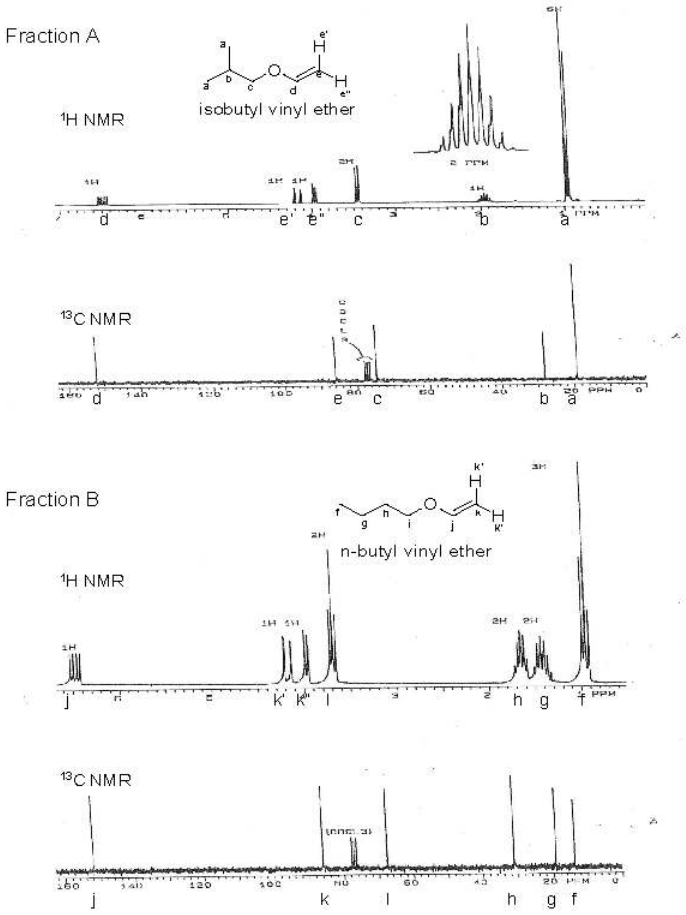


Answer

2.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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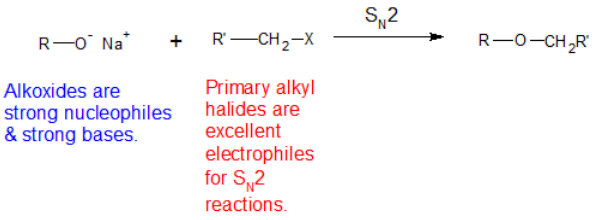
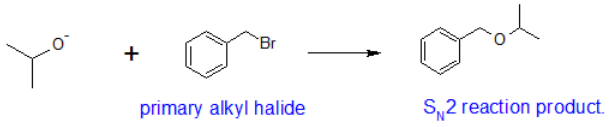
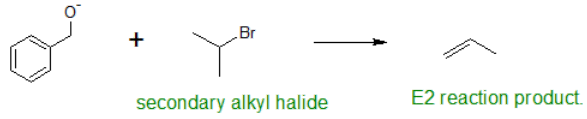
14.3: The Williamson Ether Synthesis

One important procedure, known as the Williamson Ether Synthesis, proceeds by an S_N2 reaction of an alkoxide nucleophile with an alkyl halide. There are four reaction pathways possible between an alkoxide and alkyl halide: S_N2, S_N1, E2, and E1. To maximize the amount of ether produced by the S_N2 mechanism, use a 1º alkyl halide as the electrophile because the strong alkoxide base leads to E2 elimination with 2º and 3º alkyl halides.



The reactions below show how alkoxide and alkyl halide structure can influence the products when applied to an unsymmetrical ether. Two different combinations of reactants are possible. Of these one is usually better than the other for ether synthesis. The first reaction gives a better and cleaner yield of benzyl isopropyl ether, while the second reaction generates considerable elimination product.

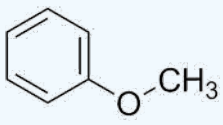


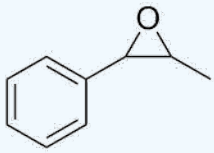


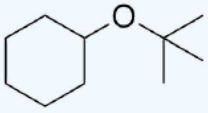
Exercises

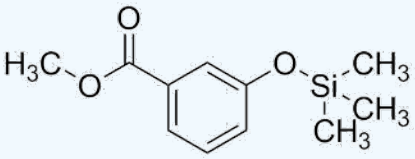
3. When preparing ethers using the Williamson ether synthesis, what factors are important when considering the nucleophile and the electrophile?

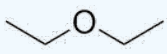
4. How would you synthesize the following ethers? Keep in mind there are multiple ways. The Williamson ether synthesis, alkoxymercuration of alkenes, and also the acid catalyzed substitution.

(a) 

(b) 

(c) 

(d) 

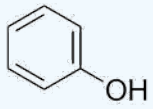
(e) 

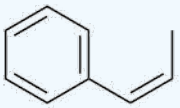
5. Draw the electron arrow pushing mechanism for the formation of diethyl ether in the previous problem.

Answer

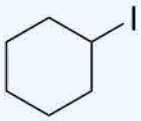
3. The nucleophile ideally should be very basic, yet not sterically hindered. This will minimize any elimination reactions. The electrophile should have the characteristics of a good S_N2 electrophile, preferably primary to minimize any elimination reactions.

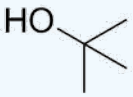
4. The Williamson ether syntheses require added catalytic base. Also, most of the halides can be interchanged, say for example for a -Br or a -Cl. Although, typically -I is the best leaving group.

(a) 

(b) 

+ Oxyacid

(c) 



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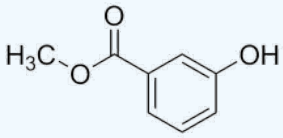
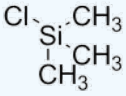
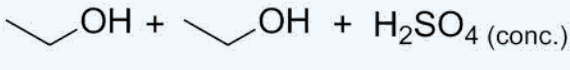
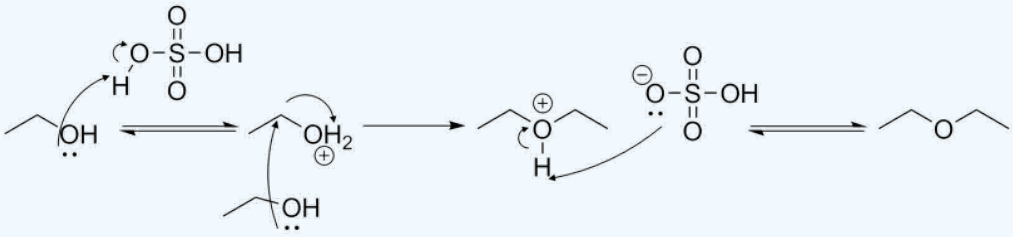




Note, there is only one ether (also called a silyl ether, and often used as an alcohol protecting group.) The other group is an ester.

(e) 

5.



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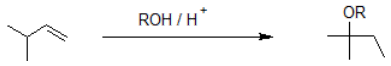
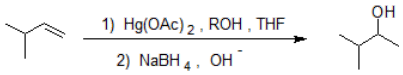
14.4: Alkoxymercuration-Demercuration Synthesis of Ethers

Introduction

Acid-catalyzed ether synthesis from alkenes is limited by carbocation stability. Carbocation rearrangement can occur to form a more stable ion as shown in the example below.



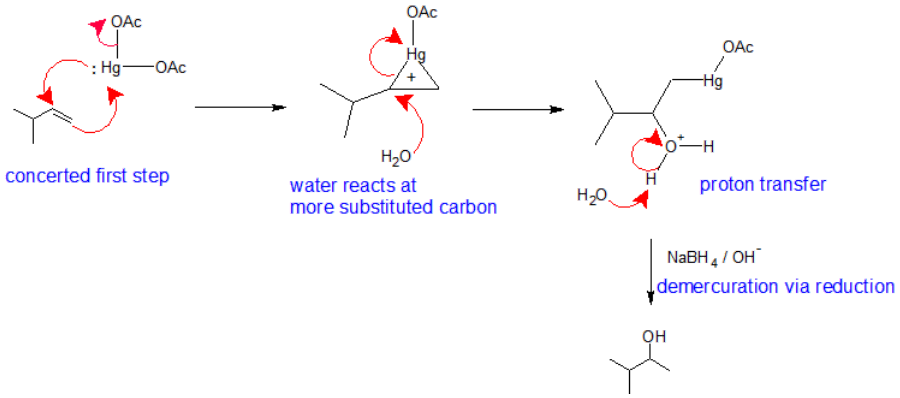
Acid-catalyzed ether synthesis using the alkoxymercuration-demercuration reaction pathway reliably produces the Markovnikov product **without** carbocation rearrangment as shown in the example below.



Alkoxymercuration-demercuration is a two step pathway used to produce ethers that proceeds in a Markovnikov manner and is stereospecific (***anti addition)***. The two steps of alkoxymerecuration-demercuraton take place on opposite faces of the double bond creating ***trans*** stereochemistry.

Alkoxymercuration-Demercuration Mechanism

This reaction follows electrophilic addition mechanism we have learned. The major difference is that a mercurium ion bridge stabilizes the carbocation intermediate so that it cannot rearrange. Metals are electropositive. Mercury carries a partial positive charge in the acetate complex and is the electrophile. During the first step of this mechanism, the pi electrons form a bond to mercury while the lone pair on the mercury simultaneously bonds to the other vinyl carbon creating a mercurium ion bridge. The mercurium ion forms in conjunction with the loss of an acetate ion. The mercurium ion stabilizes the carbocation so that it does not rearrange. In the second step of this mechanism, an alcohol molecule reacts with the most substituted carbon to open the mercurium ion bridge. The third step of this mechanism is a proton transfer to a solvent alcohol molecule to neutralize the addition product. The fourth step of the reaction pathway is the reduction of the organomercury intermediate with sodium borohydride under basic conditions. The mechanism of the fourth step is beyond the scope of first year organic chemistry.



Notice that overall, the alkoxymercuration - demercuration mechanism follows Markovnikov's regioselectivity with the OR group attached to the most substituted carbon and the H attached to the least substituted carbon. The reaction is useful, because strong acids are not required and carbocation rearrangements are avoided because no discreet carbocation intermediate forms.

Exercise

6. Show how 3-methyl-2-isopropoxypentane may be synthesized by

a) Williamson ether synthesis

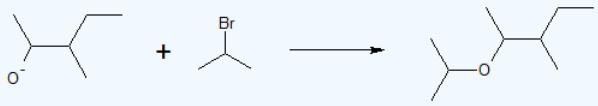
b) Alkoxymercuration-demercuration

c) Which synthesis is better? Why?

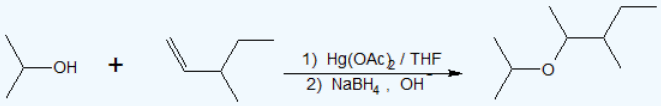
Answer

6.

a)



b)



c) The alkoxymercuration-demercuration is more effective because the Williamson Synthesis would use a bulky base and secondary alkyl halide. These reactants would favor the elimination mechanism. Additionally, the alkene can under go carbocation rearrangement, so the mercurium ion stabilization of the reactive intermediate is needed.

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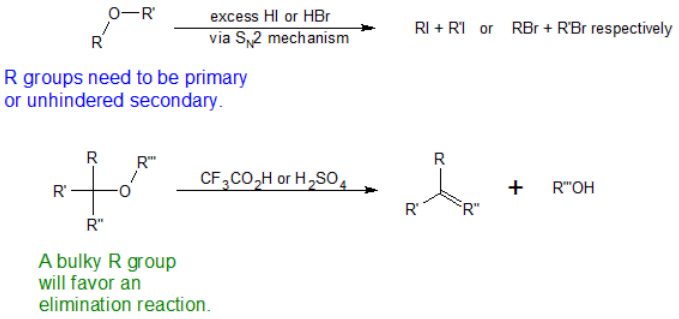
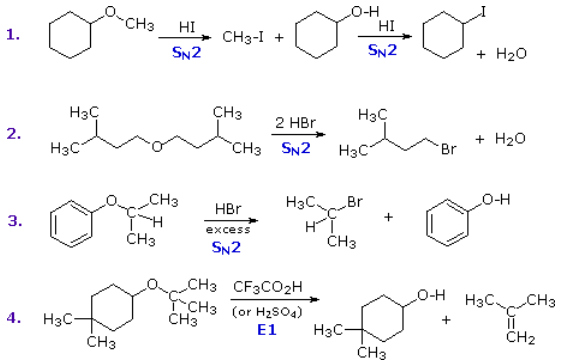
14.5: Acidic Cleavage of Ethers

The most common reaction of ethers is cleavage of the C–O bond by strong acids. This may occur by S_N1 or E1 mechanisms for 3º-alkyl groups or by an S_N2 mechanism for 1º-alkyl groups.



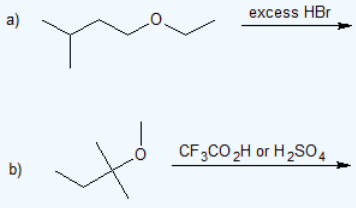
Some examples are shown in the following diagram. The conjugate acid of the ether is an intermediate in all these reactions, just as conjugate acids were intermediates in certain alcohol reactions.



The first two reactions proceed by a sequence of S_N2 steps in which the iodide or bromide anion displaces an alcohol in the first step, and then converts the conjugate acid of that alcohol to an alkyl halide in the second. Since S_N2 reactions are favored at least hindered sites, the methyl group in example #1 is cleaved first. The 2º-alkyl group in example #3 is probably cleaved by an S_N2 mechanism, but the S_N1 alternative cannot be ruled out. The phenol formed in this reaction does not react further, since S_N2, S_N1 and E1 reactions do not take place on aromatic rings. The last example shows the cleavage of a 3º-alkyl group by a strong acid. Acids having poorly nucleophilic conjugate bases are often chosen for this purpose so that E1 products are favored.

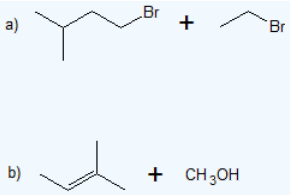
Exercise

7. Draw the bond-line structures of the product(s) for each reaction below.



Answer

7.



Contributors and Attributions

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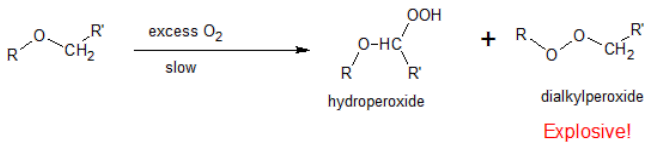
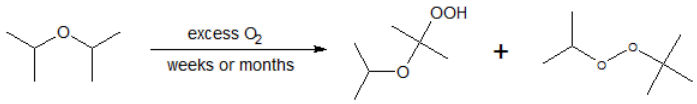
14.6: Autoxidation of Ethers

Over time ethers that are exposed to air will autoxidize to peroxides which are potentially explosive. The general reaction is shown below.



Explosive!

For example, diisopropyl ether will autoxidize to the products shown in the reaction below.



How to avoid explosions.

1. buy ether in small quantities
2. keep containers tightly sealed
3. use opened containers promptly
4. discard suspect containers

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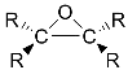
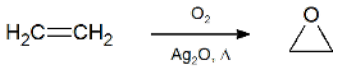
14.7: Synthesis of Epoxides

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.



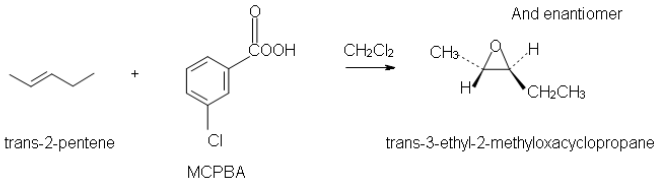
The most important and simplest epoxide is ethylene oxide which is prepared on an industrial scale by catalytic oxidation of ethylene by air.



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.

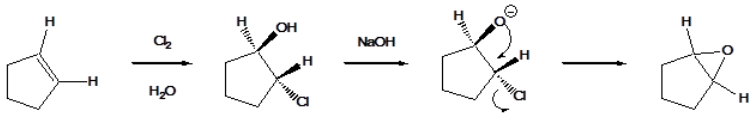
Peroxyacid reactions with Alkenes

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.



Intramolecular Williamson Ether Synthesis via Halohydrins

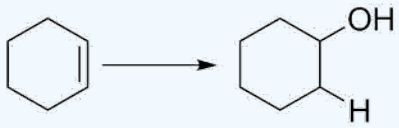
Epoxides can also be synthesized by the treatment of a halohydrin with a base. This causes an intramolecular Williamson ether synthesis.



Exercise

8. What reagents would you use to perform the following transformations?

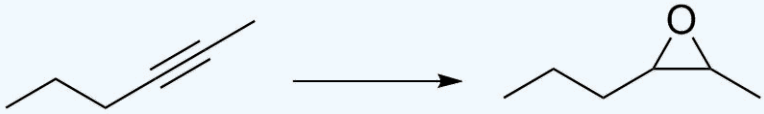
(a)



(b)

(c)

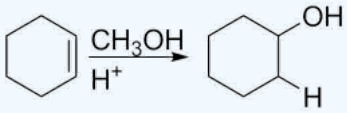
(d)



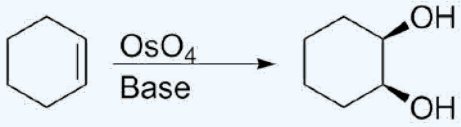
Answer

8.

(a)

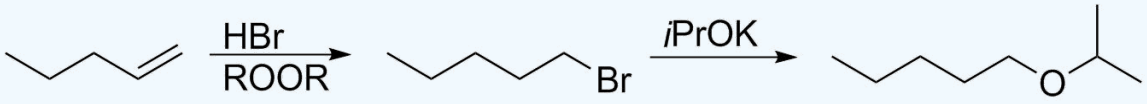


(b)



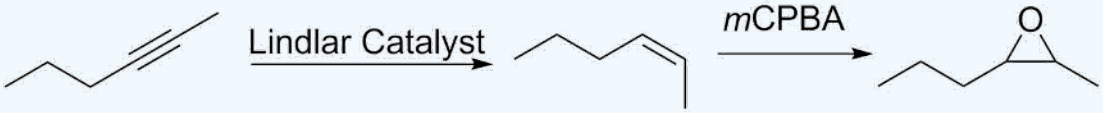
Note the cis addition

(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.

(d)



Lindlar's catalyst reduces alkynes to cis/Z alkenes. This stereochemistry is retained after epoxidation.

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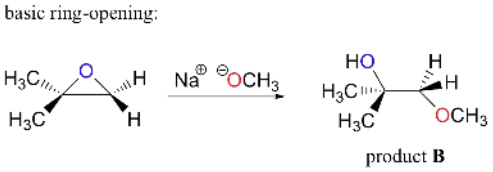
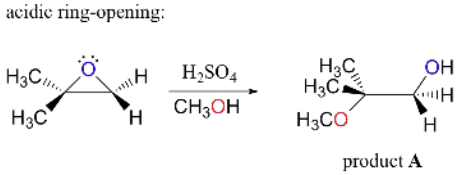
14.8: Opening of Epoxides

Epoxide ring-opening reactions - S_N1 vs. S_N2, regioselectivity, and stereoselectivity

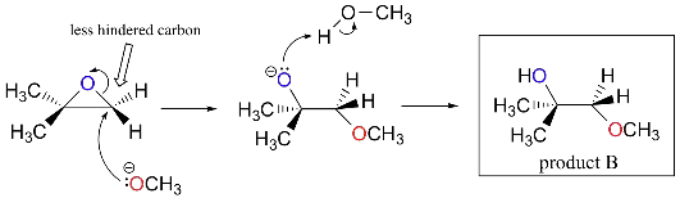
The ring-opening reactions of epoxides provide an excellent review of the differences between S_N1 and S_N2 reactions. Both mechanisms are good examples of **regioselective reactions**. In a regioselective reaction, two (or more) different constitutional isomers are possible as products, but one is formed preferentially (or sometimes exclusively). 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. For the S_N1 mechanism, the stability of the charged intermediate determines the regioselectivity. For the concerted S_N2 mechanism, sterics are the dominating consideration. If the epoxide is asymmetric, the structure of the product will vary according to which mechanism dominates. When an asymmetric epoxide undergoes solvolysis in basic methanol, ring-opening occurs by an S_N2 mechanism, and the *less* substituted carbon is the site of nucleophilic reaction, leading to what we will refer to as 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 reaction. As a result, product A predominates.



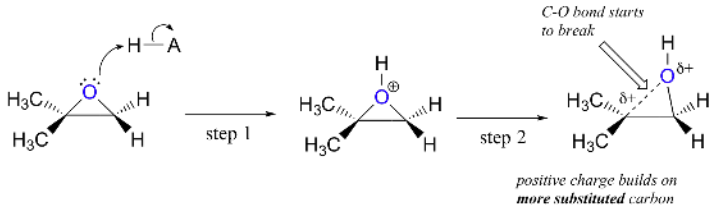
Let us examine the basic, S_N2 case first. The leaving group is an alkoxide anion, because there is no acid available to protonate the oxygen prior to ring opening. An alkoxide is a poor leaving group, and thus the ring is unlikely to open without a 'push' from the nucleophile.



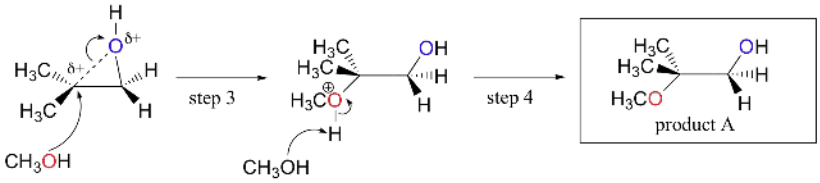
The nucleophile itself is a potent, deprotonated, negatively charged methoxide ion. When a nucleophilic substitution reaction involves a poor leaving group and a powerful nucleophile, it is very likely to proceed by an S_N2 mechanism.

What about the electrophile? 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, bimolecular, nucleophilic substitution reactions take place from the backside, resulting in inversion at the electrophilic carbon.

The acid-catalyzed epoxide ring-opening reaction mechanism is analogous to the formation of the bromonium ion in halogenation of alkenes and mercurium ion formation in oxymercuration/demercuratioin or alkoxymercuration/demercuration. 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 carbocation stability).



Unlike in an S_N2 reaction, the nucleophile reacts with the electrophilic carbon (step 3) before a complete carbocation intermediate has a chance to form.

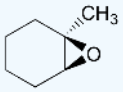


The reaction takes place preferentially from the backside (like in an S_N2 reaction) because the carbon-oxygen bond is still to some degree in place, and the oxygen blocks reaction from the front side. Notice, however, how the regiochemical outcome is different from the base-catalyzed reaction: in the acid-catalyzed process, the nucleophile reacts with the more substituted carbon because this carbon that holds a greater degree of positive charge.

Example

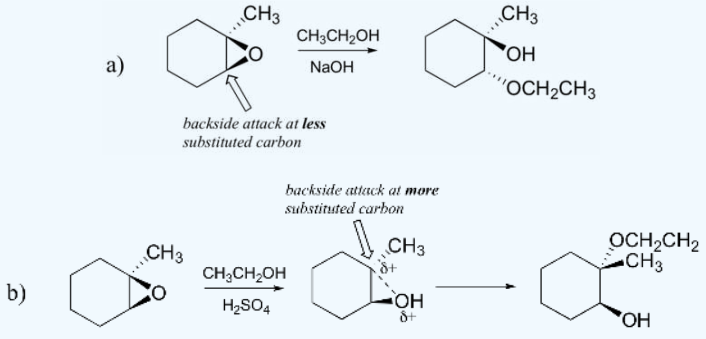
Predict the major product(s) of the ring opening reaction that occurs when the epoxide shown below is treated with:

a. ethanol and a small amount of sodium hydroxide
b. ethanol and a small amount of sulfuric acid



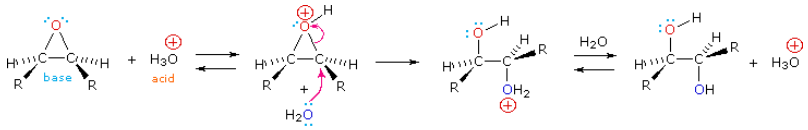
*Hint: be sure to consider both regiochemistry **and** stereochemistry!*

Answer



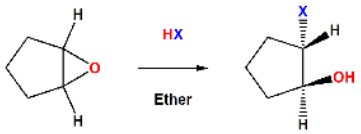
Anti Dihydroxylation

Epoxides may be cleaved by aqueous acid to give glycols that are often diastereomeric with those prepared by the syn-hydroxylation reaction. 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 the following equation this procedure is illustrated for a cis-disubstituted epoxide, which can be prepared from the corresponding cis-alkene. This hydration of an epoxide does not change the oxidation state of any atoms or groups.



Addition of HX

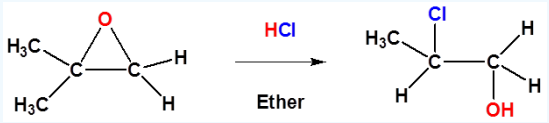
Epoxides can also be opened by other anhydrous acids (HX) to form a trans halohydrin. When both the epoxide carbons are either primary or secondary the halogen anion will react with the less substituted carbon and an S_N2 like reaction. However, if one of the epoxide carbons is tertiary, the halogen anion will primarily react with the tertiary carbon in a S_N1 like reaction.



Example

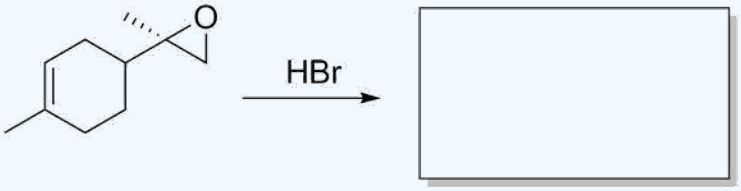
In the first example, the epoxide is formed by a secondary and primary carbon. The reaction with the Cl^- nucleophile proceeds via the S_N2 mechanism and reacts with the least substituted carbon.

In the second example, the epoxide is formed by a tertiary and primary carbon. The reaction with Cl^- nucleophile proceeds via the S_N1 like mechanism and reacts with the most substituted carbon because it carries the greater partial positive charge.

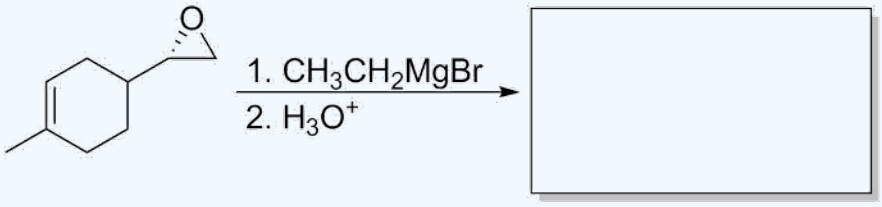


Exercise

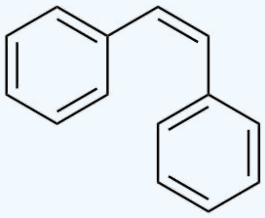
9. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



10. Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

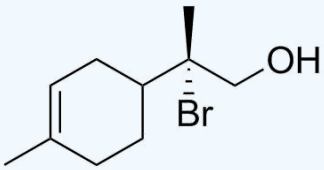


11. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



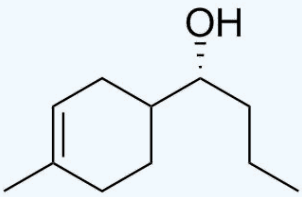
Answer

9.



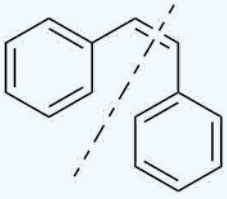
Note that the stereochemistry has been inverted

10.

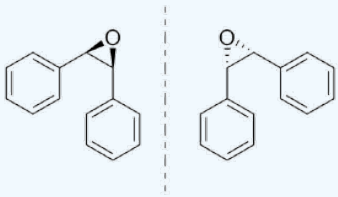


11.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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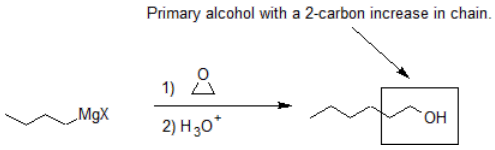
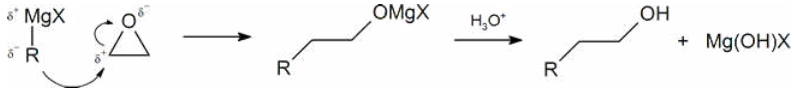
14.9: Reactions of Epoxides with Grignard and Organolithium Reagents

Grignard Reactions with Epoxides

Grignard reactions with ethylene oxide produce a primary alcohol containing two more carbon atoms than the original Grignard reagent.

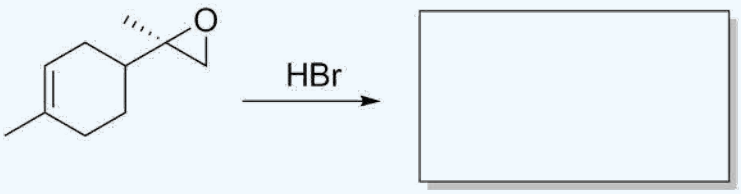


The first step of the mechanism is shown below. With the second step following the protonation step common to the other reaction pathways studied in this section. This reaction follows the same S_N2 mechanism as the opening of epoxide rings under basic conditions since Grignard reagents are both strong nucleophiles and strong bases.

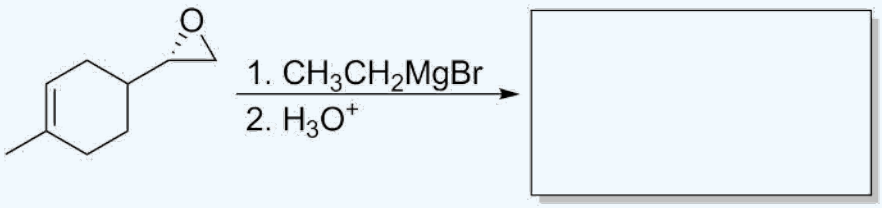


Exercise

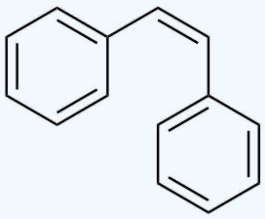
12. Given the following, predict the product assuming only the epoxide is affected. (Remember stereochemistry)



13. Predict the product of the following, similar to above but a different nucleophile is used and not in acidic conditions. (Remember stereochemistry)

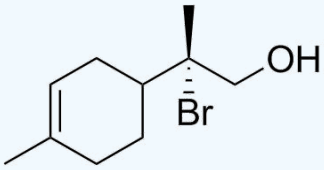


14. Epoxides are often very useful reagents to use in synthesis when the desired product is a single stereoisomer. If the following alkene were reacted with an oxyacid to form an epoxide, would the result be a enantiomerically pure? If not, what would it be?



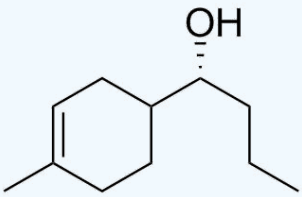
Answer

12.



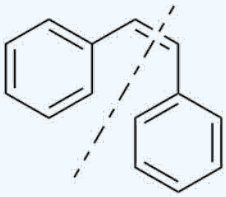
Note that the stereochemistry has been inverted

13.

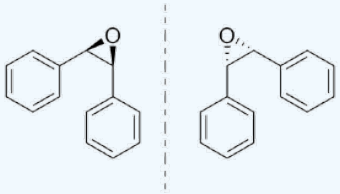


14.

First, look at the symmetry of the alkene. There is a mirror plane, shown here.



Then, think about the mechanism of epoxidation with an oxyacid, take for example *m*CPBA. The mechanism is concerted, so the original *cis* stereochemistry is not changed. This leads to "two" epoxides.



However, these two mirror images are actually identical due to the mirror plane of the *cis* geometry. It is a meso compound, so the final result is a single stereoisomer, but not a single enantiomer.

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14.10: Crown Ethers

A “crown ether ” is a cyclic ether containing several (i.e., 4, 5, 6 or more) oxygen atoms. It is possible to dissolve ionic compounds in organic solvents using crown ethers. Cyclic polyether with four or more oxygen atoms separated by two or three carbon atoms. All crown ethers have a central cavity that can accommodate a metal ion coordinated to the ring of oxygen atoms., cyclic compounds with the general formula $(OCH_2CH_2)_n$. Crown ethers 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 (part (a) in Figure 18.7.1). The cavity in the center of the crown ether molecule is lined with oxygen atoms and is large enough to be occupied by a cation, such as K^+. The cation is stabilized by interacting with lone pairs of electrons on the surrounding oxygen atoms. Thus crown ethers solvate cations inside a hydrophilic cavity, whereas the outer shell, consisting of C–H bonds, is hydrophobic. Crown ethers are useful for dissolving ionic substances such as $KMnO_4$ in organic solvents such as isopropanol $[(CH_3)_2CHOH]$ (Figure 18.7.1). The availability of crown ethers with cavities of different sizes allows specific cations to be solvated with a high degree of selectivity.

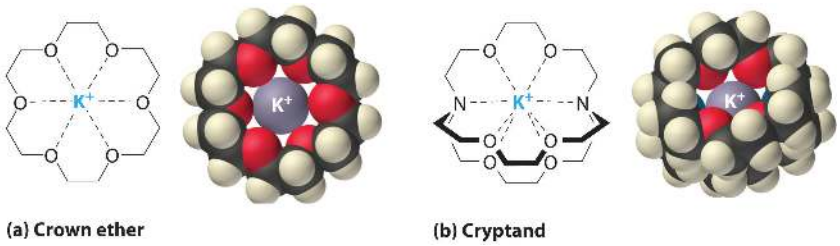

Figure: 1 Crown Ethers and Cryptands (a) The potassium complex of the crown ether 18-crown-6. Note how the cation is nestled within the central cavity of the molecule and interacts with lone pairs of electrons on the oxygen atoms. (b) The potassium complex of 2,2,2-cryptand, showing how the cation is almost hidden by the cryptand. Cryptands solvate cations via lone pairs of electrons on both oxygen and nitrogen atoms.

Figure 2: Effect of a Crown Ether on the Solubility of KMnO4 in Benzene*. Normally which is intensely purple, is completely insoluble in benzene which has a relatively low dielectric constant. In the presence of a small amount of crown ether, KMnO4 dissolves in benzene as shown by the reddish purple color caused by the permanganate ions in solution.*

Cryptands (from the Greek *kryptós*, meaning “hidden”) are compounds that can completely surround a cation with lone pairs of electrons on oxygen and nitrogen atoms (Figure 18.7.1b). The number in the name of the cryptand is the number of oxygen atoms in each strand of the molecule. Like crown ethers, cryptands can be used to prepare solutions of ionic compounds in solvents that are otherwise too nonpolar to dissolve them.

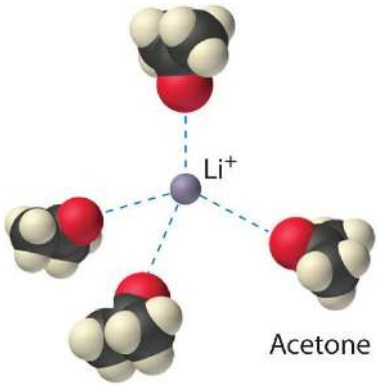

Figure 18.7.3: Ion–Dipole Interactions in the Solvation of Li^+ Ions by Acetone, a Polar Solvent

Contributors and Attributions

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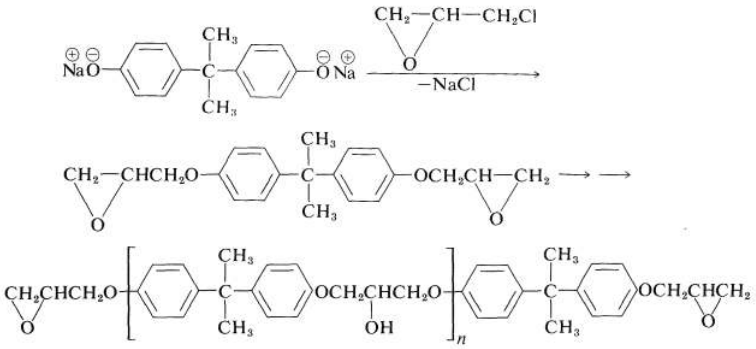
14.11: Epoxy Resins: The Advent of Modern Glues

A very useful group of adhesives and plastics is based on condensation polymers of bisphenol A and chloromethyloxacyclopropane (epichlorohydrin). The first step in the formation of epoxy resins is to form a prepolymer by condensation polymerization of the sodium salt of bisphenol A with the epoxide:



The formation of a prepolymer involves two different kinds of reactions. One is an S_N2-type displacement, and the other is oxide-ring opening of the product by attack of more bisphenol A. Usually, for practical purposes the degree of polymerization n of the prepolymer is small (5 to 12 units).

The epoxy prepolymer can be cured, that is, converted to a three-dimensional network, in several different ways. A trifunctional amine, such as $NH_2CH_2CH_2NHCH_2CH_2NH_2$, can be mixed in and will extend the chain of the polymer and form cross-links by reacting with the oxide rings:

Alternatively, a polybasic acid anhydride can be used to link the chains through combination with secondary alcohol functions and then the oxide rings.

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14.12: Thioethers (Sulfides) and Silyl Ethers

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

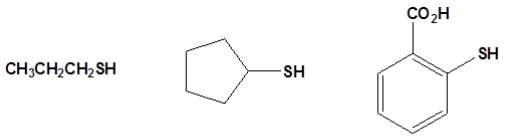
Oxygen assumes only two oxidation states in its organic compounds (–1 in peroxides and –2 in other compounds). Sulfur, on the other hand, is found in oxidation states ranging from –2 to +6, as shown in the following table (some simple inorganic compounds are displayed in orange).

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

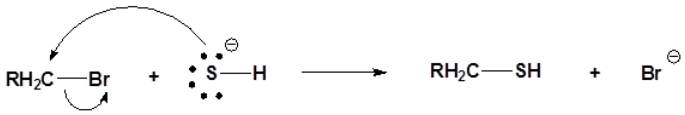
Thiols

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. They are named in a similar fashion as alcohols except the suffix -thiol is used in place of -ol. By itself the -SH group is called a mercapto group.

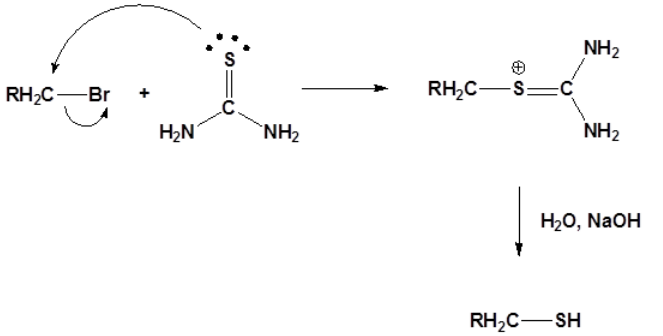


Propanethiol Cyclopentanethiol o-Mercaptobenzoic acid

Thiols are usually prepared by using the hydrosulfide anion (-SH) as a nucleophile in an S_N2 reaction with alkyl halides.



On problem with this reaction is that the thiol product can 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 reaction first produces an alkyl isothiourea salt and an intermediate. This salt is then hydrolyzed by a reaction with aqueous base.



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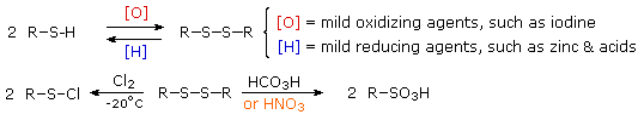
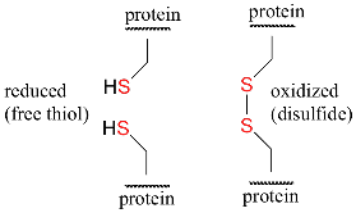
Disulfides

Oxidation of thiols and other sulfur compounds changes the oxidation state of sulfur rather than carbon. We see some representative sulfur oxidations in the following examples. In the first case, mild oxidation converts thiols to disufides. An equivalent oxidation of alcohols to peroxides is not normally observed. The reasons for this different behavior are not hard to identify. The S–S single bond is nearly twice as strong as the O–O bond in peroxides, and the O–H bond is more than 25 kcal/mole stronger than an S–H bond. Thus, thermodynamics favors disulfide formation over peroxide.

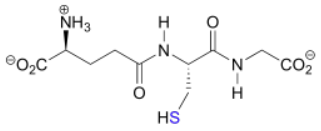


Disulfide bridges in proteins

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.



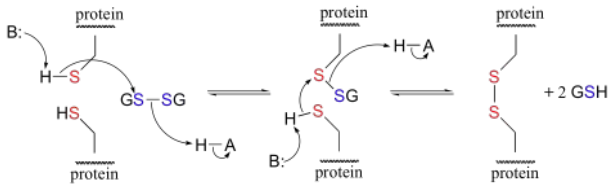
Notice that in the oxidized (disulfide) state, each sulfur atom has lost a bond to hydrogen and gained a bond to a sulfur - this is why the disulfide state is considered to be oxidized relative to the thiol state. The redox agent that mediates the formation and degradation of disulfide bridges in most proteins is glutathione, a versatile coenzyme that we have met before in a different context (section 14.2A). 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 GSSH, 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.

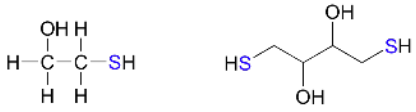


In its reduced (thiol) state, glutathione can reduce disulfides bridges in proteins through the reverse of the above reaction.

Disulfide bridges exist for the most part only in proteins that are located outside the cell. Inside the cell, cysteines are kept in their reduced (free thiol) state by a high intracellular concentration of GSH, which in turn is kept in a reduced state (ie. GSH rather than GSSG) by a flavin-dependent enzyme called glutathione reductase.

Disulfide bridges in proteins can also be directly reduced by another flavin-dependent enzyme called 'thioredoxin'. In both cases, NADPH is the ultimate electron donor, reducing FAD back to $FADH_2$ in each catalytic cycle.

In the biochemistry lab, proteins are often maintained in their reduced (free thiol) state by incubation in buffer containing an excess concentration of b-mercaptoethanol (BME) or dithiothreitol (DTT). These reducing agents function in a manner similar to that of GSH, except that DTT, because it has two thiol groups, forms an intramolecular disulfide in its oxidized form.



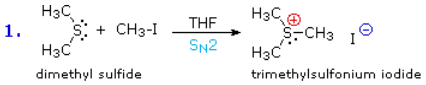
β-mercaptoethanol (BME) dithiothreitol (DTT)

Sulfides

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). The chemical behavior of sulfides contrasts with that of ethers in some important ways. Since hydrogen sulfide (H_2S) is a much stronger acid than water (by more than ten million fold), we expect, and find, thiols to be stronger acids than equivalent alcohols and phenols. Thiolate conjugate bases are easily formed, and have proven to be excellent nucleophiles in S_N2 reactions of alkyl halides and tosylates.

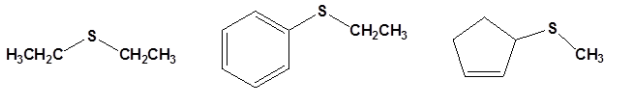
$$R–S^{(–)}\ Na^{(+)} + (CH_3)_2CH–Br \longrightarrow (CH_3)_2CH–S–R + Na^{(+)}\ Br^{(–)}$$

Although the basicity of ethers is roughly a hundred times greater than that of equivalent sulfides, the nucleophilicity of sulfur is 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. Sulfides, for example, react with alkyl halides to give ternary sulfonium salts (equation # 1) in the same manner that 3º-amines are alkylated to quaternary ammonium salts. Although equivalent oxonium salts of ethers are known, they are only prepared under extreme conditions, and are exceptionally reactive.



dimethyl sulfide trimethylsulfonium iodide

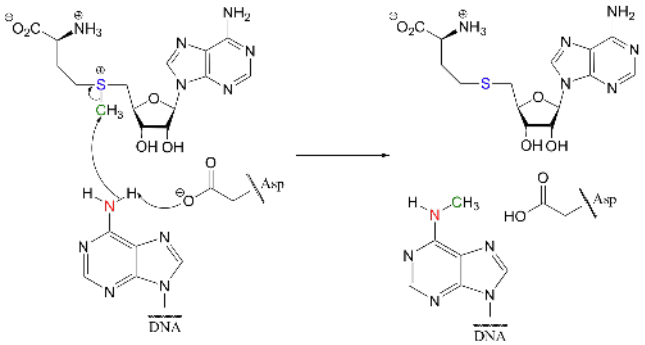
sulfides are named using the same rules as ethers except *sulfide* is used in the place of *ether*. For more complex substance alkylthio is used instead of alkoxy.



Diethyl sulfide Ethyl phenyl sulfide 3-(Methylthio)cyclopentene

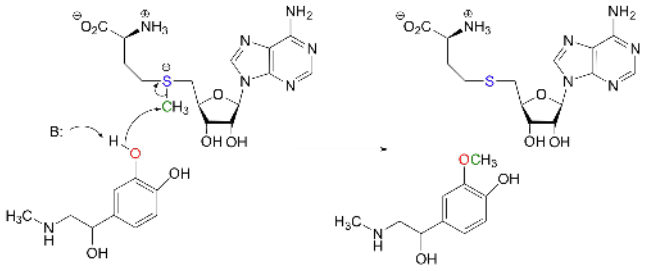
SAM methyltransferases

The most common example of sulfonium ions in a living organism is the reaction of S-Adenosylmethionine. 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:



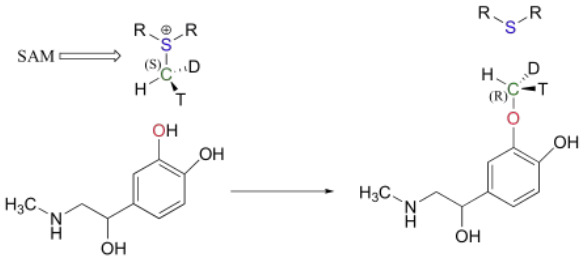
(*Nucleic Acids Res.* **2000**, *28*, 3950).

Another SAM-dependent methylation reaction is catalyzed by an enzyme called catechol-O-methyltransferase. The substrate here is epinephrine, also known as adrenaline.



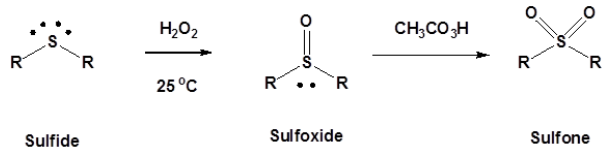
Notice that in this example, the attacking nucleophile is an alcohol rather than an amine (that's why the enzyme is called an O-methyltransferase). In both cases, though, a basic amino acid side chain is positioned in the active site in just the right place to deprotonate the nucleophilic group as it 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).

Sulfides can be easily oxidized. Reacting a sulfide with hydrogen peroxide, H_2O_2, as room termpeature produces a sulfoxide (R_2SO). The oxidation can be continued by reaction with a peroxyacid to produce the sulfone (R_2SO_2)



A common example of a sulfoxide is the solvent dimethyl sulfoxide (DMSO). DMSO is polar aprotic solvent.

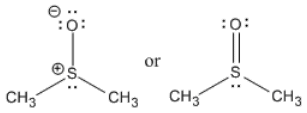


Figure AB16.3. DMSO is a very polar, aprotic solvent.

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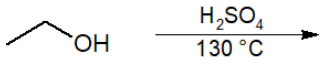
14.13: Additional Exercises

Industrial Synthesis of Ethers using Bimolecular Condensation

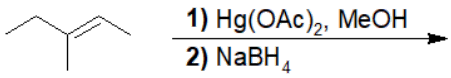
15-1 Give the final product of the following reaction.



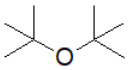
15-2 Draw the mechanism for the reaction in the previous problem, **15-1**.

Synthesis of Ethers by Alkoxymercuration-Demercuration

15-3 Predict the product of the following reaction and give its correct IUPAC nomenclature.



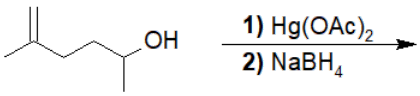
15-4 Propose a route of synthesis (that includes an alkoxymercuration-demercuration reaction) for the following ether starting with a carbon molecule containing no more than 3 carbons.



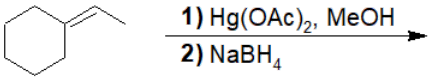
2-*tert*-butoxy-2-methylpropane

15-5 Predict the products of the following reactions.

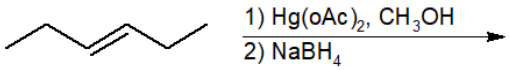
a)



b)

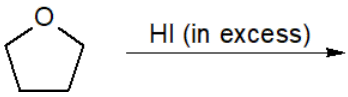


15-6 Give the final product for the following reaction.



Cleavage of Ethers

15-7 Choose the correct IUPAC name for the product of the following reaction.



a) Butan-1-ol

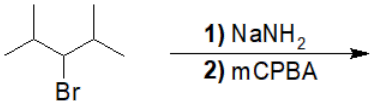
b) 1-iodobutane

c) 1,4-diiodobutane

d) 2-iodooxolane

Synthesis of Epoxides

15-8 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



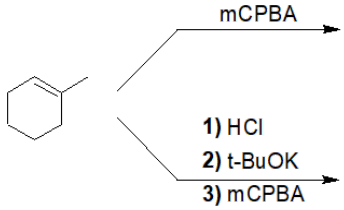
a) 2,2-dimethyl-3-(propan-2-yl)oxirane

b) 2,4-dimethylpentan-2-ol

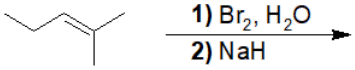
c) 2,4-dimethylpent-2-en-3-ol

d) 2-methyl-2-(2-methylpropyl)oxirane

15-9 Predict the products of the following reactions.

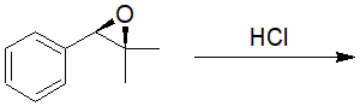


15-10 Predict the product of the following reaction. Be sure to include proper stereochemistry.

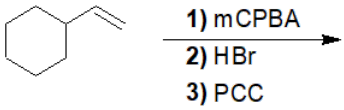


Reactions of Epoxides

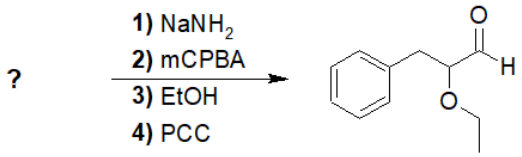
15-11 Provide the structure of the product of the following reaction. Be sure to include proper stereochemistry.



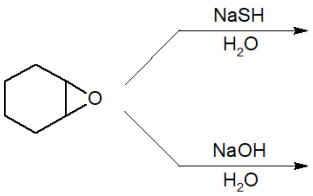
15-12 Predict the product of the following reaction.



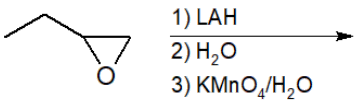
15-13 Suggest the structure of the starting brominated molecule that was used in the following reaction to make the final product.



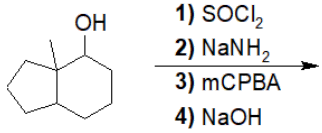
15-14 Provide the final products of the following reactions.



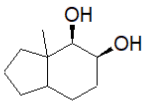
15-15 Provide the final product of the following reaction.



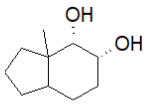
15-16 Choose the correct product of the following reaction.



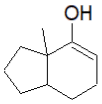
a)



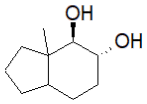
b)



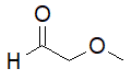
c)



d)



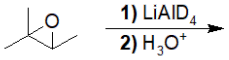
15-17 Suggest a route of synthesis (that includes an epoxide intermediate) for the following compound, starting with ethane and using any other necessary reagents.



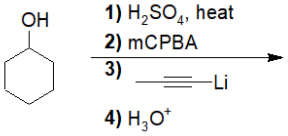
methoxyacetaldehyde

15-18 Predict the products of the following reactions. Be sure to include stereochemistry where applicable.

a)

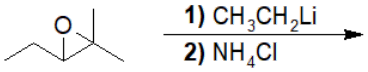


b)

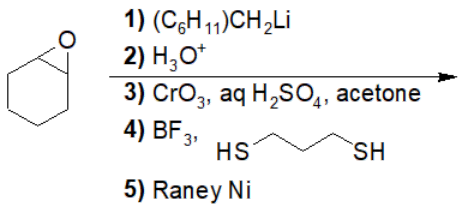


Reactions of Epoxides with Grignard and Organolithium Reagents

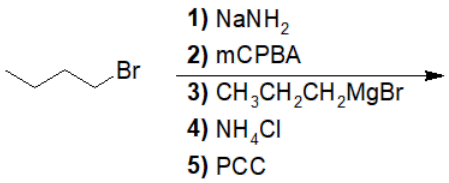
15-19 Predict the product of the following reaction and give the proper IUPAC nomenclature.



15-20 Predict the product of the following reaction.



15-21 Choose the correct IUPAC nomenclature of a product of the following reaction.



a) heptan-4-one

b) heptan-3-one

c) 3-aminoheptan-3-ol

d) (3Z)-hept-3-en-3-ol

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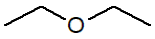
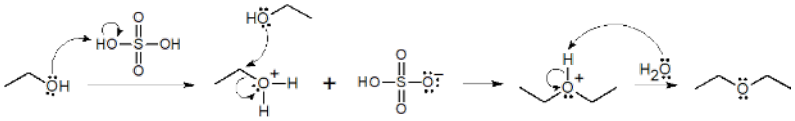
14.14: Solutions to Additional Exercises

Industrial Synthesis of Ethers using Bimolecular Condensation

15-1:

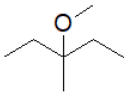


15-2:



Synthesis of Ethers by Alkoxymercuration-Demercuration

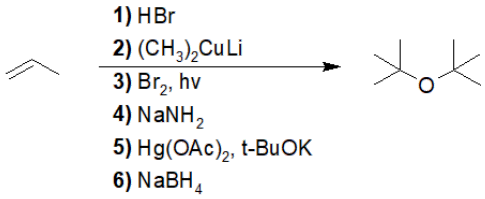
15-3:



3-methoxy-3-methylpentane

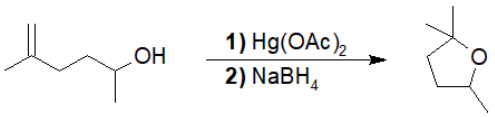
15-4:

Possible route of synthesis:

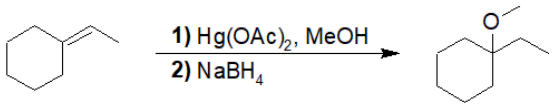


15-5:

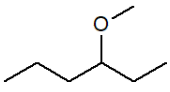
a)



b)



15-6:



Cleavage of Ethers

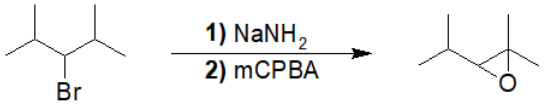
15-7:

Answer: C

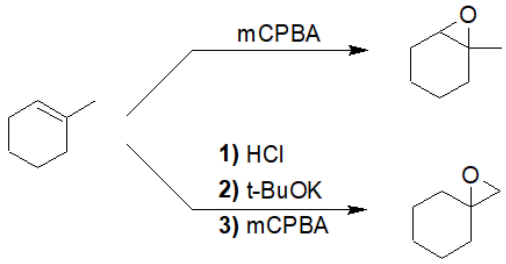
Synthesis of Epoxides

15-8:

Answer: A



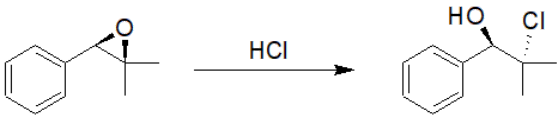
15-9:



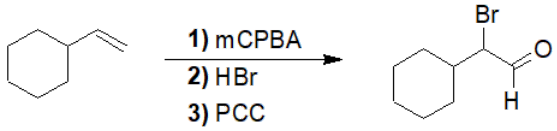
15-10:

Reactions of Epoxides

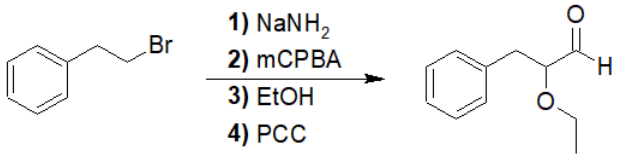
15-11:



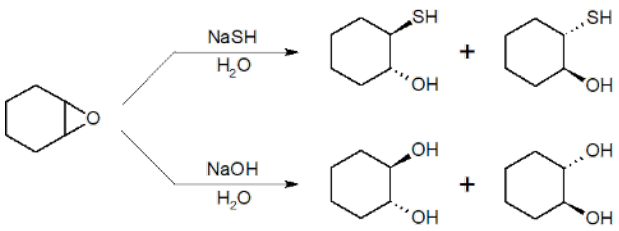
15-12:



15-13:



15-14:



15-15:

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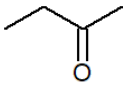
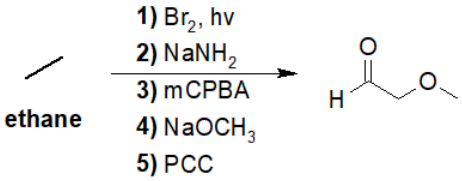


15-16:

Answer: D

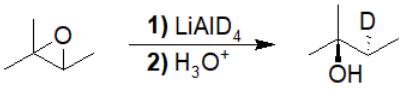
15-17:

Possible route of synthesis:

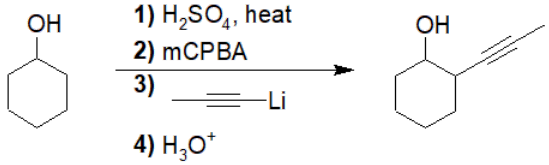


15-18:

a)

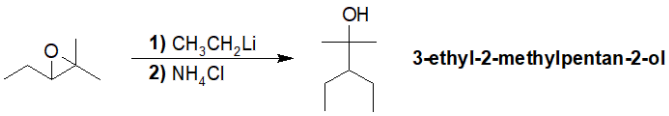


b)

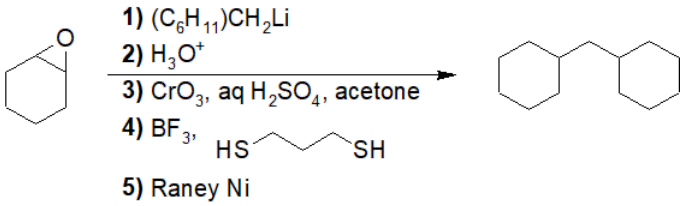


Reactions of Epoxides with Grignard and Organolithium Reagents

15-19:



15-20:



15-21:

Answer: B

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CHAPTER OVERVIEW

15: Conjugated Systems, Orbital Symmetry, and Ultraviolet Spectroscopy

learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- construct & interpret MO diagrams of ethene, butadiene and allylic systems (refer to section 16.1)
- recognize reactions that are enhanced by resonance stabilization of the allylic intermediate (refer to section 16.2)
- predict the products and specify the reagents for electrophilic addition reactions (EAR) of conjugated dienes (refer to section 16.3)
- specify reaction conditions to promote thermodynamic or kinetic control of the reaction mechanism; correlate these conditions to reaction energy diagrams (section 16.4)
- predict the products and specify the reagents for bimolecular substitution reactions (S_N2) of allylic halides (refer to section 16.5)
- predict the products of Diels-Alder reactions with stereochemistry, including the orientation of cycloaddition with asymmetrical reagents (refer to sections 16.6 and 16.7)
- develop mechanisms to explain the observed products of 1,2- & 1,4- addition reactions, including the resonance forms of the stabilized intermediates (refer to section 16.6)
- use MO theory to predict whether cycloaddition reactions will be thermally or photochemically allowed (refer to section 16.6 and 16.7)
- recognize the effect of conjugation on UV absorption (refer to section 16.9 and 16.10)
- use Beer's Law in UV absorption calculations (refer to section 16.9 and 16.10)
- explain how light, the conjugation of double bonds, and the stereochemistry of double bonds contribute to visualizing color

15.1: Stability of Conjugated Dienes - Molecular Orbital Theory
15.2: Allylic Cations
15.3: Electrophilic Additions to Conjugated Dienes
15.4: Kinetic versus Thermodynamic Control
15.5: SN2 Reactions of Allylic Halides and Tosylates
15.6: The Diels-Alder (4 2) Cycloaddition Reaction
15.7: Diels-Alder Stereochemistry
15.8: Diene Polymers - Natural and Synthetic Rubbers
15.9: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy
15.10: Interpreting Ultraviolet Spectra - The Effect of Conjugation
15.11: 16.11:Conjugation, Color, and the Chemistry of Vision
15.12: Additional Exercises
15.13: Solutions to Additional Exercises

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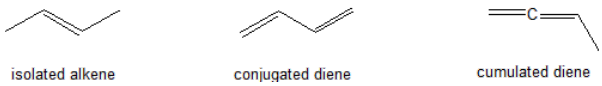
15.1: Stability of Conjugated Dienes - Molecular Orbital Theory

Introduction

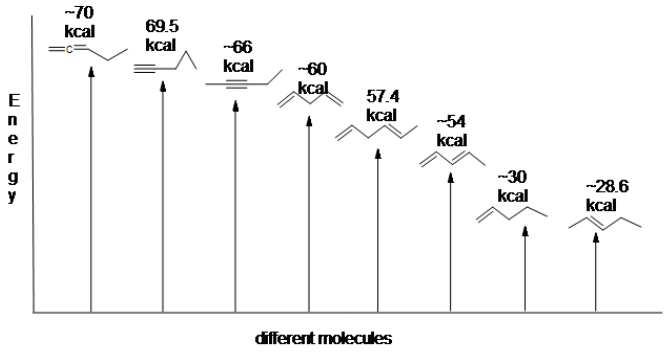
Conjugated dienes are characterized by alternating carbon-carbon double bonds separated by carbon-carbon single bonds. Cumulated dienes are characterized by adjacent carbon-carbon double bonds. While conjugated dienes are energetically more stable than isolated double bonds. Cumulated double bonds are unstable. The chemistry of cumulated double bonds can be explored in advance organic chemistry courses. The chemistry of isolated alkenes is covered in Chapters 8 and 9 of this LibreText. The chemistry of conjugated double bonds is the focus of this chapter.



Conjugated Diene Stability

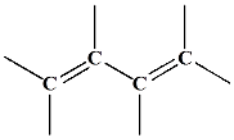
Conjugated dienes are more stable than non conjugated dienes (both isolated and cumulated) due to factors such as delocalization of charge through resonance and hybridization energy. This stability can be seen in the differences in the energies of hydrogenation between isolated and conjugated alkenes. Since the higher the heat of hydrogenation the less stable the compound, it is shown below that conjugated dienes (~54 kcal) have a lower heat of hydrogenation than their isolated (~60 kcal) and cumulated diene (~70 kcal) counterparts.

Here is an energy diagram comparing different types of bonds with their heats of hydrogenation to show relative stability of each molecule:

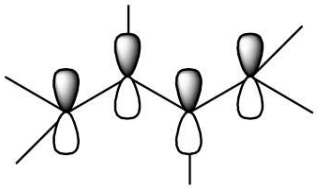


Stability of Conjugated Dienes - The Resonance Explanation

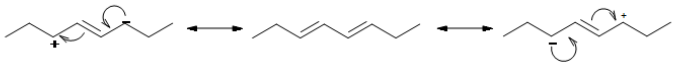
Conjugated double bonds are separated by a single bond. 1,3-dienes are an excellent example of a conjugated system. Each carbon in 1,3 dienes is sp^2 hybridized and therefore has one *p* orbital. The four *p* orbitals in 1,3-butadiene overlap to form a conjugated system.



1,3-Diene

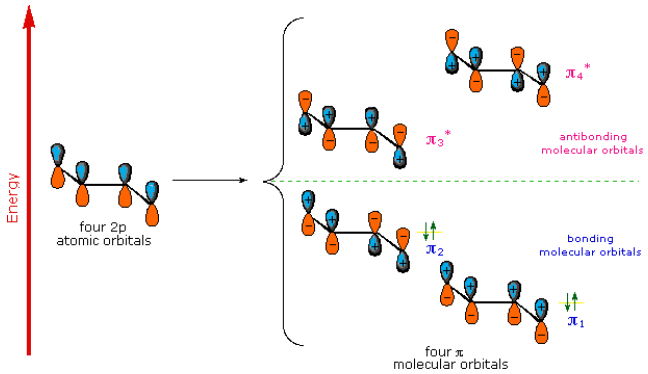


The resonance structure shown below gives a good understanding of how the pi electrons are delocalized across the four carbons in this conjugated diene. This delocalization of electrons stablizes the conjugated diene:



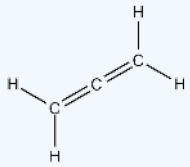
Stability of Conjugated Dienes - The Molecular Orbitals Explanation

A molecular orbital model for 1,3-butadiene is shown below. Note that the lobes of the four p-orbital components in each pi-orbital are colored differently and carry a plus or minus sign. This distinction refers to different phases, defined by the mathematical wave equations for such orbitals. Regions in which adjacent orbital lobes undergo a phase change are called **nodes**. Orbital electron density is zero in such regions. Thus a single p-orbital has a node at the nucleus, and all the pi-orbitals shown here have a nodal plane that is defined by the atoms of the diene. This is the only nodal surface in the lowest energy pi-orbital, π_1. Higher energy pi-orbitals have an increasing number of nodes. Since 1,3-butadiene has four pi electrons. The two bonding molecular orbitals are filled to explain the measurable stability of conjugated double bonds.



Exercise

1. The heat of hydrogenation for allene is about 300 kJ/mol. Order a conjugated diene, a non-conjugated diene, and allene in increasing stability.



Allene

Answer

1. allene < non-conjugated diene < conjugated diene (most stable)

Contributors and Attributions

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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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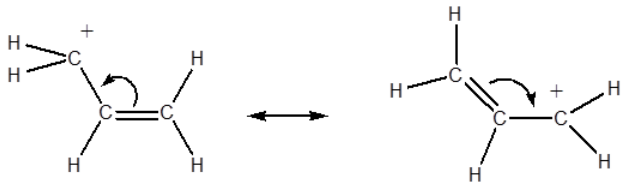
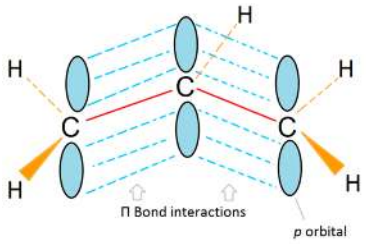
15.2: Allylic Cations

Resonance and Allylic Carbocation Stability

Conjugation occurs when p orbital on three or more adjacent atoms can overlap. Conjugation tends to stabilize molecules. Allylic carbocations are a common conjugated system. The resonance structures below help explain the stability of allylic carbocations. The true structure of the conjugated allyl carbocation is a hybrid of of the two resonance structure so the positive charge is delocalized over the two terminal carbons. This delocalization stablizes the allyl carbocation making it more stable than a normal primary carbocation.



The positive charge of a carbocation is contained in a p orbital of a sp^2 hybridized carbon. This allows for overlap with double bonds. The positive charge is more stable because it is spread over 2 carbons.



Molecular Orbitals and Allylic Carbocation Stability

The stability of the carbocation of propene is due to a conjugated π electron system. A "double bond" doesn't really exist. Instead, it is a group of 3 adjacent, overlapping, non-hybridized *p* orbitals we call a **conjugated π electron system**. You can clearly see the interactions between all three of the *p* orbitals from the three carbons resulting in a really stable cation. It all comes down to where the location of the electron-deficient carbon is.

Molecular orbital descriptions can explain allylic stability in yet another way using 2-propenyl. Fig.6

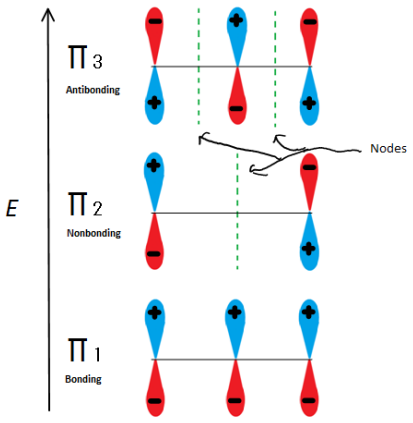


Figure: The 3 possible Molecular orbitals of 2-propenyl

If we just take the π molecular orbital and not any of the s, we get three of them. π_1 is bonding with no nodes, π_2 is nonbonding (In other words, the same energy as a regular *p*-orbital) with a node, and π_3 is antibonding with 2 nodes (none of the orbitals are interacting). The first two electrons will go into the π_1 molecular orbital, regardless of whether it is a cation, radical, or anion. If it is a radical or anion, the next electron goes into the π_2 molecular orbital. The last anion electron goes into the nonbonding orbital also. So no matter what kind of carbon center exists, no electron will ever go into the antibonding orbital.

The Bonding orbitals are the lowest energy orbitals and are favorable, which is why they are filled first. Even though the nonbonding orbitals can be filled, the overall energy of the system is still lower and more stable due to the filled bonding molecular orbitals.

This figure also shows that π_2 is the only molecular orbital where the electrion differs, and it is also where a single node passes through the middle. Because of this, the charges of the molecule are mainly on the two terminal carbons and not the middle carbon.

This molecular orbital description can also illustrate the stability of allylic carbon centers in figure 7.

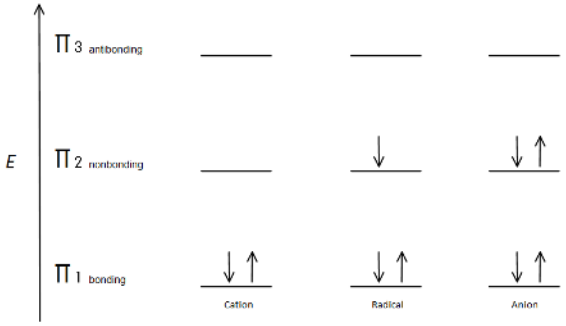
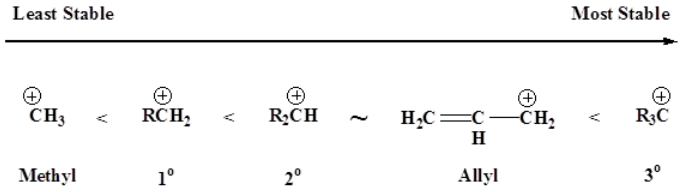


Figure: Diagram showing how the electrons fill based on the Aufbau principle.

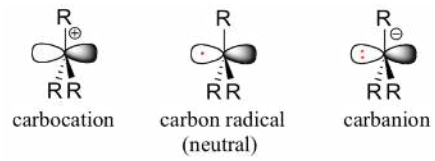
The π bonding orbital is lower in energy than the nonbonding *p* orbital. Since every carbon center shown has two electrons in the lower energy, bonding π orbitals, the energy of each system is lowered overall (and thus more stable), regardless of cation, radical, or anion.

Relative Stabilities of Carbocations



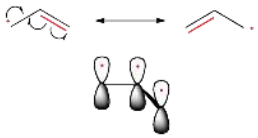
Allylic Radicals

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

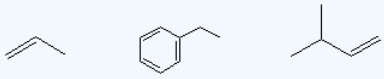
delocalized over a system of conjugated pi bonds. An allylic radical, for example, can be pictured as a system of three parallel $2p_z$ orbitals sharing three electrons.



This can also explain why allylic radicals are much more stable than secondary or even tertiary carbocations. This is all due to the positioning of the pi orbitals and ability for overlap to occur to strengthen the single bond between the two double bonds.

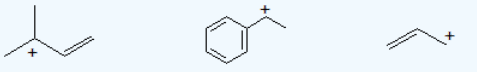
Exercise

2. Draw the bond-line structure for the most stable carbocation that can be formed from each hydrocarbon below. Arrange the carbocations in order of decreasing stability.



Answer

2. Carbocations in order of decreasing stability.



Contributors and Attributions

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15.3: Electrophilic Additions to Conjugated Dienes

OBJECTIVES

- After completing this section, you should be able to
- write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a nonconjugated diene.
- write an equation for the addition of one or two mole equivalents of a halogen or a hydrogen halide to a conjugated diene.
- 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.
- explain the stability of allylic carbocations in terms of resonance.
- draw the resonance contributors for a given allylic carbocation.
- predict the products formed from the reaction of a given conjugated diene with one mole equivalent of halogen or hydrogen halide.
- 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.
- 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

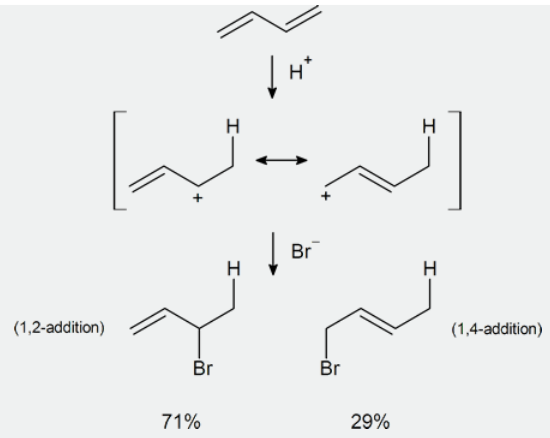
- Make certain that you can define, and use in context, the key terms below.
- 1,2-addition
- 1,4-addition

STUDY NOTES

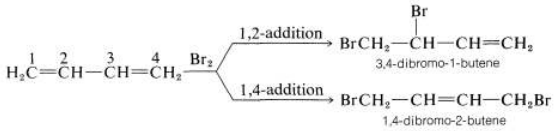
Notice that the numbers used in the expressions 1,2-addition and 1,4-addition do *not* refer to the positions of the carbon atoms in the diene molecule. Here, 1,2 indicates two neighbouring carbon atoms, while 1,4 indicates two carbon atoms which are separated in the carbon chain by two additional carbon 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.

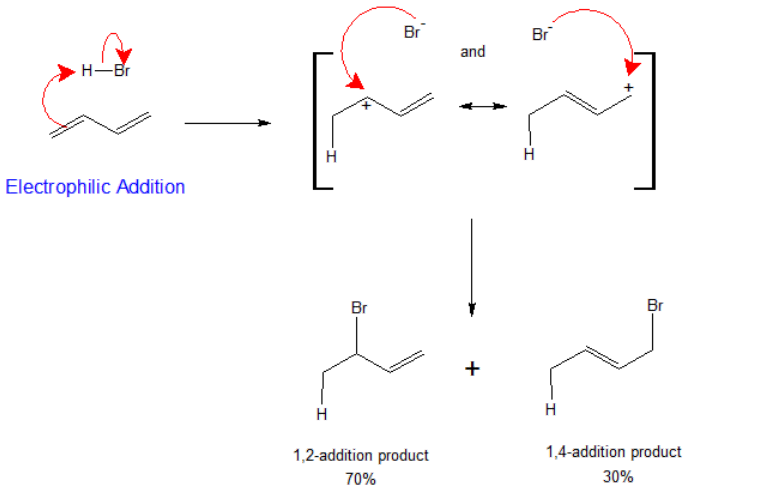
The term “monoadduct” should be interpreted as meaning the product or products formed when one mole of reagent adds to one mole of substrate. In the objectives above, this process is referred to as the addition of one mole equivalent (or one mol equiv).

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.



The reactions of 1,3-butadiene are reasonably typical of conjugated dienes. The compound undergoes the usual reactions of alkenes, such as catalytic hydrogenation or radical and polar additions, but it does so *more readily* than most alkenes or dienes that have isolated double bonds. Furthermore, the products frequently are those of 1,2 *and* **1,4 addition:**





The 1,2-addition product is favored because its secondary allylic carbocation intermediate is more stable.

Formation of both 1,2- and 1,4-addition products occurs not only with halogens, but also with other electrophiles such as the hydrogen halides. The mechanistic course of the reaction of 1,3-butadiene with hydrogen chloride is shown in Equation 13-1. The first step, as with alkenes, is formation of a carbocation. However, with 1,3-butadiene, if the proton is added to C1C1 (but not C2C2), the resulting cation has a substantial delocalization energy, with the charge distributed over two carbons (review Sections 6-5 and 6-5C if this is not clear to you). Attack of Cl⊖Cl⊖ as a nucleophile at one or the other of the positive carbons yields the 1,2- or the 1,4- addition product:

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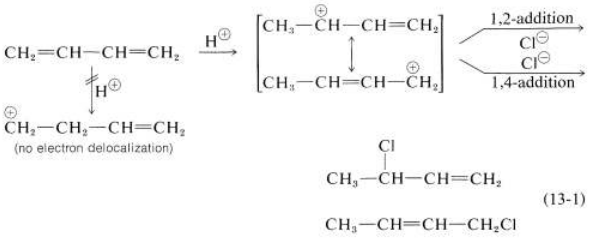
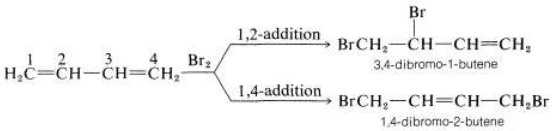


An important feature of reactions in which 1,2 and 1,4 additions occur in competition with one another is that the ratio of the products can depend on the temperature, the solvent, and also on the *total time of reaction*.

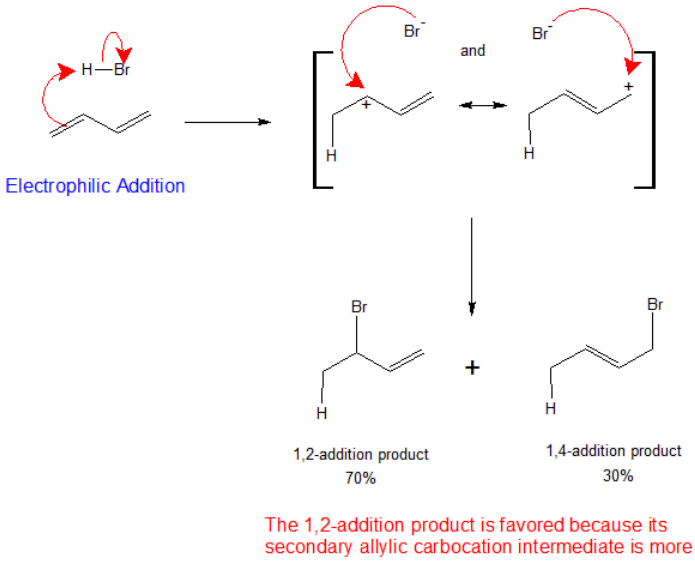
Direct vs Conjugate Addition

The description of direct versus conjugate addition uses numbers localized within the conjugate system and have nothing to do with the numbering system used to determine the IUPAC name for a conjugated diene. The reactions of 1,3-butadiene are reasonably typical of conjugated dienes and illustrate the difference in the numbering system to describe the reaction versus the IUPAC nomenclature numbers.



Mechanism for the Electrophilic Addition to Conjugate Dienes

The mechanism below explains the formation and distribution of addition products to conjugated dienes using 1,3-butadiene as an example. The first step, as with isolated alkenes, is the formation of a carbocation. For 1,3-butadiene, the proton is added to form the allylic, resonance stabilized carbocation intermediate. The resulting cation has a substantial delocalization energy, with the charge distributed over two carbons. The nucleophile reacts with both carbons, but favors the carbon bearing the larger partial positive charge. The reaction yields both the 1,2- or the 1,4- addition products. The more stable the intermediate produces the greater the percentage of the final products as shown in the mechanism below.



Formation of both 1,2- and 1,4-addition products occurs not only with hydrohalic acids, but with halogens, catalytic hydrogenation or radical, and other polar additions associated with the electrophilic addition reactions of isolated alkenes.

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

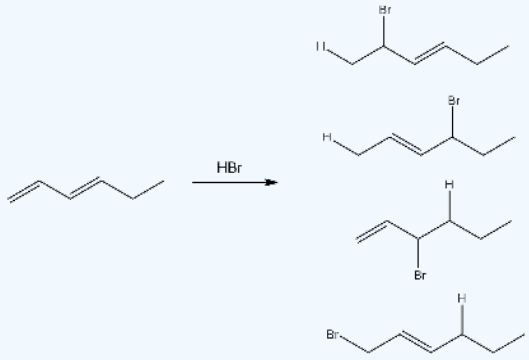
Exercise

3. Give the 1,2 and the 1,4 products of the addition of one equivalent of HBr to 1,3-hexa-diene.

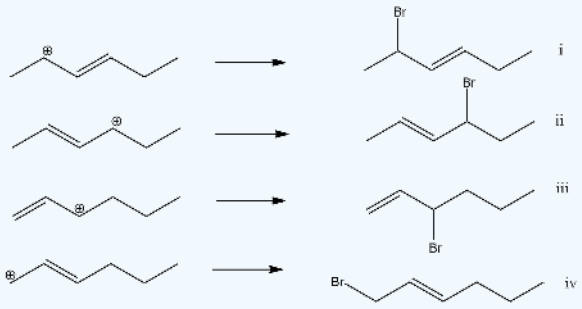
4. Look at the previous addition reaction of HBr with a diene. Consider the transition states, predict which of them would be the major products and which will be the minor.

Answer

3.



4. 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.



Contributors and Attributions

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- John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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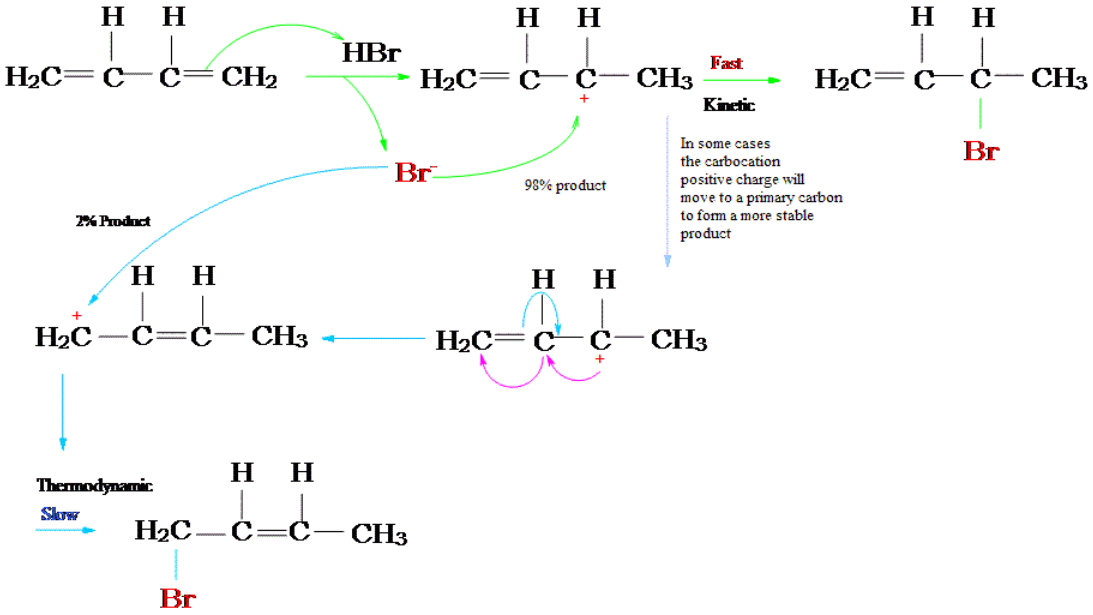
15.4: Kinetic versus Thermodynamic Control

Thermodynamic vs Kinetic Control

Upon electrophilic addition, the conjugated diene forms a mixture of two products—the kinetic product and the thermodynamic product—whose ratio is determined by the conditions of the reaction. A reaction yielding more thermodynamic product is under thermodynamic control, and likewise, a reaction that yields more kinetic product is under kinetic control. The reaction of one equivalent of hydrogen bromide with 1,3-butadiene gives different ratios of products under different reaction conditions to illustrate the difference between thermodynamic and kinetic control.

The green mechanism arrows show the formation of the kinetically favored 1,2-addition product. As shown in the reaction energy diagram below the reaction, the 1,2-addition reaction has a smaller activation energy and faster reaction rate. This faster reaction rate is what led to the term "kinetic control". This reaction is favored by low temperatures where the activation energy becomes the primary barrier to chemical reactivity.

The blue mechanism arrows show the formation of the 1,4-addition product, the thermodynamically favored product. As shown in the reaction energy diagram below the reaction, the product of the 1,4-addition reaction is lower in potential energy. Its formation is favored by reactions at high temperatures where there is adequate thermodynamic energy to overcome all of the activation energy barriers. This reaction is favored by elevated temperatures which led to the term "thermodynamic control".



Reaction Energy Diagram for 1,3-butadiene + HBr

The table below summarizes the empirically derived reactivity patterns for conjugated dienes at four different reaction conditions. Becoming familiar with the reactivity data and patterns in this table helps us build wisdom for determining the optimum reaction conditions when competing mechanisms are possible.

Table : Conjugated Dienes: Kinetic vs. Thermodynamic Conditions

Temperature	Kinetic or Thermodynamically Controlled	Speed of Reaction	1,2-adduct : 1,4-adduct Ratio
-15 °C	Kinetic	Fast	70:30
0 °C	Kinetic	Fast	60:40
40 °C	Thermodynamic	Slow	15:85
60 °C	Thermodynamic	Slow	10:90

A Warning: Not every reaction has different thermodynamic and kinetic products!

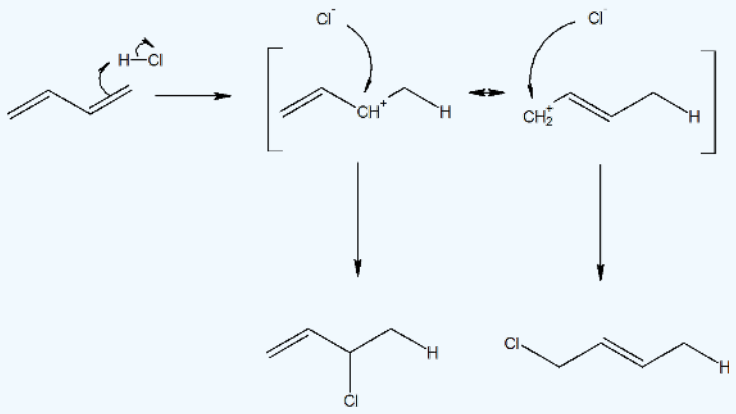
Note that not every reaction has an energy profile diagram like Figure **15.4.1**, and not every reaction has different thermodynamic and kinetic products! If the transition states leading to the formation of **C** (e.g., T_{C1}, *and* T_{C2}) were to be higher in energy than that leading to **B** (e.g., T_{B1}, *and* T_{B2}), then **B** would simultaneously be both the thermodynamic and kinetic product. There are plenty of reactions in which the more stable product (*thermodynamic*) is also formed faster (*kinetic*).

Exercise

5. Consider the reaction with 1,3-buta-diene reacting with HCl. Propose a mechanism for the reaction.

Answer

5.



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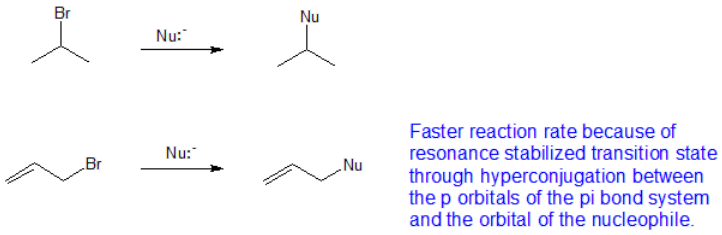
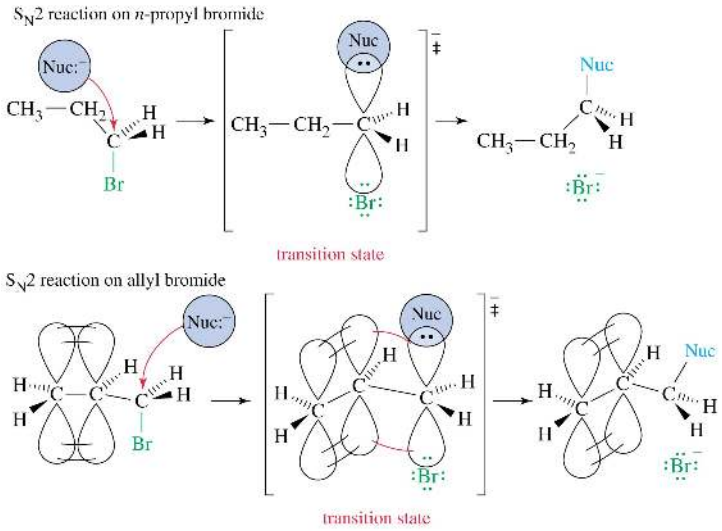
15.5: SN2 Reactions of Allylic Halides and Tosylates

S_N2 Reactions of Allylic Halides and Tosylates

Allylic halides and tosylates are excellent electrophiles for bimolecular nucleophilic substitution reactions (S_N2).



They exhibit faster S_N2 reactivity than secondary alkyl halides because the bimolecular transition state is stabilized by hyperconjugation between the orbital of the nucleophile and the conjugated pi bond of the allylic group as shown in the diagram below.

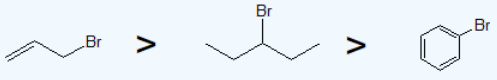


Exercise

6. Arrange the compounds 3-bromopentane, bromobenzene, and 3-bromo-1-propene in order of decreasing S_N2 reactivity using their bond-line structures.

Answer

6.



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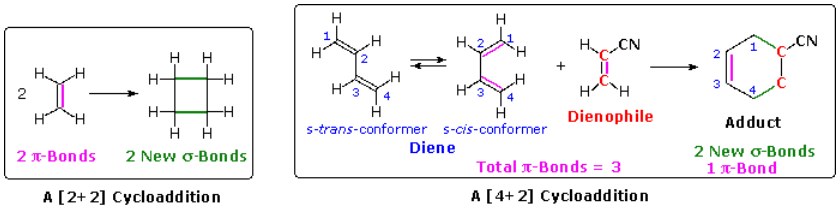
15.6: The Diels-Alder (4 2) Cycloaddition Reaction

The Diels-Alder (4+2) Cycloaddition Reaction

A cycloaddition reaction is the concerted bonding together of two independent pi-electron systems to form a new ring of atoms. When this occurs, two pi-bonds are converted to two sigma-bonds, the simplest example being the hypothetical combination of two ethene molecules to give cyclobutane. This does not occur under normal conditions, but the cycloaddition of 1,3-butadiene to cyanoethene (acrylonitrile) does, and this is an example of the Diels-Alder reaction. The following diagram illustrates two cycloadditions, and introduces several terms that are useful in discussing reactions of this kind.

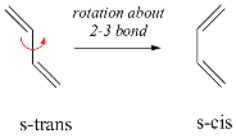


In the hypothetical ethylene dimerization on the left, each reactant molecule has a pi-bond (colored orange) occupied by two electrons. The cycloaddition converts these pi-bonds into new sigma-bonds (colored green), and this transformation is then designated a [2+2] cycloaddition, to enumerate the reactant pi-electrons that change their bonding location.

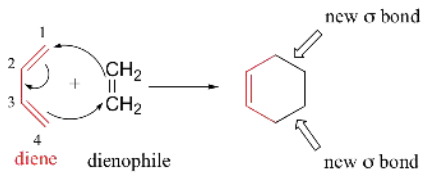
The Diels-Alder reaction is an important and widely used method for making six-membered rings, as shown on the right. The reactants used in such reactions are a conjugated diene, simply referred to as the **diene**, and a double or triple bond co-reactant called the **dienophile**, because it combines with (has an affinity for) the diene. The Diels-Alder cycloaddition is classified as a [4+2] process because the diene has four pi-electrons that shift position in the reaction and the dienophile has two.

Diels-Alder Mechanism

The Diels-Alder reaction is a single step process, so the diene component must adopt an s-cisconformation 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. In order for a Diels-Alder reaction to occur, the diene molecule must adopt what is called the **s-cis conformation**:



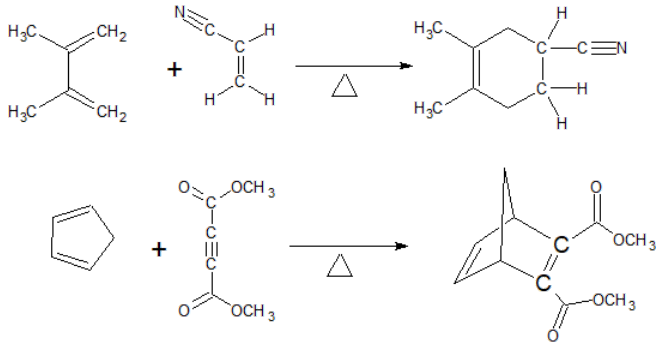
In its usual form, the diene component is electron rich, and the best dienophiles are electron poor due to electron withdrawing substituents such as CN, C=O & NO_2. The initial bonding interaction reflects this electron imbalance, with the two new sigma-bonds being formed simultaneously, but not necessarily at equal rates. Essentially, this process involves overlap of the 2p orbitals on carbons 1 and 4 of the diene with the two 2p orbitals on the sp^2-hybridized carbons of the dienophile. Both of these new overlaps form new sigma bonds, and a new pi bond is formed between carbon 2 and 3 of the diene.



One of the most important things to understand about this process is that it is *concerted* – all of the electron rearrangement takes place at once, with no carbocation intermediates.

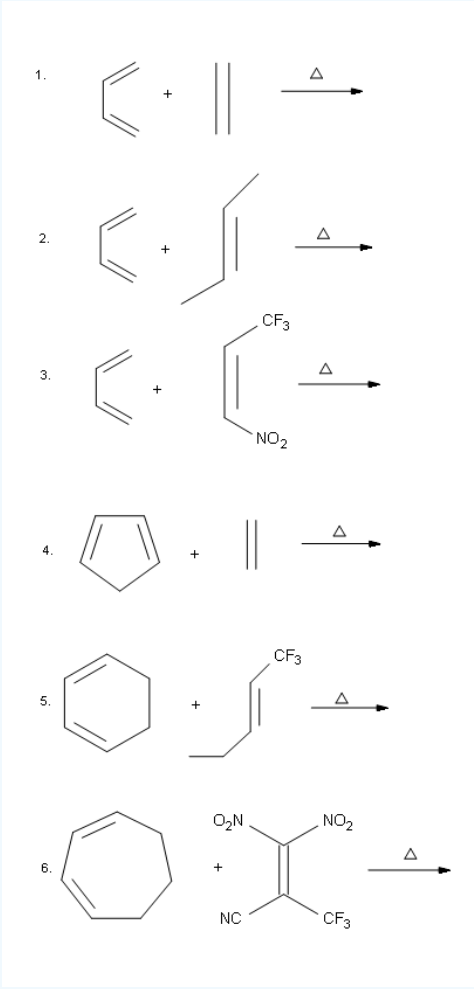
Since the diene takes the role of the nucleophile, electron donating group increase the reactivity of the diene. While the dienophile takes the role of the electrophile, electronwithdrawing groups increase the reactivity of the dienophile. The reactions below are

examples of the Diels-Alder reaction.



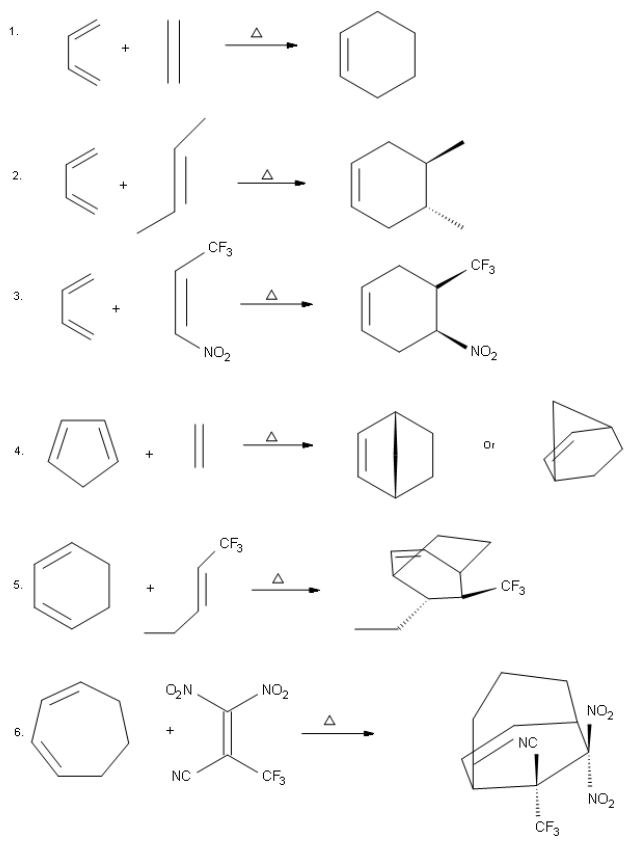
Exercise

7. Draw the bond-line structures for the reactions below.



Answer

7.



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- Amar Patel (UCD)

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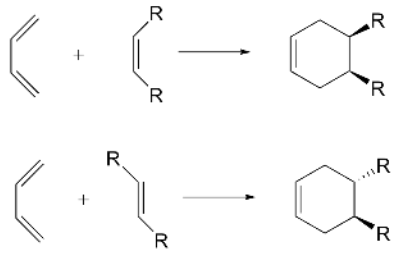
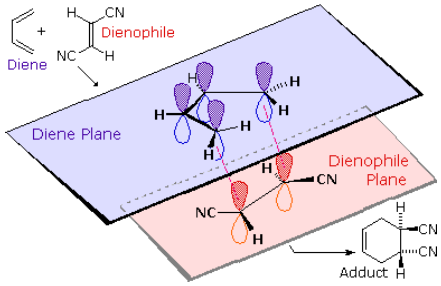
15.7: Diels-Alder Stereochemistry

Diels-Alder Reactions are Stereospecific

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 two new stereocenters are formed, and the reaction is inherently stereospecific. A *cis* dienophile will generate a ring with *cis* substitution, while a *trans* dienophile will generate a ring with *trans* substitution:

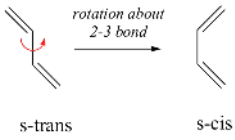


We noted earlier that addition reactions of alkenes often exhibited stereoselectivity, in that the reagent elements in some cases added syn and in other cases anti to the the plane of the double bond. Both reactants in the Diels-Alder reaction may demonstrate stereoisomerism, and when they do it is found that the relative configurations of the reactants are preserved in the product (the adduct). The following drawing 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. Likewise, if the terminal carbons of the diene bear substituents, their relative configuration will be retained in the adduct. Using the earlier terminology, we could say that bonding to both the diene and the dienophile is syn. An alternative description, however, refers to the planar nature of both reactants and terms the bonding in each case to be **suprafacial** (i.e. to or from the same face of each plane). This stereospecificity also confirms the synchronous nature of the 1,4-bonding that takes place.

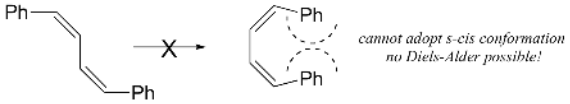


Diene Substituents and Diels-Alder Reactivity

In order for a Diels-Alder reaction to occur, the diene molecule must adopt what is called the **s-cis conformation**:



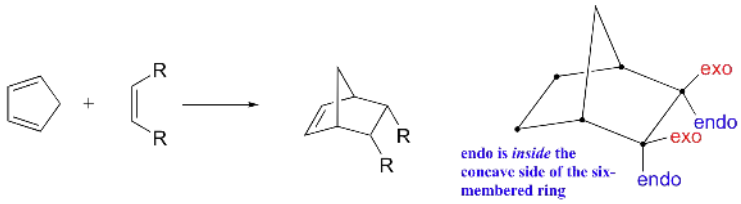
The s-cis conformation is higher in energy than the s-trans conformation, due to steric hindrance. For some dienes, extreme steric hindrance causes the s-cis conformation to be highly strained, and for this reason such dienes do not readily undergo Diels-Alder reactions.



Bicyclic Ring Formation and the Exo- and Endo- Positions

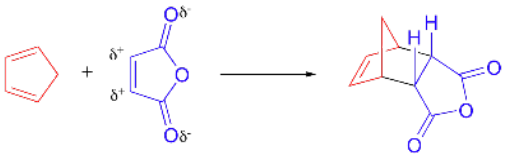
Cyclic dienes that are 'locked' in the s-cis conformation are especially reactive. The result of a Diels-Alder reaction involving a cyclic diene is a **bicyclic** structure:

Here, we see another element of stereopecificity: Diels-Alder reactions with cyclic dienes favor the formation of bicyclic structures in which substituents are in the **endo position**.



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.

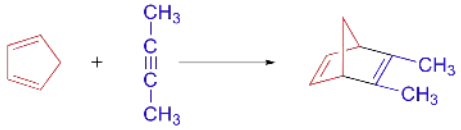
The rate at which a Diels-Alder reaction takes place depends on electronic as well as steric factors. A particularly rapid Diels-Alder reaction takes place between cyclopentadiene and maleic anhydride.



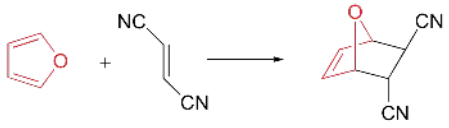
We already know that cyclopentadiene is a good diene because of its inherent s-cis conformation. Maleic anhydride is also a very good dienophile, because the electron-withdrawing effect of the carbonyl groups causes the two alkene carbons to be electron-poor, and thus a good target for reaction with the pi electrons in the diene.

In general, Diels-Alder reactions proceed fastest with electron-donating groups on the diene (eg. alkyl groups) and electron-withdrawing groups on the dienophile.

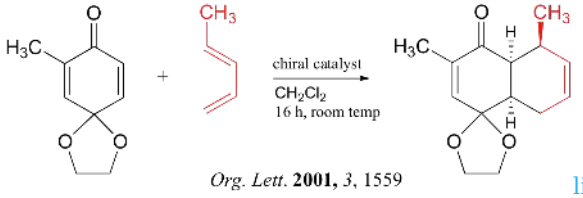
Alkynes can also serve as dienophiles in Diels-Alder reactions:



Below are three examples of Diels-Alder reactions that have been reported in recent years:



J. Med. Chem. **2008,** *51*, 424 link



Org. Lett. **2001,** *3*, 1559 link

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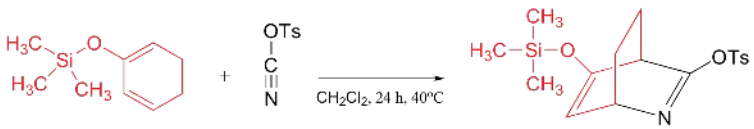


J. Org. Chem. **2003,** *68,* 8256 link

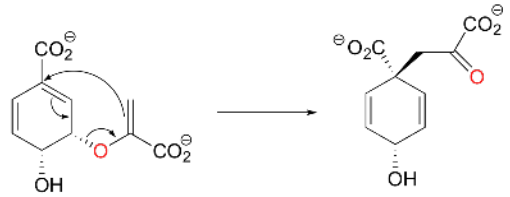
Other Pericyclic Reactions

The Diels-Alder reaction is just one example of a **pericyclic** reaction: this is a general term that refers to concerted rearrangements that proceed though cyclic transition states. Two well-studied intramolecular pericyclic reactions are known as the Cope rearrangement . . .

. . .and the Claisen rearrangement (when an oxygen is involved):

Notice that the both of these reactions require compounds in which two double bonds are separated by three single bonds.

Pericyclic reactions are rare in biological chemistry, but here is one example: the Claisen rearrangement catalyzed by chorismate mutase in the aromatic amino acid biosynthetic pathway.



chorismate prephenate

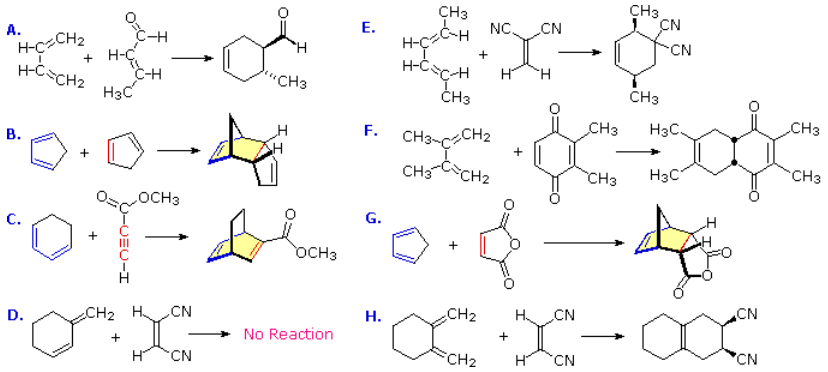
The study of pericyclic reactions is an area of physical organic chemistry that blossomed in the mid-1960s, due mainly to the work of R.B. Woodward, Roald Hoffman, and Kenichi Fukui. The **Woodward-Hoffman rules** for pericyclic reactions (and a simplified version introduced by Fukui) use molecular orbital theory to explain why some pericyclic processes take place and others do not. A full discussion is beyond the scope of this text, but if you go on to study organic chemistry at the advanced undergraduate or graduate level you are sure to be introduced to this fascinating area of inquiry.

Diels-Alder Reaction Summary

The essential characteristics of the Diels-Alder cycloaddition reaction may be summarized as follows:

1. The reaction always creates a new six-membered ring. When intramolecular, another ring may also be formed.
2. The diene component must be able to assume a s-cis conformation.
3. Electron withdrawing groups on the dienophile facilitate reaction.
4. Electron donating groups on the diene facilitate reaction.
5. Steric hindrance at the bonding sites may inhibit or prevent reaction.
6. The reaction is stereospecific with respect to substituent configuration in both the dienophile and the diene.

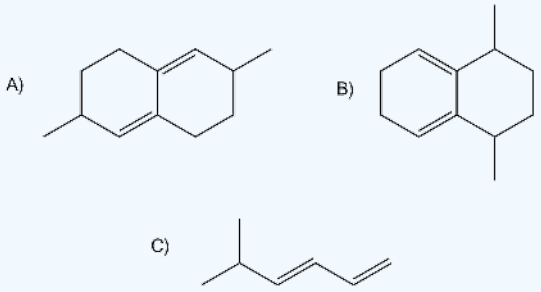
These features are illustrated by the following eight examples, one of which does not give a Diels-Alder cycloaddition.



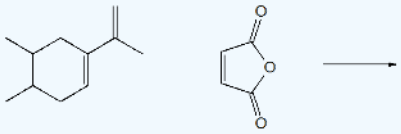
There is no reaction in example **D** because this diene cannot adopt an s-cis orientation. In examples **B, C, F, G & H** at least one of the reactants is cyclic so that the product has more than one ring, but the newly formed ring is always six-membered. In example **B** the the same cyclic compound acts as both the diene colored blue) and the dienophile (colored red). The adduct has three rings, two of which are the five-membered rings present in the reactant, and the third is the new six-membered ring (shaded light yellow). Example **C** has an alkyne as a dienophile (colored red), so the adduct retains a double bond at that location. This double bond could still serve as a dienophile, but in the present case the diene is sufficiently hindered to retard a second cycloaddition. The quinone dienophile in reaction **F** has two dienophilic double bonds. However, the double bond with two methyl substituents is less reactive than the unsubstituted dienophile due in part to the electron donating properties of the methyl groups and in part to steric hindrance. The stereospecificity of the Diels-Alder reaction is demonstrated by examples **A, E & H**. In **A & H** the stereogenic centers lie on the dienophile, whereas in **E** these centers are on the diene. In all cases the configuration of the reactant is preserved in the adduct.

Exercise

8. 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?



9. Predict the product of the following reaction.



Answer

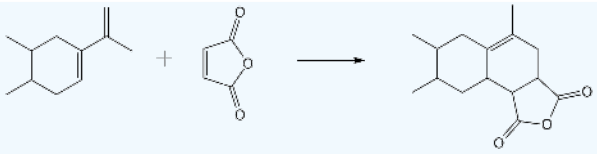
8.

A) s-trans, unable to rotate to become s-cis

B) s-cis

C) s-trans, can rotate to become s-cis.

9.



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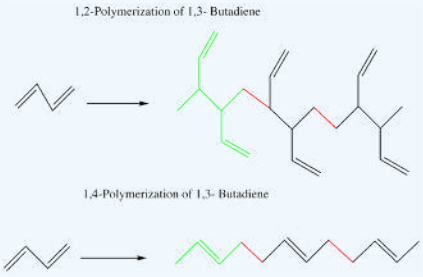
15.8: Diene Polymers - Natural and Synthetic Rubbers

Conjugated dienes (alkenes with two double bonds and a single bond in between) can be polymerized to form important compounds like rubber. This takes place, in different forms, both in nature and in the laboratory. Interactions between double bonds on multiple chains leads to cross-linkage which creates elasticity within the compound.

Polymerization of 1,3-Butadiene

For rubber compounds to be synthesized, 1,3-butadiene must be polymerized. Below is a simple illustration of how this compound is formed into a chain. The 1,4 polymerization is much more useful to polymerization reactions.



Above, the green structures represent the base units of the polymers that are synthesized and the red represents the bonds between these units which form these polymers. Whether the 1,3 product or the 1,4 product is formed depends on whether the reaction is thermally or kinetically controlled.

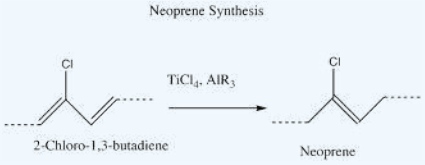
Natural Rubber

Natural rubber is an addition polymer that is obtained as a milky white fluid known as latex from a tropical rubber tree. Natural rubber is from the monomer isoprene (2-methyl-1,3-butadiene), which is a conjugated diene hydrocarbon as mentioned above. In natural rubber, most of the double fonds formed in the polymer chain have the Z configuration, resulting in natural rubber's elastomer qualities.

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. Vulcanization causes shorter chains to cross link through the sulfur to longer chains. The development of vulcanized rubber for automobile tires greatly aided this industry.

Synthetic Rubber

The most important synthetic rubber is Neoprene which is produced by the polymerization of 2-chloro-1,3-butadiene.



In this illustration, the dashed lines represent repetition of the same base units, so both the products and reactants are polymers. The reaction proceeds with a mechanism similar to the Friedel-Crafts mechanism. Cross-linkage between the chlorine atom of one chain and the double bond of another contributes to the overall elasticity of neoprene. This cross-linkage occurs as the chains lie next to each other at random angles, and the attractions between double bonds prevent them from sliding back and forth.

Outside links

- "Dienes," http://en.Wikipedia.org/wiki/Diene
- "Rubber," http://en.Wikipedia.org/wiki/Rubber
- "Neoprene," en.Wikipedia.org/wiki/Neoprene

References

1. Vollhardt, Peter, and Neil E. Schore. Organic Chemistry: Structure and Function. New York: W. H. Freeman & Company, 2007.
2. Buehr, Walter. Rubber: Natural and Synthetic. Morrow, 1964.

Exercise

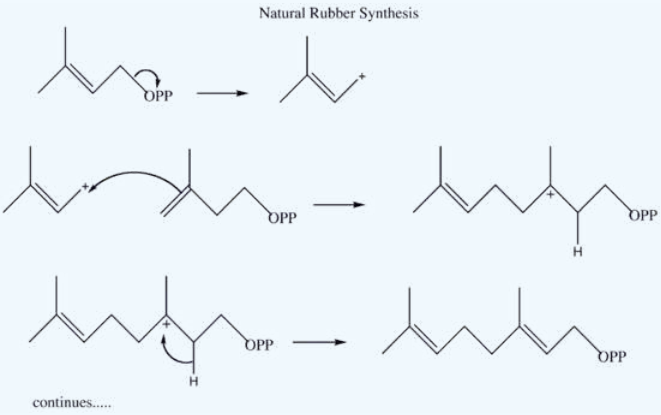
10. Draw out the mechanism for the natural synthesis of rubber from 3-methyl-3-butenyl pyrophosphate and 2-methyl-1,3-butadiene. Show the movement of electrons with arrows.

11. Draw a segment for the polymer that may be made from 2-*tert*-butyl-1,3-butadiene.

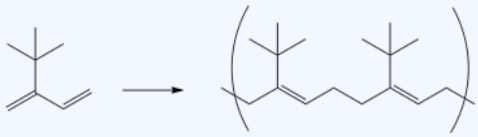
12. Propose the mechanism for the acid catalyzed polymerization of 2-methyl-1,3-butadiene.

Answer

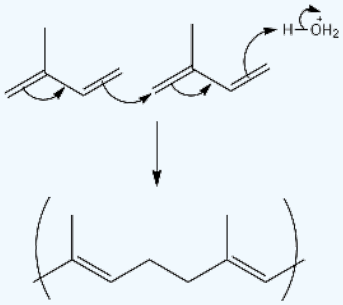
10.



11.



12. The initial step is an addition of a hydrogen from the acid, followed by the polymerization.



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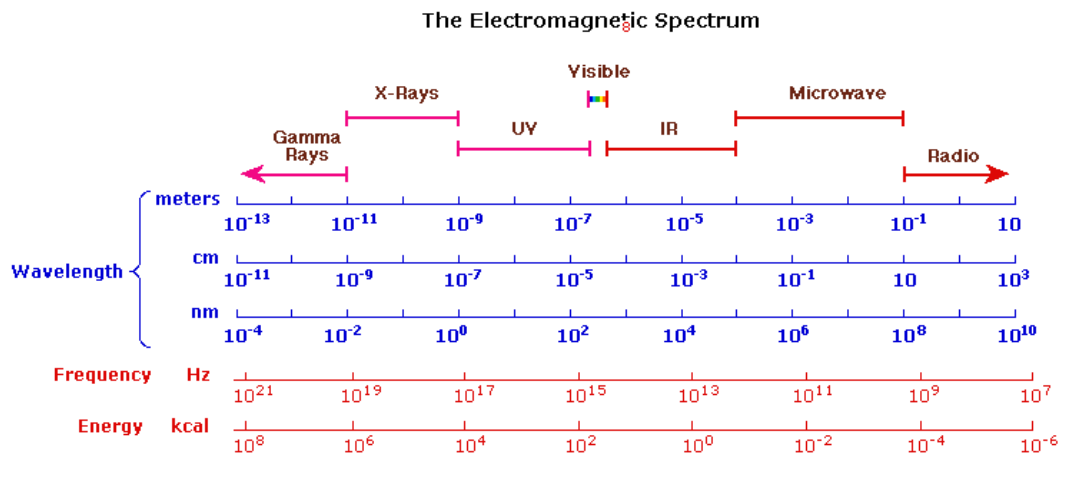
15.9: Structure Determination in Conjugated Systems - Ultraviolet Spectroscopy

The Electromagnetic Spectrum

The visible spectrum constitutes but a small part of the total radiation spectrum. Most of the radiation that surrounds us cannot be seen, but can be detected by dedicated sensing instruments. This **electromagnetic spectrum** ranges from very short wavelengths (including gamma and x-rays) to very long wavelengths (including microwaves and broadcast radio waves). The following chart displays many of the important regions of this spectrum, and demonstrates the inverse relationship between wavelength and frequency (shown in the top equation below the chart).

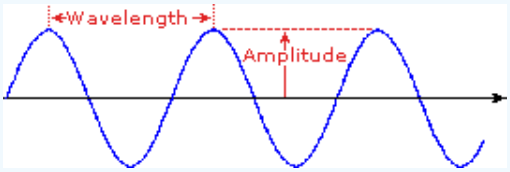


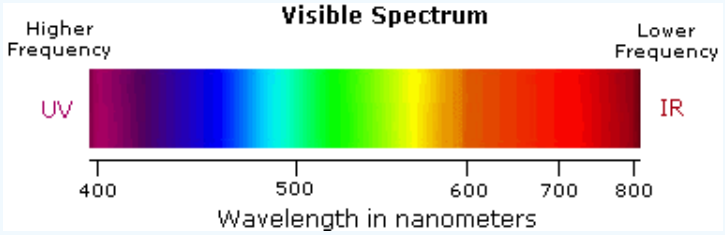
The energy associated with a given segment of the spectrum is proportional to its frequency. The bottom equation describes this relationship, which provides the energy carried by a photon of a given wavelength of radiation.

$\upsilon = c/\lambda$ υ=frequency, λ=wavelength, c=velocity of light ($c = 3 \cdot 10^{10}$ cm/sec)

$\Delta E = h\upsilon$ E=energy, υ=frequency, h=Planck's constant ($h = 6.6 \cdot 10^{-27}$ erg sec)

To obtain specific frequency, wavelength and energy values use this calculator.

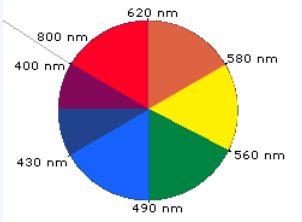




- **Indigo:** 420 - 440 nm
- **Green:** 490 - 570 nm
- **Orange:** 585 - 620 nm
- **Red:** 620 - 780 nm

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 420-430 nm light renders a substance yellow, and absorption of 500-520 nm light makes it red. Green is unique in that it can be created by absoption close to 400 nm as well as absorption near 800 nm.

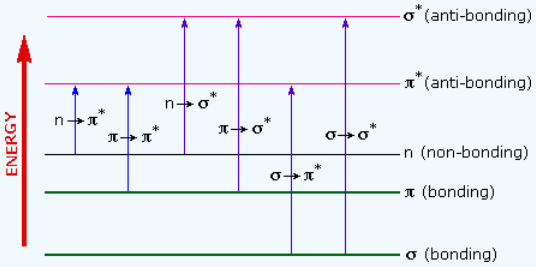


Early humans valued colored pigments, and used them for decorative purposes. Many of these were inorganic minerals, but several important organic dyes were also known. These included the crimson pigment, kermesic acid, the blue dye, indigo, and the yellow saffron pigment, crocetin. A rare dibromo-indigo derivative, punicin, was used to color the robes of the royal and wealthy. The deep orange hydrocarbon carotene is widely distributed in plants, but is not sufficiently stable to be used as permanent pigment, other than for food coloring. A common feature of all these colored compounds, displayed below, is a system of **extensively conjugated π-electrons**.

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.

The visible region of the spectrum comprises photon energies of 36 to 72 kcal/mole, and the near ultraviolet region, out to 200 nm, extends this energy range to 143 kcal/mole. Ultraviolet radiation having wavelengths less than 200 nm is difficult to handle, and is seldom used as a routine tool for structural analysis.

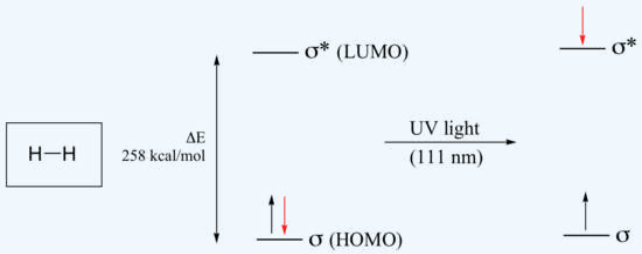


The energies noted above are sufficient to promote or excite a molecular electron to a higher energy orbital. Consequently, absorption spectroscopy carried out in this region is sometimes called "electronic spectroscopy". A diagram showing the various kinds of electronic excitation that may occur in organic molecules is shown on the left. Of the six transitions outlined, only the two lowest energy ones (left-most, colored blue) are achieved by the energies available in the 200 to 800 nm spectrum. 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**.

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. An optical spectrometer records the wavelengths at which absorption occurs, together with the degree of absorption at each wavelength. 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. **Absorbance** usually ranges from 0 (no absorption) to 2 (99% absorption), and is precisely defined in context with spectrometer operation.

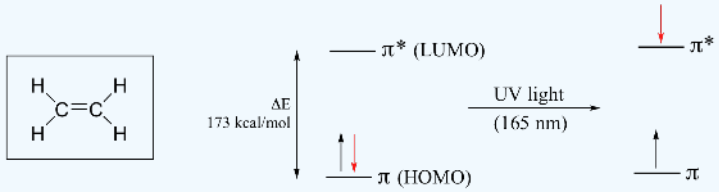
Electronic transitions

Let's take as our first example the simple case of molecular hydrogen, H_2. As you may recall from section 2.1A, the molecular orbital picture for the hydrogen molecule 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).



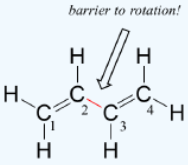
If the molecule is exposed to light of a wavelength with energy equal to **ΔE**, the HOMO-LUMO energy gap, this wavelength will be absorbed and the energy used to bump one of the electrons from the HOMO to the LUMO – in other words, from the σ to the σ* orbital. This is referred to as a **σ - σ* transition**. **Δ**E 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.



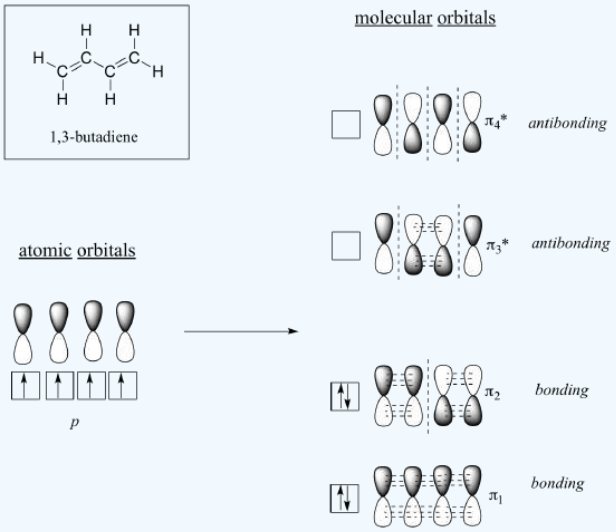
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with 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. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

Next, we'll consider the 1,3-butadiene molecule. From valence orbital theory alone we might expect that the C_2-C_3 bond in this molecule, because it is a sigma bond, would be able to rotate freely.



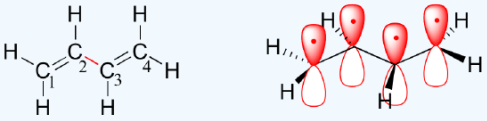
Experimentally, however, it is observed that there is a significant barrier to rotation about the C_2-C_3 bond, and that the entire molecule is planar. In addition, the C_2-C_3 bond is 148 pm long, shorter than a typical carbon-carbon single bond (about 154 pm), though longer than a typical double bond (about 134 pm).

Molecular orbital theory accounts for these observations with the concept of **delocalized π bonds**. In this picture, the four *p* atomic orbitals combine mathematically to form four pi molecular orbitals of increasing energy. Two of these - the bonding pi orbitals - are lower in energy than the *p* atomic orbitals from which they are formed, while two - the antibonding pi orbitals - are higher in energy.



The lowest energy molecular orbital, pi_1, has only constructive interaction and zero nodes. Higher in energy, but still lower than the isolated *p* orbitals, the pi_2 orbital has one node but two constructive interactions - thus it is still a bonding orbital overall. Looking at the two antibonding orbitals, pi_3* has two nodes and one constructive interaction, while pi_4* has three nodes and zero constructive interactions.

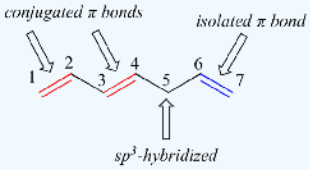
By the *aufbau* principle, the four electrons from the isolated $2p_z$ atomic orbitals are placed in the bonding pi_1 and pi_2 MO's. Because pi_1 includes constructive interaction between C_2 and C_3, there is a degree, in the 1,3-butadiene molecule, of pi-bonding interaction between these two carbons, which accounts for its shorter length and the barrier to rotation. The valence bond picture of 1,3-butadiene shows the two pi bonds as being isolated from one another, with each pair of pi electrons 'stuck' in its own pi bond. However, molecular orbital theory predicts (accurately) that the four pi electrons are to some extent delocalized, or 'spread out', over the whole pi system.



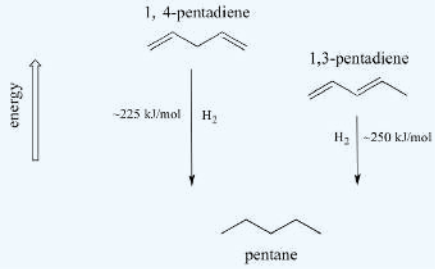
1,3-butadiene

space-filling view

1,3-butadiene is the simplest example of a system of **conjugated pi bonds**. To be considered conjugated, two or more pi bonds must be separated by only one single bond – in other words, there cannot be an intervening sp^3-hybridized carbon, because this would break up the overlapping system of parallel *p* orbitals. In the compound below, for example, the C_1-C_2 and C_3-C_4 double bonds are conjugated, while the C_6-C_7 double bond is **isolated** from the other two pi bonds by sp^3-hybridized C_5.

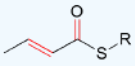


A very important concept to keep in mind is that *there is an inherent thermodynamic stability associated with conjugation.* This stability can be measured experimentally by comparing the **heat of hydrogenation** of two different dienes. (Hydrogenation is a reaction type that we will learn much more about in chapter 15: essentially, it is the process of adding a hydrogen molecule - two protons and two electrons - to a p bond). When the two *conjugated* double bonds of 1,3-pentadiene are 'hydrogenated' to produce pentane, about 225 kJ is released per mole of pentane formed. Compare that to the approximately 250 kJ/mol released when the two *isolated* double bonds in 1,4-pentadiene are hydrogenated, also forming pentane.

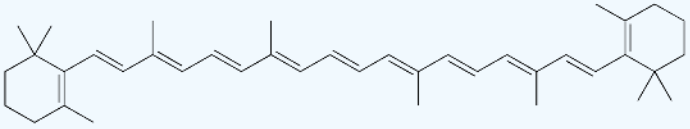


The conjugated diene is lower in energy: in other words, it is more stable. In general, conjugated pi bonds are more stable than isolated pi bonds.

Conjugated pi systems can involve oxygen and nitrogen atoms as well as carbon. In the metabolism of fat molecules, some of the key reactions involve alkenes that are conjugated to carbonyl groups.



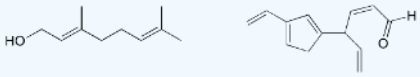
In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds, absorbs light with wavelengths in the blue region of the visible spectrum while allowing other visible wavelengths – mainly those in the red-yellow region - to be transmitted. This is why carrots are orange.



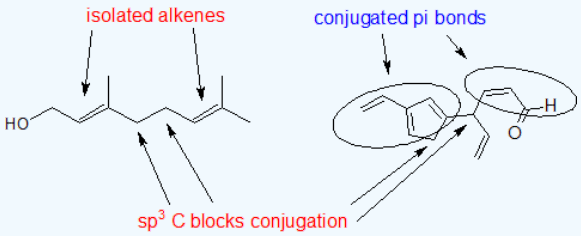
β-carotene

EXAMPLE 1

Identify all conjugated and isolated double bonds in the structures below. For each conjugated pi system, specify the number of overlapping *p* orbitals, and how many pi electrons are shared among them.

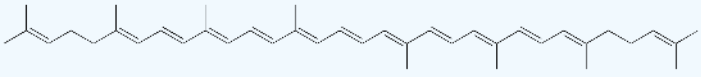


Solution: Look for sp^3 hybridized carbons to find disruptions in conjugation.



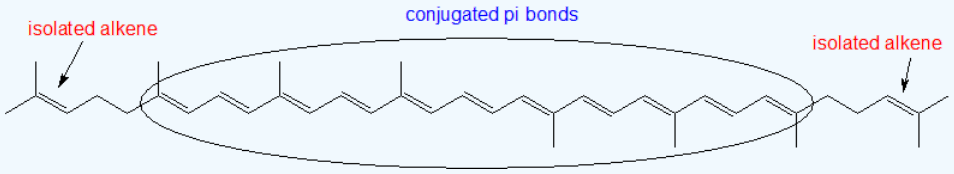
EXAMPLE 2

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

Solution: There are 11 conjugated pi bonds for a total of 22 pi electrons and 2 isolated pi bonds.



Exercise

13. 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?

Answer

13.

$E = hc/\lambda$

$E = (6.62 \times 10^{-34}\ \text{Js})(3.00 \times 10^{8}\ \text{m/s})/(3.00 \times 10^{-7}\ \text{m})$

$E = 6.62 \times 10^{-19}\ \text{J}$

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.

Contributors

- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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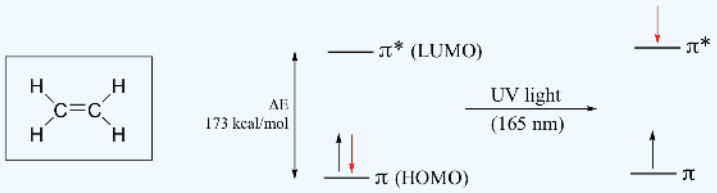
15.10: Interpreting Ultraviolet Spectra - The Effect of Conjugation

UV Spectroscopy and Pi Electron Transitions between the HOMO and LUMO

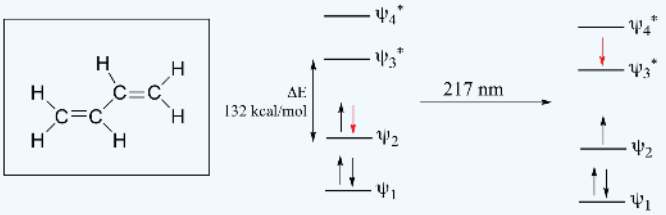
The ultraviolet absorption maximum of a conjugated molecule is dependent upon the extent of conjugation. As the conjugation increases, the Molecular Orbital energy decreases so that the pi electron transitions occur in the UV and visible regions of the electromagnetic spectrum. Molecules or parts of molecules that absorb light strongly in the UV-vis region are called **chromophores**.

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.



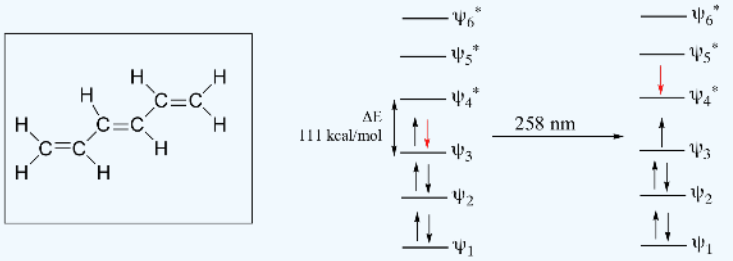
The electronic transitions of both molecular hydrogen and ethene are too energetic to be accurately recorded by standard UV spectrophotometers, which generally have a range of 220 – 700 nm. Where UV-vis spectroscopy becomes useful to most organic and biological chemists is in the study of molecules with 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.

Let's revisit the MO picture 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 bonding, while the upper two are anti-bonding.



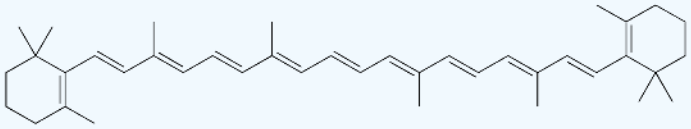
Comparing this MO picture to that of ethene, our isolated pi-bond example, we see that the HOMO-LUMO energy gap is indeed smaller for the conjugated system. 1,3-butadiene absorbs UV light with a wavelength of 217 nm.

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.



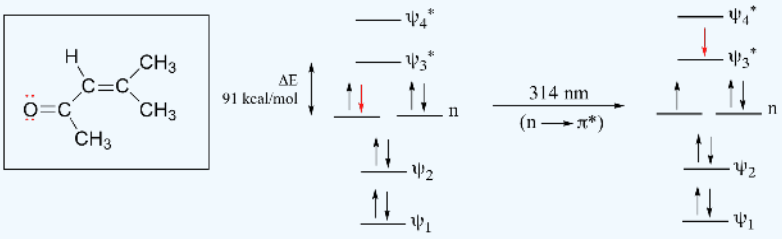
In molecules with extended pi systems, the HOMO-LUMO energy gap becomes so small that absorption occurs in the visible rather then the UV region of the electromagnetic spectrum. Beta-carotene, with its system of 11 conjugated double bonds,

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

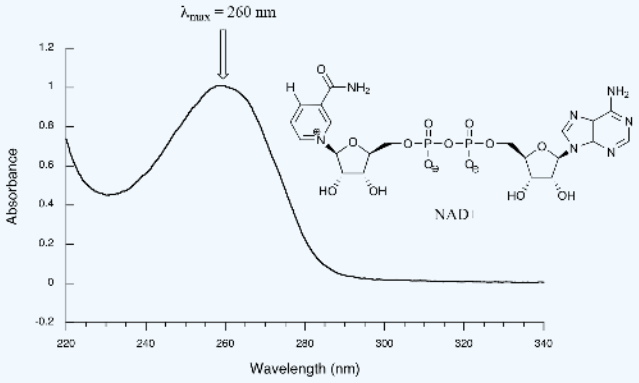
The conjugated pi system in 4-methyl-3-penten-2-one gives rise to a strong UV absorbance at 236 nm due to a π - π* transition. However, this molecule also absorbs at 314 nm. This second absorbance is due to the transition of a non-bonding (lone pair) electron on the oxygen up to a π* antibonding MO:



This is referred to as an **n - π* transition**. The nonbonding (n) MO's are higher in energy than the highest bonding p orbitals, so the energy gap for an n - π* transition is smaller that that of a π - π* transition – and thus the n - π* peak is at a longer wavelength. In general, n - π* transitions are weaker (less light absorbed) than those due to π - π* transitions.

Looking at UV-vis spectra

We have been talking in general terms about how molecules absorb UV and visible light – now let's look at some actual examples of data from a UV-vis absorbance spectrophotometer. The basic setup is the same as for IR spectroscopy: radiation with a range of wavelengths is directed through a sample of interest, and a detector records which wavelengths were absorbed and to what extent the absorption occurred. Below is the absorbance spectrum of an important biological molecule called nicotinamide adenine dinucleotide, abbreviated NAD^+ (we'll learn what it does in section 16.4) This compound absorbs light in the UV range due to the presence of conjugated pi-bonding systems.



You'll notice that this UV spectrum is much simpler than the IR spectra we saw earlier: this one has only one peak, although many molecules have more than one. Notice also 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.

Peaks in UV spectra tend to be quite broad, often spanning well over 20 nm at half-maximal height. Typically, there are two things that we look for and record from a UV-Vis spectrum.. The first is λ_{max}, which is the wavelength at maximal light absorbance. As you can see, NAD^+ has λ_{max} = 260 nm. We also want to record how much light is absorbed at λ_{max}. Here we use a unitless number called **absorbance**, abbreviated 'A'. This contains the same information as the 'percent transmittance'

number used in IR spectroscopy, just expressed in slightly different terms. 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:

$A = \log I_0/I$

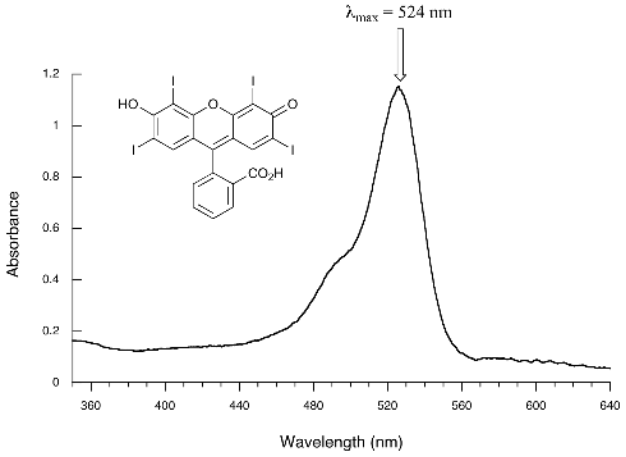
You can see that the absorbance value at 260 nm (A_{260}) is about 1.0 in this spectrum.

Exercise

14. Express A = 1.0 in terms of percent transmittance (%T, the unit usually used in IR spectroscopy (and sometimes in UV-vis as well).

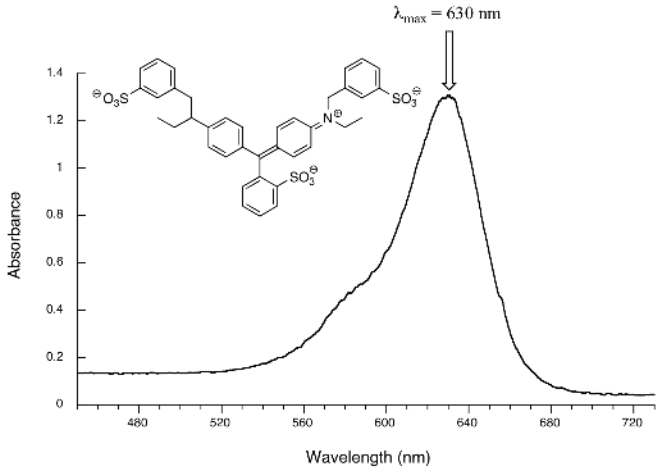
Solution

Here is the absorbance spectrum of the common food coloring Red #3:



Here, we see that 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.

Now, take a look at the spectrum of another food coloring, Blue #1:



Here, maximum absorbance is at 630 nm, in the orange range of the visible spectrum, and the compound appears blue.

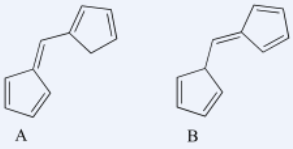
Exercise

15. How large is the π - π* transition in 4-methyl-3-penten-2-one?

Solution

Exercise

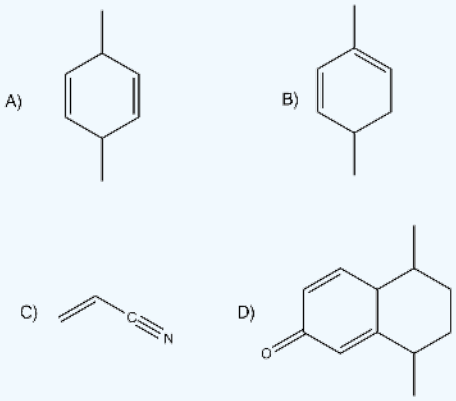
16. Which of the following molecules would you expect absorb at a longer wavelength in the UV region of the electromagnetic spectrum? Explain your answer.



Solution

Exercise

17. Which of the following would show UV absorptions in the 200-300 nm range?



Answer

17. B would be the only one to show in that range.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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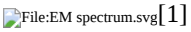
15.11: 16.11:Conjugation, Color, and the Chemistry of Vision

Introduction

Light is one of the most important resources for civilization, it provides energy as it pass along by the sun. Light influence our everyday live. Living organisms sense light from the environment by photoreceptors. Light, as waves carry energy, contains energy by different wavelength. In vision, light is the stimulus input. Light energy goes into the eye and stimulates its photoreceptors.

Physical Characteristics of Light

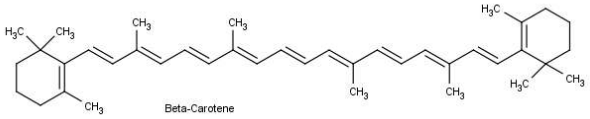


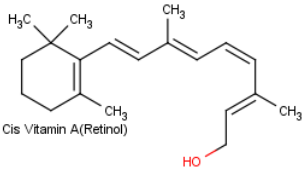
[1]

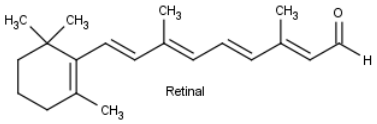
The energy of light can be determined from its wavelength. The energy of light increases from long wavelength to short wavelength. The visible spectrum ranges from 400 nm to 700 nm.

Energy converting chemicals

Light energy can convert chemical to other forms. Vitamin A, also known as retinol, anti-dry eye vitamins, is a required nutrition for human health. The predecessor of vitamin A is present in the variety of plant carotene. Vitamin A is critical for vision because it is needed by the retina of eye. Retinol can be convert to retinal, and retinal is a chemical necessary for rhodopsin. As light enters the eye, the 11-*cis*-retinal is isomerized to the all-"trans" form.

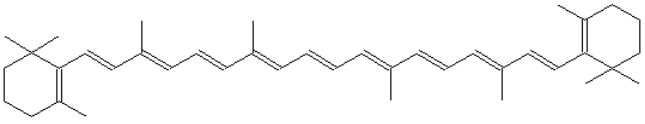






Colored molecules

The conjugated double bonds in beta-carotene produce the orange color in carrots. The conjugated double bonds in lycopene produce the red color in tomatoes.

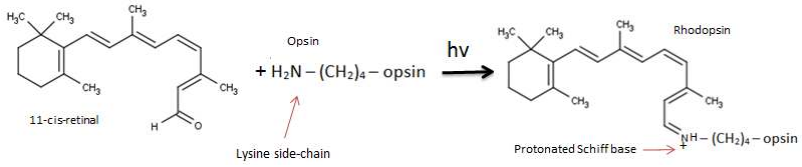


ß carotene

lycopene

Mechanism of Vision

We now know in rhodopsin, there is protein and retinal. The large protein is called opsin. Opsin does not absorb visible light, but when it bonded with 11-cis-retinal by its lysine side-chain to from rhodopsin, the new molecule has a very broad absorption band in the visible region of the spectrum.[2][3]

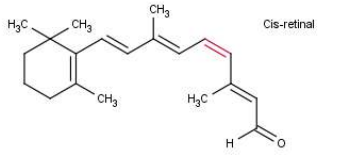


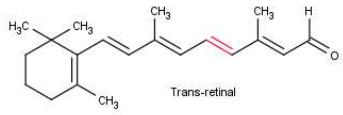
The reaction above shows Lysine side-chain from the opsin react with 11-cis-retinal when stimulated. By removing the oxygen atom form the retinal and two hydrogen atom form the free amino group of the lysine, the linkage show on the picture above is formed, and it is called Schiff base.

Signal transduction pathway

In human eyes, rod and cones react to light stimulation, and a series of chemical reactions happen in cells. These cells receive light, and pass on signals to other receiver cells. This chain of process is class signal transduction pathway. Signal transduction pathway is a mechanism that describe the ways cells react and response to stimulation.

The molecule cis-retinal can absorb light at a specific wavelength. When visible light hits the cis-retinal, the cis-retinal undergoes an isomerization, or change in molecular arrangement, to all-trans-retinal. The new form of trans-retinal does not fit as well into the protein, and so a series of geometry changes in the protein begins. The resulting complex is referred to a bathrhodopsin (there are other intermediates in this process, but we'll ignore them for now).





As the protein changes its geometry, it initiates a cascade of biochemical reactions that results in changes in charge so that a large potential difference builds up across the plasma membrane. 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.

References

1. Biochemistry, L. Stryer (W.H. Freeman and Co, San Francisco, 1975).
2. *The Cambridge Guide to the Material World*, Rodney Cotterill (Cambridge University Press, Cambridge, 1985)

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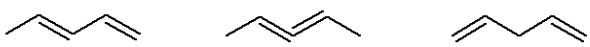
15.12: Additional Exercises

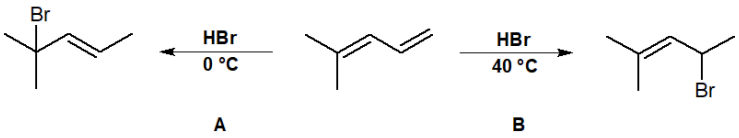
General Review

16-1 Identify which of the following dienes are isolated, conjugated, or cumulated.

a) b) c)

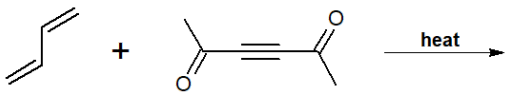


16-2 Identify which pathway gives the thermodynamic or the kinetic product and provide a reason for your answer.



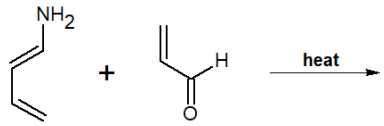
16-3 Draw the resonance structures of the following molecule.

16-4 Provide the final product of the following reaction.



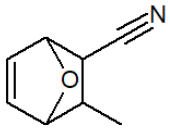
16-5 Predict the final product for the following reactions.

a)

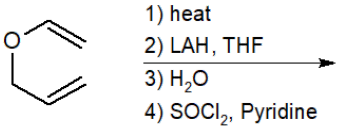


b)

16-6 For the following compound, predict which bonds could be broken to give the most probable Diels-Alder dienes that reacted to make the compound. Provide the resulting dienes from the prediction.

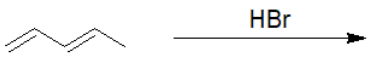


16-7 Give the final product of the following reaction chain..



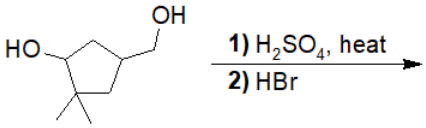
1,2- and 1,4-Addition to Conjugated Dienes

16-8 Predict all possible products of the following reaction.



16-9 Identify the kinetic and thermodynamic products of the previous problem, **16-8**.

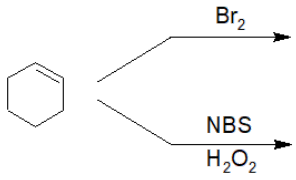
16-10 Predict the kinetic product(s) of the following reaction and provide proper IUPAC nomenclature.



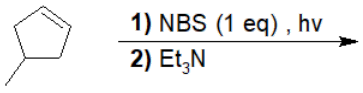
Allylic Radicals

16-11 Draw arrows to show the movement of electrons in the following allylic radical.

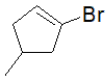
16-12 Show the products of the following reactions.



16-13 Choose the correct answer of the following reaction.



a)



b)

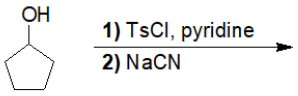
c)

d)

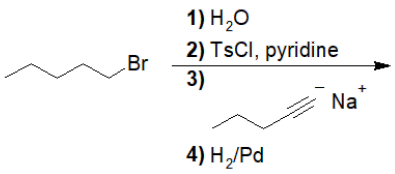
S_N2 Displacement Reactions of Allylic Halides and Tosylates

16-14 Predict the products of the following reactions.

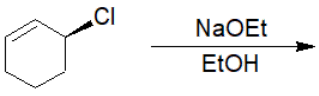
a)



b)



16-15 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



a) (3R)-3-ethoxycyclohex-1-ene

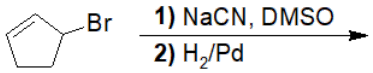
https://chem.libretexts.org/@go/page/183060

b) (3S)-3-ethoxycyclohex-1-ene

c) ethoxycyclohexane

d) cyclohexa-1,3-diene

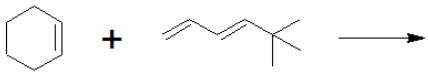
16-16 Predict the product of the following reaction.



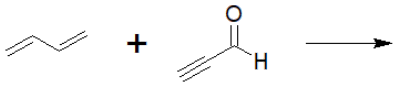
Diels-Alder Reactions

16-17 Predict the products of the following Diels-Alder reactions.

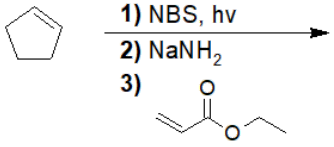
a)



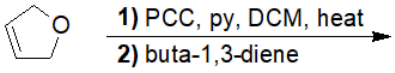
b)



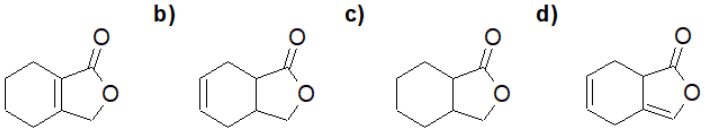
16-18 Predict the product of the following reaction.



16-19 Choose the correct answer.



a) **b)** **c)** **d)**



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15.13: Solutions to Additional Exercises

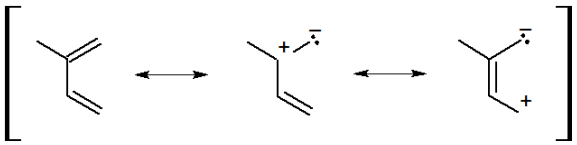
General Review

16-1

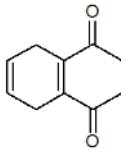
1. Conjugated
2. Cumulated
3. Isolated

16-2 Pathway A leads to the kinetic product. Since the intermediate formed during this pathway is the most stable intermediate, it forms the fastest and will always give the kinetic product. Pathway B forms the thermodynamic product, which is the most stable final product.

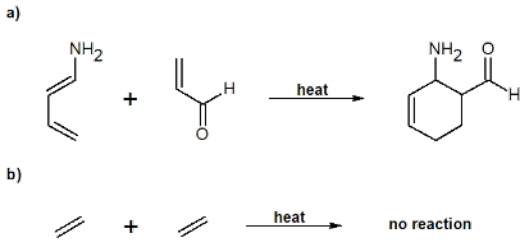
16-3



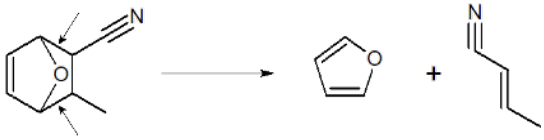
16-4



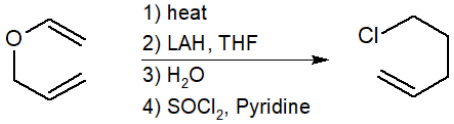
16-5



16-6

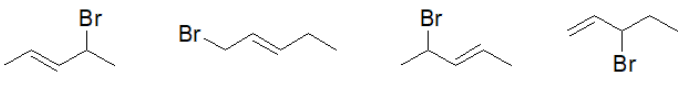


16-7



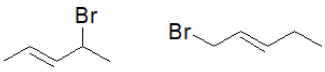
1,2- and 1,4-Addition to Conjugated Dienes

16-8:

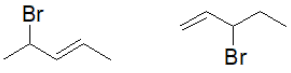


16-9:

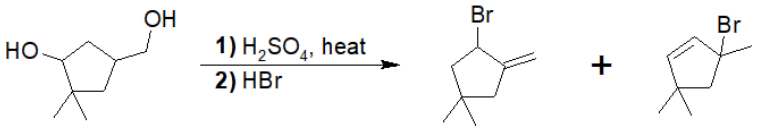
Thermodynamic:



Kinetic:

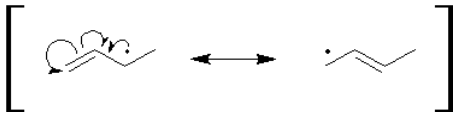


16-10:

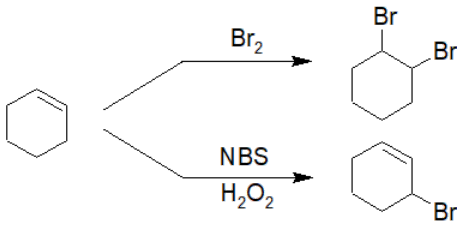


Allylic Radicals

16-11:



16-12:

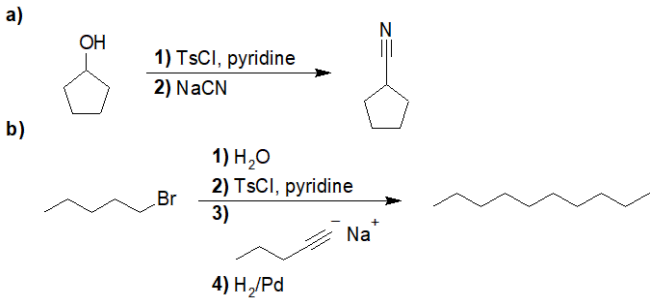


16-13:

Answer: C

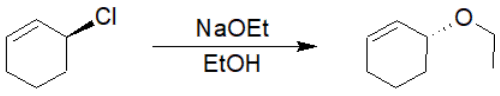
S_N2 Displacement Reactions of Allylic Halides and Tosylates

16-14:



16-15:

Answer:



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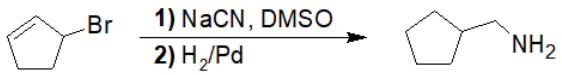
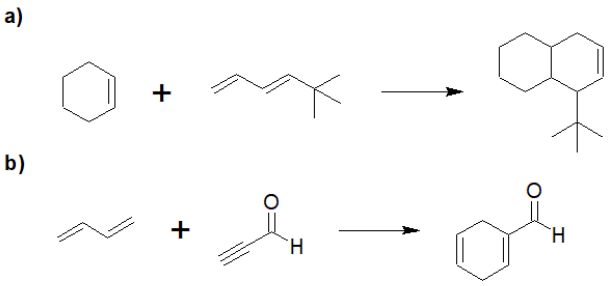
16-16:



Diels-Alder Reactions

16-17:



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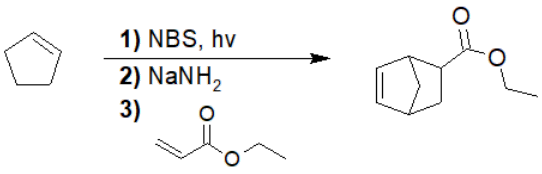

16-19:

Answer: B

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CHAPTER OVERVIEW

16: Aromatic Compounds
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- summarize the discovery of the structure of benzene (refer to section 17.1)
- predict the physical properties of aromatic compounds using IMFs (refer to section 17.2)
- apply resonance and MO Theory to the structure of benzene (refer to section 17.3)
- apply MO Theory to cyclobutadiene (refer to section 17.4)
- apply resonance to aromatic compounds and ions (refer to sections 17.5 and 17.6)
- use Hückel's rule to predict whether a given cyclic compound or ion is aromatic, antiaromatic or nonaromatic (refer to sections 17.5 and 17.6)
- for heterocycles, determine whether the lone pairs of the heteroatoms occupy p orbitals or sp^2 orbitals (refer to sections 17.5 and 17.7)
- for heterocyclic amines, and predict whether the nitrogen atom is weakly or strongly basic (refer to sections 17.5 and 17.7)
- use Huckel's Rule to prdict whether polycyclic aromatic hydrocarbons are aromatic (refer to setions 17.5 and 17.8)
- use IR, NMR, UV and mass spectra to determine the structures of aromatic compounds (refer to section 17.9)
- given an aromatic compound, predict the important features of its spectra (refer to section 17.9)

Please note: IUPAC nomenclature and important common names of alcohols were explained in Chapter 3.

Topic hierarchy

16.1: Introduction: The Discovery of Benzene
16.2: The Structure and Properties of Benzene and its Derivatives
16.3: Resonance and the Molecular Orbitals of Benzene
16.4: The Molecular Orbital Picture of Cyclobutadiene
16.5: Aromaticity and Huckel's Rule
16.6: Aromatic Ions - a closer look
16.7: Heterocyclic Aromatic Compounds - a closer look
16.8: Polycyclic Aromatic Hydrocarbons
16.9: Spectroscopy of Aromatic Compounds
16.10: Additional Exercises
16.11: Solutions to Additional Exercises

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16.1: Introduction: The Discovery of Benzene

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.

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16.2: The Structure and Properties of Benzene and its Derivatives

Benzene

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:

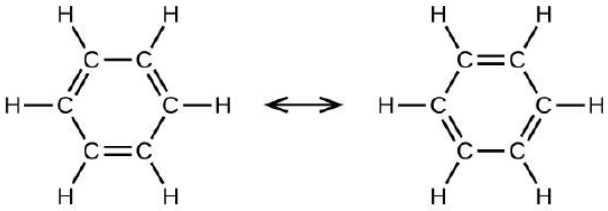


Figure **16.2.10**.

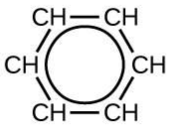
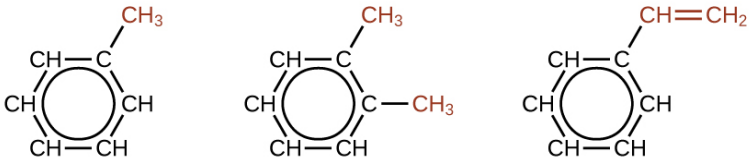


Figure : This diagram shows the unique bonding structure of benzene.

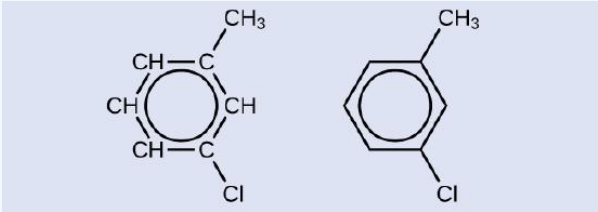
There are many derivatives of benzene. The hydrogen atoms can be replaced by many different substituents. Aromatic compounds more readily undergo substitution reactions than addition reactions; replacement of one of the hydrogen atoms with another substituent will leave the delocalized double bonds intact. 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.

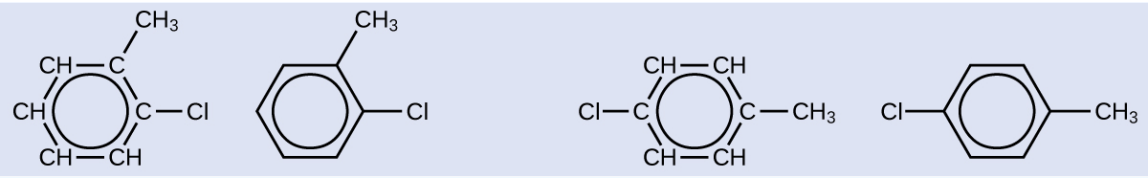
Example: Structure of Aromatic Hydrocarbons

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

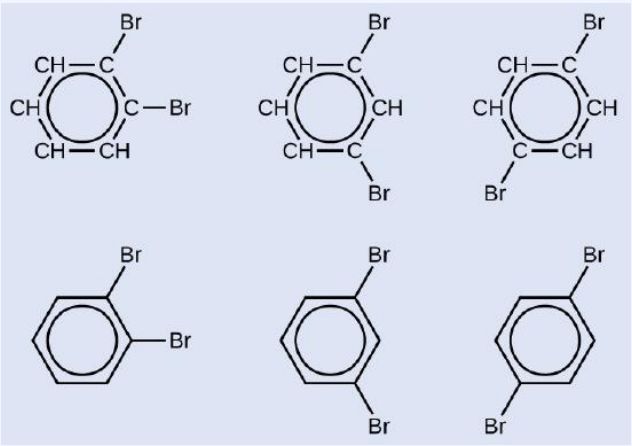
Since the six-carbon ring with alternating double bonds is necessary for the molecule to be classified as aromatic, appropriate isomers can be produced only by changing the positions of the chloro-substituent relative to the methyl-substituent:



Exercise

1. Draw three isomers of a six-membered aromatic ring compound substituted with two bromine atoms.

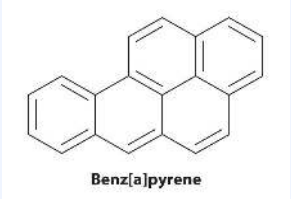
Answer



Larger Arenes

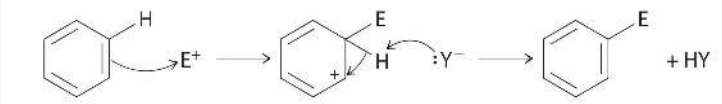
Most arenes that contain a single six-membered ring are volatile liquids, such as benzene and the xylenes, although some arenes with substituents on the ring are solids at room temperature. In the gas phase, the dipole moment of benzene is zero, but the presence of electronegative or electropositive 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 as shown below.

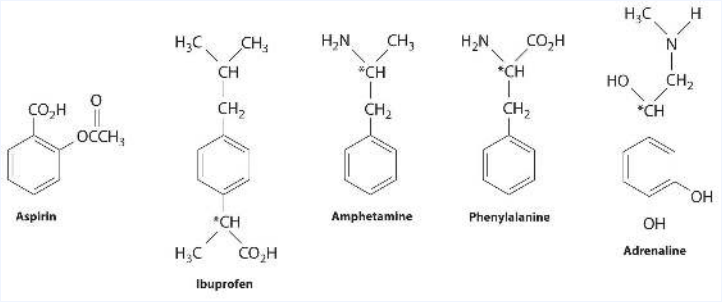


Figure: Biologically Active Substituted Arenes; Chiral centers are indicated with an asterisk.

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.

Physical Properties

The physical properties of aromatic compounds are similar to other hydrocarbons. As hydrocarbons, the dominant IMF is the London Dispersion Force. This relatively weak IMF results in more volatile compounds which led to the term "aromatic". Chemists can frequently recognize the presence of an aromatic compound by simply smelling its aroma.

Contributors and Attributions

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- Paul Flowers (University of North Carolina - Pembroke), Klaus Theopold (University of Delaware) and Richard Langley (Stephen F. Austin State University) with contributing authors. Textbook content produced by OpenStax College is licensed under a Creative Commons Attribution License 4.0 license. Download for free at http://cnx.org/contents/85abf193-2bd...a7ac8df6@9.110).

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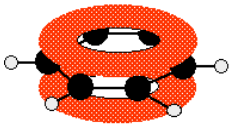
16.3: Resonance and the Molecular Orbitals of Benzene

Benzene Structure

Among the many distinctive features of benzene, its aromaticity is the major contributor to why it is so unreactive. This section will try to clarify the theory of aromaticity and why aromaticity gives unique qualities that make these conjugated alkenes inert to compounds such as Br_2 and even hydrochloric acid. It will also go into detail about the unusually large resonance energy due to the six conjugated carbons of benzene.

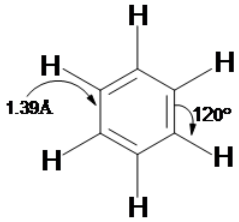
The delocalization of the p-orbital carbons on the sp^2 hybridized carbons is what gives the aromatic qualities of benzene.



This diagram shows one of the molecular orbitals containing two of the delocalized electrons, which may be found anywhere within the two "doughnuts". The other molecular orbitals are almost never drawn.

- Benzene (C_6H_6) is a planar molecule containing a ring of six carbon atoms, each with a hydrogen atom attached.
- The six carbon atoms form a perfectly regular hexagon. All of the carbon-carbon bonds have exactly the same lengths - somewhere between single and double bonds.
- There are delocalized electrons above and below the plane of the ring, which makes benzene particularly stable.
- Benzene resists addition reactions because those reactions would involve breaking the delocalization and losing that stability.

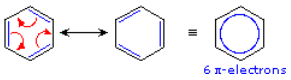
Because of the aromaticity of benzene, the resulting molecule is planar in shape with each C-C bond being 1.39 Å in length and each bond angle being 120°. You might ask yourselves how it's possible to have all of the bonds to be the same length if the ring is conjugated with both single (1.47 Å) and double (1.34 Å), but it is important to note that there are no distinct single or double bonds within the benzene. Rather, the delocalization of the ring makes each count as one and a half bonds between the carbons which makes sense because experimentally we find that the actual bond length is somewhere in between a single and double bond. Finally, there are a total of six p-orbital electrons that form the stabilizing electron clouds above and below the aromatic ring.



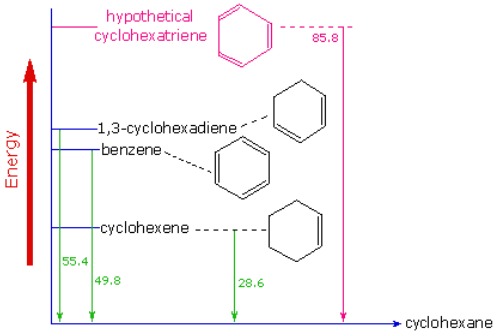
If benzene is forced to react by increasing the temperature and/or by addition of a catalyst, It undergoes **substitution reactions** rather than the addition reactions that are typical of alkenes. This further confirms the previous indication that the six-carbon benzene core is unusually stable to chemical 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 a regular-hexagonal, planar ring of carbons was adopted, and the exceptional thermodynamic and chemical stability of this system was attributed to resonance stabilization of a conjugated cyclic triene.

The High Stability of Benzene

Here, two structurally and energetically equivalent electronic structures for a stable compound are written, but no single structure provides an accurate or even an adequate representation of the true molecule. The six-membered ring in benzene is a perfect hexagon (all carbon-carbon bonds have an identical length of 1.40 Å). The cyclohexatriene contributors would be expected to show alternating bond lengths, the double bonds being shorter (1.34 Å) than the single bonds (1.54 Å). An alternative representation for benzene (circle within a hexagon) emphasizes the pi-electron delocalization in this molecule, and has the advantage of being a single diagram. In cases such as these, the electron delocalization described by resonance enhances the stability of the molecules, and compounds composed of such molecules often show exceptional stability and related properties.



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 now accepted as a characteristic of all aromatic compounds.



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.

The Molecular Orbitals of Benzene

Since benzene has six pi electrons, all of the bonding MOs are filled which indicates a highly stable molecule.

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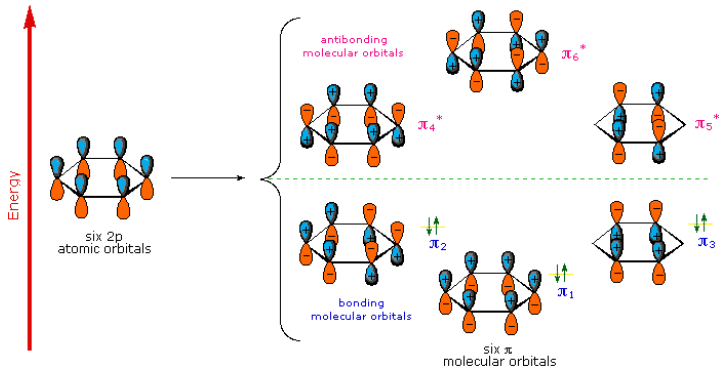
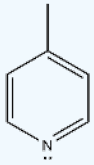


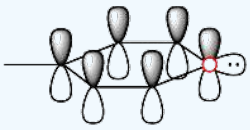
Exercise

2. The molecule shown, *p*-methylpyridine, has similar properties to benzene (flat, 120° bond angles). Draw the pi-orbitals for this compound.



Answer

2. The nitrogen has a lone pair of electrons perpendicular to the ring.



O =N

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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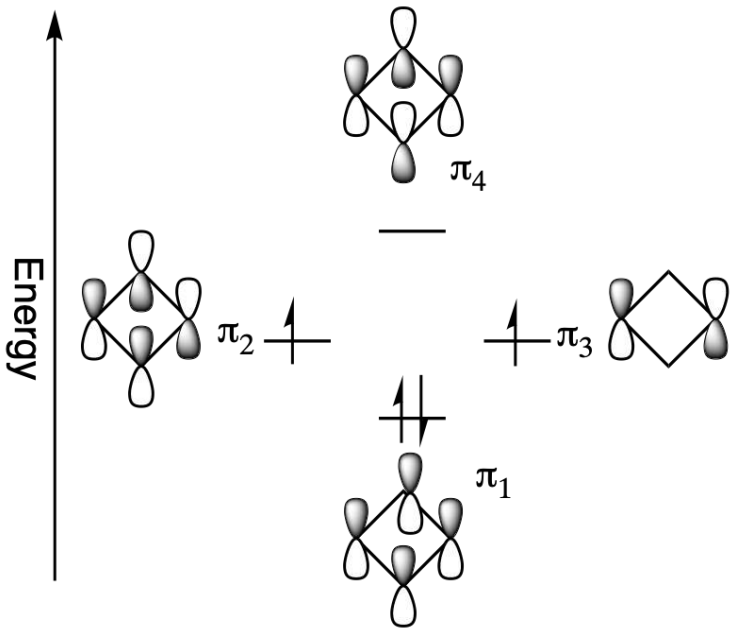
16.4: The Molecular Orbital Picture of Cyclobutadiene

Molecular Orbital Diagram for Cyclobutadiene

Cyclobutadiene is so unstable that its physical properties have not been reliably measured. The diagram below helps explain why cyclobutadiene is very unstable. With four pi electrons, both non-bonding Molecular Orbitals are singly occupied. Cyclobutadiene is so unstable relative to cyclobutane, that it is described as "antiaromatic". This term will be further explored in the next section.



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16.5: Aromaticity and Huckel's Rule

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.

Huckel's Rule: Aromatic, Antiaromatic, and Nonaromatic

Huckel's Rule is a set of algorithms that combine the number of π electrons (N) and the physical structure of the ring system to determine whether the molecule is aromatic, antiaromatic, or nonaromatic.

The number of π electrons in an **aromatic** system can be determined by the following algorithm:

$$N = 4n + 2 \tag{16.5.1}$$

where n is an integer.

The number of π electrons in an **antiaromatic** system can be determined by the following algorithm:

$$N = 4n \tag{16.5.2}$$

where n is an integer.

If a compound does not have a continuous ring of conjugated p orbitals in a planar conformation, then it is nonaromatic.

Huckel's Rule is a useful first step in evaluating the potential for a ringed molecule to be aromatic. The planar requirement of the ring may require further investigation.

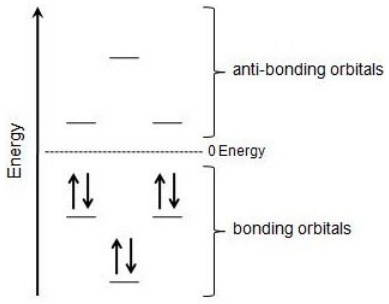
Four Criteria for Aromaticity

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)
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)

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

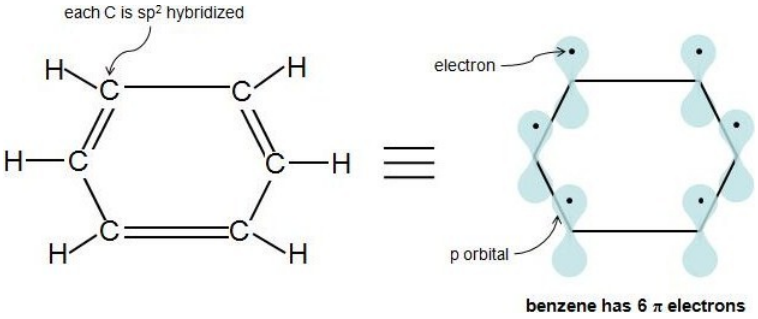
To apply the 4n+2 rule, first count the number of π electrons in the molecule. Then, set this number equal to $4n+2$ and solve for n. If is 0 or any positive integer (1, 2, 3,...), the rule has been met. For example, benzene has six π electrons:

$$\begin{aligned} 4n+2 &= 6 \\ 4n &= 4 \\ n &= 1 \end{aligned}$$

For benzene, we find that $n = 1$, which is a positive integer, so the rule is met.

How Can You Tell Which Electrons are 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. π electrons lie in p orbitals and sp^2 hybridized atoms have 1 p orbital each. So if every carbon atom in the cyclic compound is sp^2 hybridized, this means the molecule is fully conjugated (has 1 p orbital at each atom), and the electrons in these p orbitals are the π electrons. A simple way to know if an atom is sp^2 hybridized is to see if it has 3 attached atoms and no lone pairs of electrons. This video provides a very nice tutorial on how to determine an atom's hybridization. In a cyclic hydrocarbon compound with alternating single and double bonds, each carbon is attached to 1 hydrogen and 2 other carbons. Therefore, each carbon is sp^2 hybridized and has a p orbital. Let's look at our previous example, benzene:

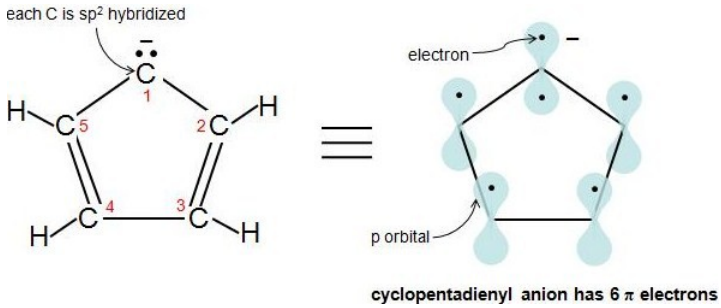


benzene has 6 π electrons

Each double bond (π bond) always contributes 2 π electrons. Benzene has 3 double bonds, so it has 6 π electrons.

Aromatic Ions

Hückel's Rule also applies to ions. As long as a compound has 4n+2 π electrons, it does not matter if the molecule is neutral or has a charge. For example, cyclopentadienyl anion is an aromatic ion. How do we know that it is fully conjugated? That is, how do we know that each atom in this molecule has 1 p orbital? Let's look at the following figure. Carbons 2-5 are sp^2 hybridized because they have 3 attached atoms and have no lone electron pairs. What about carbon 1? Another simple rule to determine if an atom is sp^2 hybridized is if an atom has 1 or more lone pairs and is attached to an sp^2 hybridized atom, then that atom is sp^2 hybridized also. This video explains the rule very clearly. Therefore, carbon 1 has a p orbital. Cyclopentadienyl anion has 6 π electrons and fulfills the 4n+2 rule.

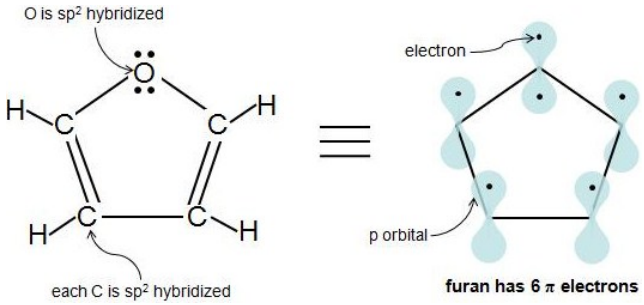


cyclopentadienyl anion has 6 π electrons

Heterocyclic Aromatic Compounds

So far, you have encountered many carbon homocyclic rings, but compounds with elements other than carbon in the ring can also be aromatic, as long as they fulfill the criteria for aromaticity. These molecules are called heterocyclic compounds because they contain 1 or more different atoms other than carbon in the ring. A common example is furan, which contains an oxygen atom. We

know that all carbons in furan are sp^2 hybridized. But is the oxygen atom sp^2 hybridized? The oxygen has at least 1 lone electron pair and is attached to an sp^2 hybridized atom, so it is sp^2 hybridized as well. Notice how oxygen has 2 lone pairs of electrons. How many of those electrons are π electrons? An sp^2 hybridized atom only has 1 p orbital, which can only hold 2 electrons, so we know that 1 electron pair is in the p orbital, while the other pair is in an sp^2 orbital. So, only 1 of oxygen's 2 lone electron pairs are π electrons. Furan has 6 π electrons and fulfills the 4n+2 rule.



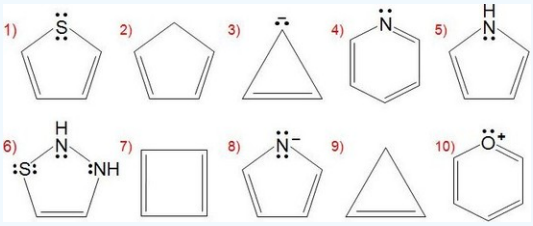
A Common Misconception

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 $\boldsymbol{sp^2}$.

The *specific* rule is that if you have an $\boldsymbol{sp^2}$ conjugated system, the lone pair will be involved ***if it makes the system more stable.*** In this case, conferring Hückel $\boldsymbol{4n+2}$ 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

3. Using the criteria for aromaticity, determine if the following molecules are aromatic:



Answer

3.

Cpd 1: Aromatic - only 1 of S's lone pairs counts as π electrons, so there are 6 π electrons, n=1 Not aromatic - not fully conjugated, top C is sp^3 hybridized

Cpd 2: Not aromatic - top C is sp^2 hybridized, but there are 4 π electrons, n=1/2

Cpd 3: 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

Cpd 4: Aromatic - there are 6 π electrons, n=1

Cpd 5: Aromatic - there are 6 π electrons, n=1 because the N assumes sp^2 hybridization.

Cpd 6: 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

Cpd 7: Not aromatic - there are 4 π electrons, n=1/2

Cpd 8: Aromatic - only 1 of N's lone pairs counts as π electrons, so there are 6 π electrons, n=1

Cpd 9: Not aromatic - not fully conjugated, top C is sp^3 hybridized

Cpd 10: 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

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Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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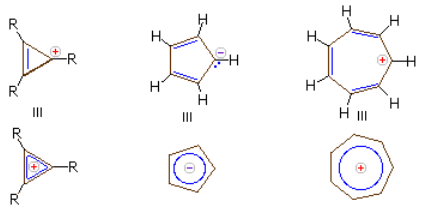
16.6: Aromatic Ions - a closer look

Cyclic anions and cations can be aromatic if they follow Huckel's Rule. Since aromatic ions have increased stability, it is important to recognize their formation when predicting reaction products.

Charged Aromatic Compounds

Carbanions and carbocations may also show aromatic stabilization. Some examples are:

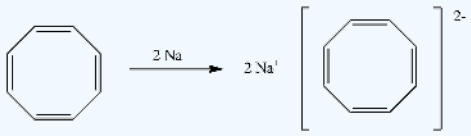


The three-membered ring cation has 2 π-electrons and is surprisingly stable, considering its ring strain. Cyclopentadiene is as acidic as ethanol, reflecting the stability of its 6 π-electron conjugate base. Salts of cycloheptatrienyl cation (tropylium ion) are stable in water solution, again reflecting the stability of this 6 π-electron cation.

Exercise

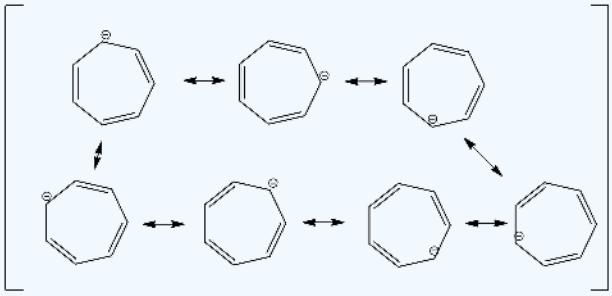
4. Draw the resonance structures for cycloheptatriene anion. Are all bonds equivalent? How many lines (signals) would you see in a H^1 C^{13} NMR?

5. The following reaction occurs readily. Propose a reason why this occurs?



Answer

4. All protons and carbons are the same, so therefore each spectrum will only have one signal each.



5. The ring becomes aromatic with the addition of two electrons. Thereby obeying the 4n+2 rule.

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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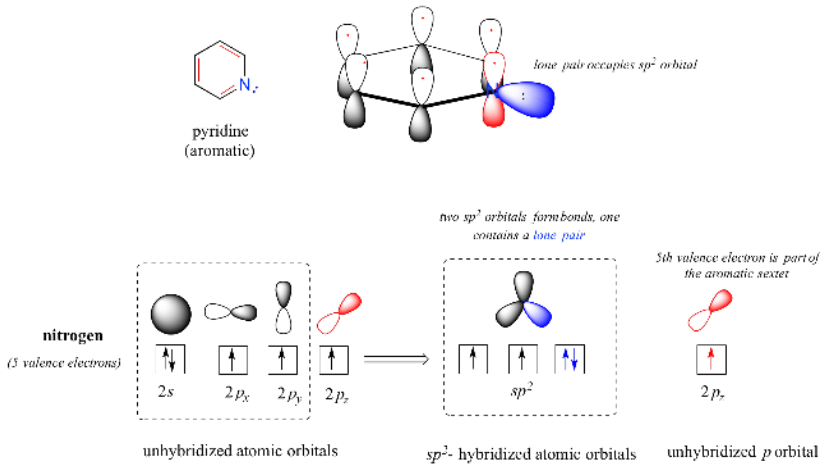
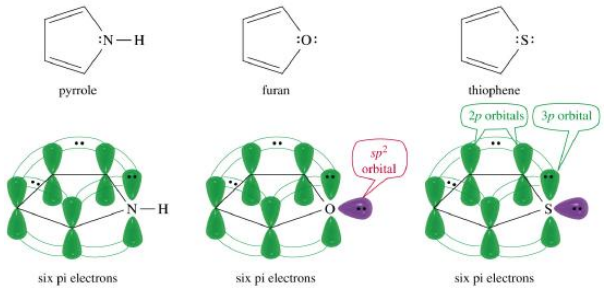
16.7: Heterocyclic Aromatic Compounds - a closer look

Aromatic Heterocycles

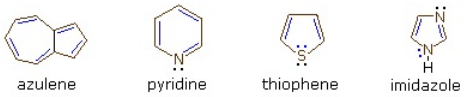
While benzene is the archetypical aromatic compound, many unsaturated cyclic compounds have exceptional properties that we now consider characteristic of "aromatic" systems. The aromatic heterocycle pyridine is similar to benzene, and is often used as a weak base for scavenging protons. In the bonding 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 system delocalized around the ring.



Pyrrole, furan, and thiophene have heterocyclic five-membered rings, in which the heteroatom has at least one pair of non-bonding valence shell electrons. By hybridizing this heteroatom to a sp^2 state, a p-orbital occupied by a pair of electrons and oriented parallel to the carbon p-orbitals is created. The resulting planar ring meets the first requirement for aromaticity, and the π-system is occupied by 6 electrons, 4 from the two double bonds and 2 from the heteroatom, thus satisfying the Hückel Rule.



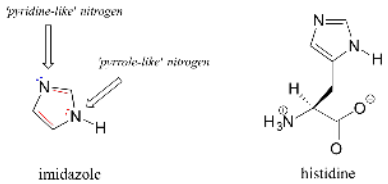
Four additional examples of heterocyclic aromatic compounds are shown below.



The first example is azulene, a blue-colored 10 π-electron aromatic hydrocarbon isomeric with naphthalene. The second and third compounds are heterocycles having aromatic properties. Pyridine has a benzene-like six-membered ring incorporating one nitrogen atom. The non-bonding electron pair on the nitrogen is not part of the aromatic π-electron sextet, and may bond to a proton or other electrophile without disrupting the aromatic system. In the case of thiophene, a sulfur analog of furan, one of the sulfur electron pairs (colored blue) participates in the aromatic ring π-electron conjugation. The last compound is imidazole, a heterocycle having two nitrogen atoms. Note that only one of the nitrogen non-bonding electron pairs is used for the aromatic π-electron sextet. The other electron pair is weakly basic and behaves similarly to the electron pair in pyridine.

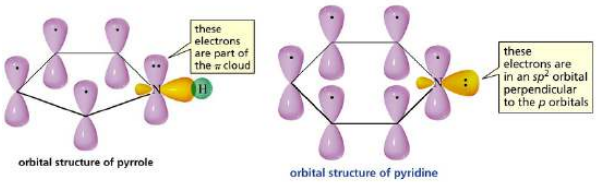
The Two Nitrogens of Imidazole

Imidazole is another important example of an aromatic heterocycle found in biomolecules - the side chain of the amino acid histidine contains an imidazole ring. In imidazole, one nitrogen is 'pyrrole-like' (the lone pair contributes to the aromatic sextet) and one nitrogen is 'pyridine-like' (the lone pair is located in an sp^2 orbital, and is *not* part of the aromatic sextet). The diagram below shows how the lone pair electrons on the nitrogen atoms differ.



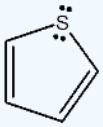
Basicity versus Aromaticity

When the nitrogen atom of an aromatic heterocycle contains a pi bond, then the lone pair occupies an sp^2 orbital and is available to react as a weak base. We can view these nitrogens as being "pyridine like". When the nitrogen atom of an aromatic heterocycle has single bonds only, then the nitrogen is still sp^2 hybridized, but the lone pair occupies the unhybridized p orbital to create aromaticity. This lone pair is part of the conjugated pi electron system and is not available to react as a weak base.

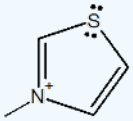


Exercise

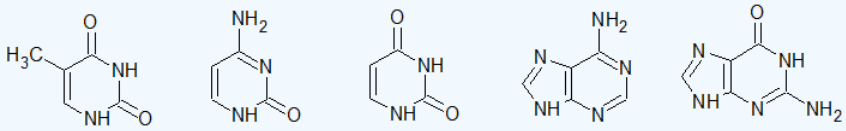
6. Draw the orbitals of thiophene to show that is aromatic.



7. The following ring is called a thiazolium ring. Describe how it is aromatic.



8. The nitrogenous bases for the nucleotides of DNA and RNA are shown below. Determine which nitrogen atoms are weak bases and which nitrogen atoms have lone pairs contributing to the aromaticity of the compound.



Answer

6. This drawing shows it has 6 electrons in the pi-orbital.

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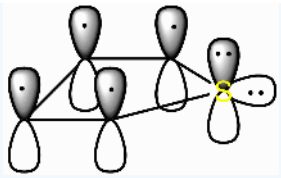
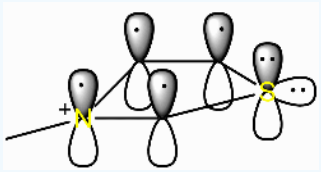
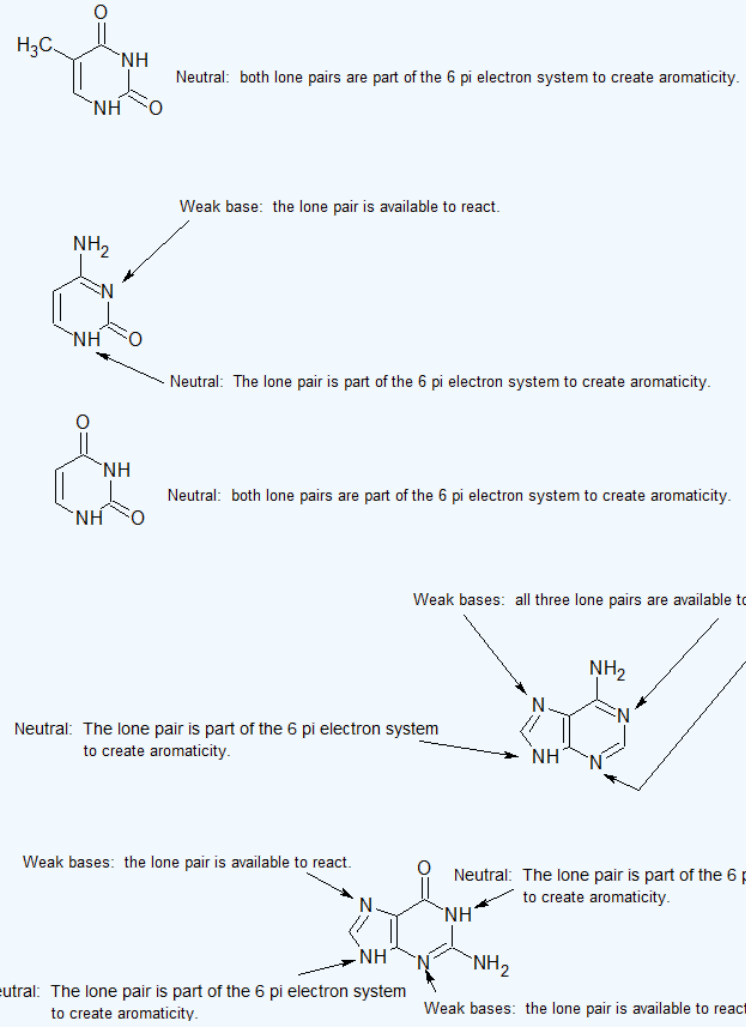


7. Similar to the last question, the drawing shows that there is only 6 electrons in the pi-system.



8.



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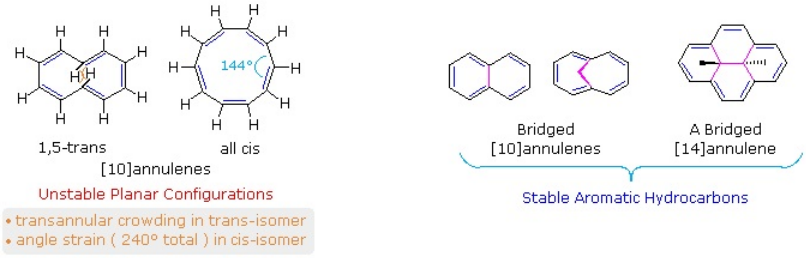
16.8: Polycyclic Aromatic Hydrocarbons

Aromatic Compound with a single ring



Aromatic Compounds with more than one ring

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. This helical configuration renders the hexahelicene molecule chiral, and it has been resolved into stable enantiomers.

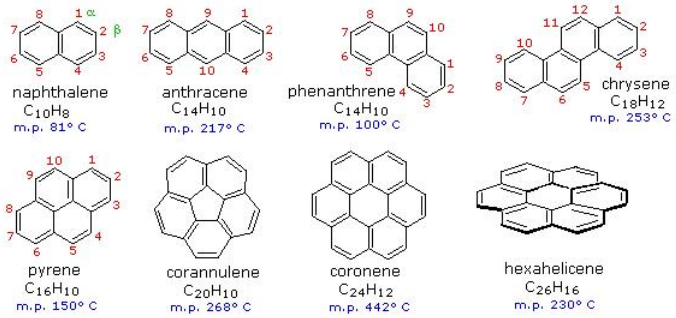
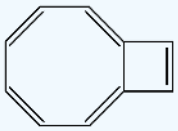


Figure 2: Examples of Polycyclic Aromatic Hydrocarbons (PAHs).

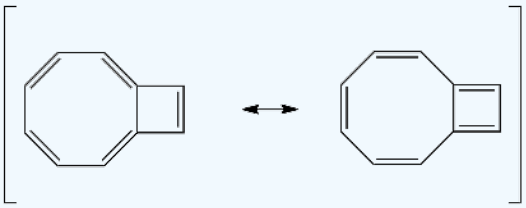
Exercise

9. This is an isomer of naphthalene. Is it aromatic? Draw a resonance structure for it.



Answer

9. Yes, it is aromatic. 4n+2 pi-electrons.



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16.9: Spectroscopy of Aromatic Compounds

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 pelectrons is delocalized around the ring. When the molecule is exposed to B_0, these pelectrons 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 pelectrons 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.

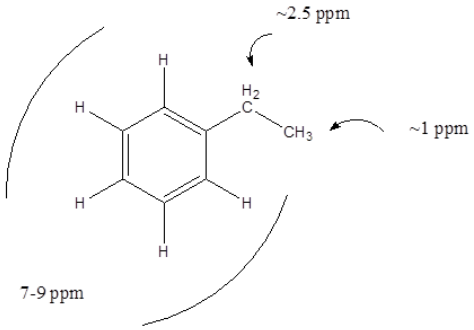
If we are at point A in the figure above, we feel a magnetic field pointing in a northerly direction. If we are at point B, however, we feel a field pointing to the south.

In the induced field generated by the aromatic ring current, the benzylic protons are at the equivalent of ‘point B’ – 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 pelectrons 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 deshielded. Their chemical shift is far downfield, in the 6.5-8 ppm region.

Characteristic NMR Absorption of Benzene Derivatives

Hydrogens directly attached to an arene ring show up about 7-9 PPM in the NMR. **This is called the aromatic region.** Hydrogen environments directly bonded to an arene ring show up about 2.5 PPM.



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}.

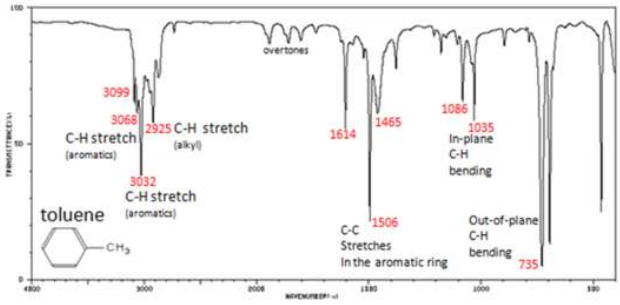
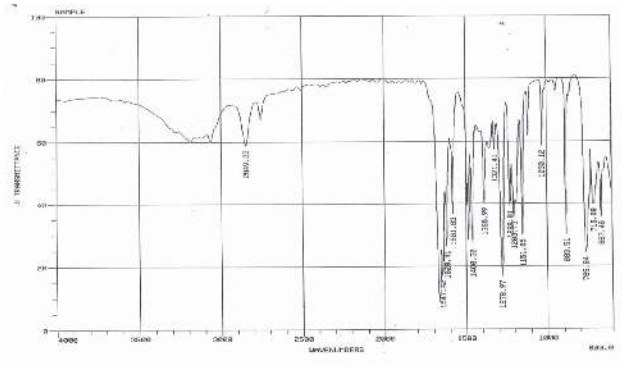


Figure. Infrared Spectrum of Toluene

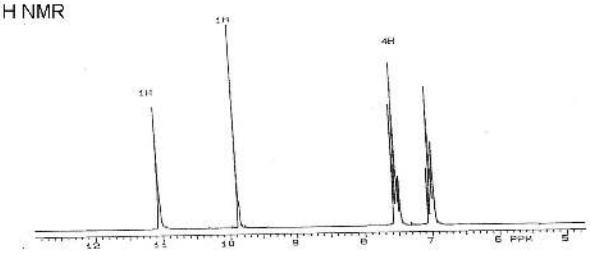
Exercise

10. A straw-colored oily liquid with a bitter almond odor and burning nut-like taste was isolated from the exudate of the castor sacs of mature North American beavers. The oily is slightly soluble in water with a boiling point of 197°C. Elemental analysis results are as follows: 68.84% C, 4.96% H, and 26.20% O. Name, draw the bond-line structure, and correlate the structure with the IR, ^{1}H NMR, and ^{13}C NMR spectral data below.

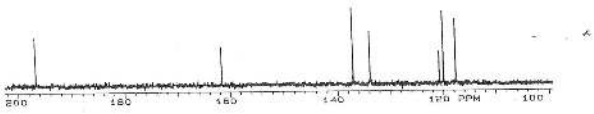
IR Spectrum



^{1}H NMR

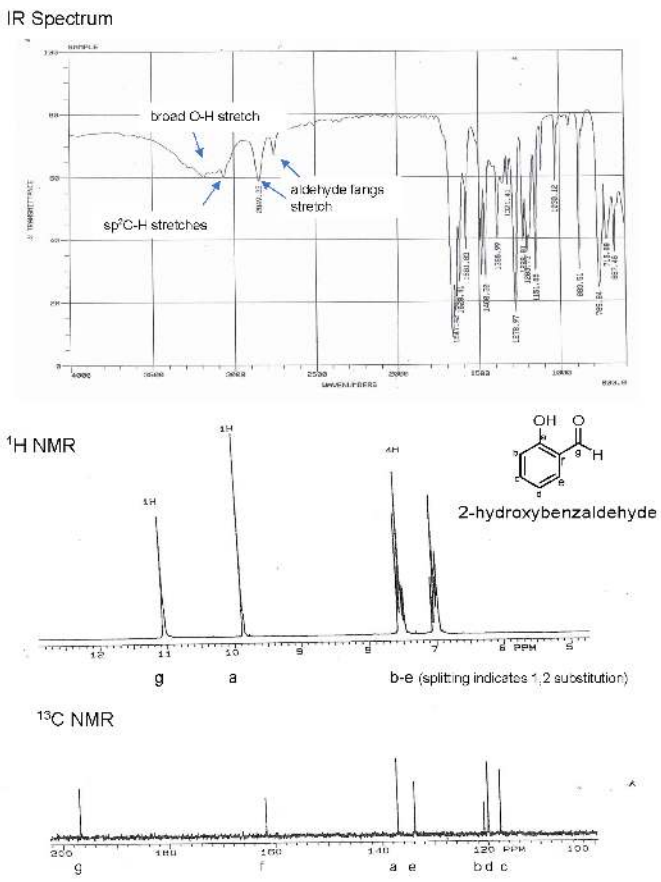


^{13}C NMR



Answer

10.



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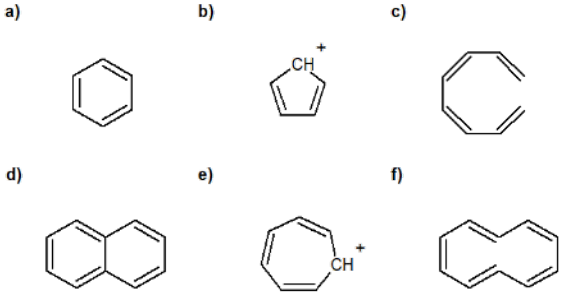
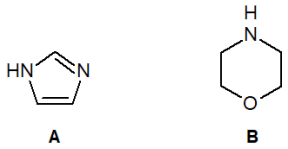
16.10: Additional Exercises

General Review

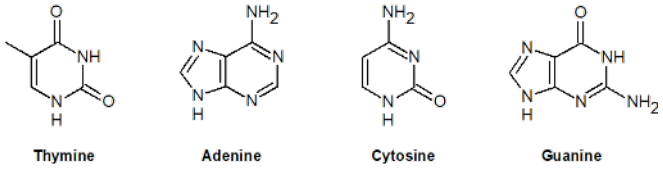
17-1 State whether the following molecules are aromatic, antiaromatic or nonaromatic.



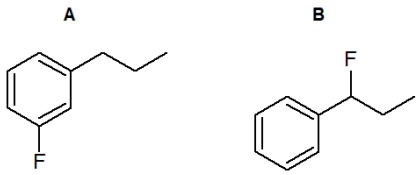
17-2 Predict which of the following nitrogen-containing heterocycles is more acidic than the other. Provide a reason for your choices.



17-3 For the following bases of DNA, identify the heterocyclic compound that makes up the core structure of each one - purine or pyrimidine?



17-4 Provide the proper IUPAC names for the following compounds.



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16.11: Solutions to Additional Exercises

General Review

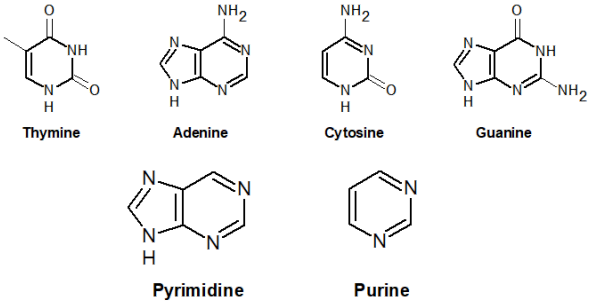
17-1

1. Aromatic
2. Antiaromatic
3. Nonaromatic
4. Aromatic
5. Aromatic
6. Nonaromatic

17-2

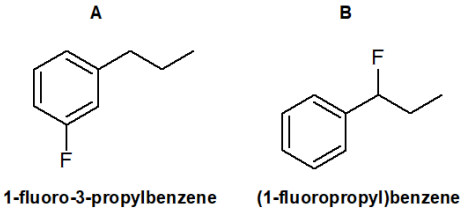
Compound A will be more acidic than compound B due to the aromaticity of its conjugate base. When compound A loses its proton, the new lone pair of electrons can delocalize with the double bonds in the ring, whereas when compound B is deprotonated, its new lone pair of electrons is localized on the nitrogen. Compound B is the stronger base.

17-3



Thymine and Cytosine are derivatives of purine. Adenine and Guanine are derivatives of pyrimidine.

17-4



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CHAPTER OVERVIEW

17: Reactions of Aromatic Compounds
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- propose mechanisms for Electrophilic Aromatic Substitution Reactions (EAS): halogenation, nitration, sulfonation, and Friedel-Crafts Alkylation & Acylation (sections 18.1 to 18.5)
- predict products and specify reagents for Electrophilic Aromatic Substitution Reactions (EAS): halogenation, nitration, sulfonation, and Friedel-Crafts Alkylation & Acylation (sections 18.1 to 18.5)
- draw resonance structures of the sigma complexes resulting from EAS rxns of substituted aromatic rings (sections 18.1 to 18.5)
- draw reaction energy diagrams for EAS reactions (sections 18.1 to 18.5)
- explain why substituents are activating or deactivating and o,p-directors or m-directors (section 18.6)
- list the major substituents in their EAS activation "pecking order" (section 18.6)
- predict the products of side chain reactions: oxidation of catechols and alkyl substituents, bromination of benzylic carbons, S_N1 and S_N2 rxns at the benzylic carbon, reduction of carbonyls, and reduction of nitro groups (sections 18.7 and 18.12)
- design multiple step syntheses that use substituent effects to create the desired isomers of multi-substituted aromatic compounds (sections 18.8 and 18.9)
- predict the products of Nucleophilic Aromatic Substitution Reactions (NAS): addition-elimination and elimination-addition (benzyne) (sections 18.10 and 18.11)
- propose mechanisms for Nucleophilic Aromatic Substitution Reactions (NAS): addition-elimination and elimination-addition (benzyne) (sections 18.10 and 18.11)

Topic hierarchy

17.1: Electrophilic Aromatic Substitution (EAS)
17.2: Halogenation of Benzene (an EAS Reaction)
17.3: Nitration of Benzene (an EAS Reaction)
17.4: Sulfonation of Benzene (an EAS Reaction)
17.5: Alkylation and Acylation of Benzene - The Friedel-Crafts EAS Reactions
17.6: Substituent Effects on the EAS Reaction
17.7: Side-Chain Reactions of Benzene Derivatives
17.8: Synthetic Strategies for Di-substituted Benzenes
17.9: Trisubstituted Benzenes - Effects of Multiple Substituents
17.10: Nucleophilic Aromatic Substitution - The Addition-Elimantion Mechanism
17.11: NAS Reactions - the Elimination-Addition (Benzyne) Mechanism
17.12: Reduction of Aromatic Compounds
17.13: Additional Exercises
17.14: Solutions to Additional Exercises

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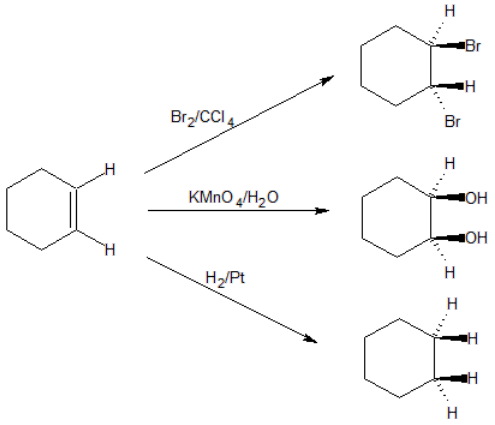
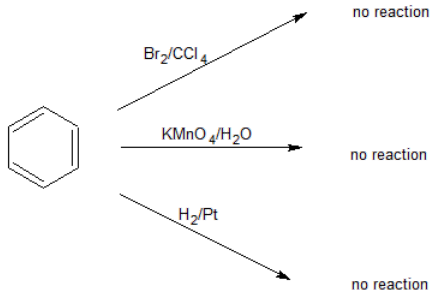
17.1: Electrophilic Aromatic Substitution (EAS)

Benzene and Electrophilic Aromatic Substitution Reactions

While it took chemists many years to determine the structure of benzene and its derivatives, chemists recognized this class of compounds by their distinct aromas and low reactivity compared to isolated alkenes.





With the stability created by the conjugated pi electron system, the lack of chemical reactivity is not surprising. However, over time chemists found ways to catalyze reactions of benzene and its derivatives. With its strong electronic character, benzene is inherently electrophilic. The majority of the reactions for benzene are Electrophilic Aromatic Substitution reactions. One of the benzene hydrogen atoms can be substituted for a different group with electrophilic properties followed by restoration of the stable aromatic ring.

Examples of Electophilic Aromatic Substitution (EAS)

Many 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	$RCO^{(+)}$

General Mechanism

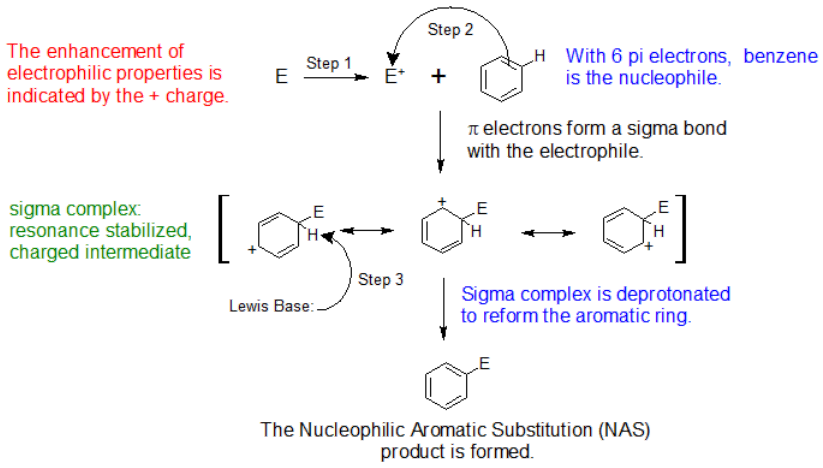
Electrophilic Aromatic Substitution (EAS) reactions include the same three mechanistic steps. Step 1 is needed to create a strong enough Electrophile to create reactivity with the pi electrons of benzene. Because the sigma complex is resonance stabilized, carbocation rearrangement is not a consideration for this intermediate.

Step 1: Formation of a Strong Electrophile

Step 2: Benzene pi electrons form a sigma bond with the Strong Electrophile to create the "sigma complex", a resonance stabilized, charged intermediate

Step 3: Deprotonation of the sigma complex to reform the aromatic ring

The generic mechanism shared by all EAS reactions is shown below.



Activating and Deactivation Groups

As we study the EAS reactions, we will learn that some substituents increase the reactivity of the benzene ring for EAS reactions and are called "activating groups". Other substituents decrease the reactivity of the benzene ring for EAS reactions and are called "deactivating groups". These groups can be recognized by their effects on the stability of the sigma complex.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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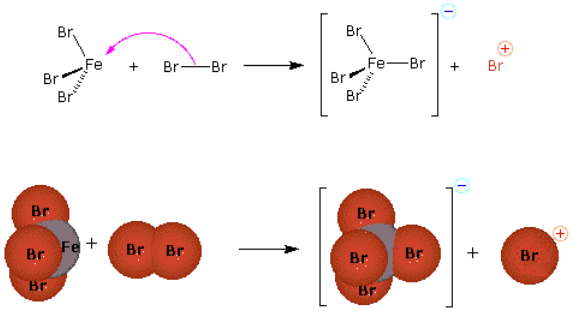
17.2: Halogenation of Benzene (an EAS Reaction)

A Mechanism for Halogenation of Benzene

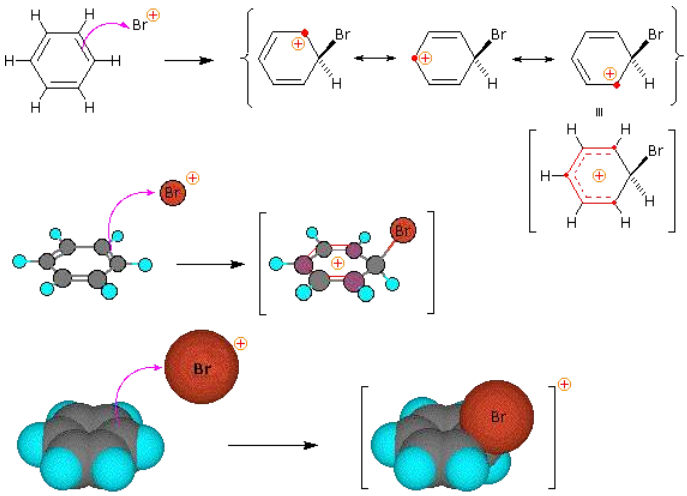
A three-step mechanism is common for many electrophilic aromatic substitution reactions. In the first step, a strong electrophile is created to entice the pi electrons of the aromatic ring to react. In the second, slow or rate-determining step a pair of pi electrons from the benzene form a sigma-bond with the electrophile generating a positively charged sigma complex (**the benzenonium intermediate for halogenation)**. In the third, fast step, a proton is removed from the sigma complex producing a halogenated benzene ring. The steps are illustrated below.

Step 1: Formation of a strong electrophile, in this case an electrophilic bromine cation.

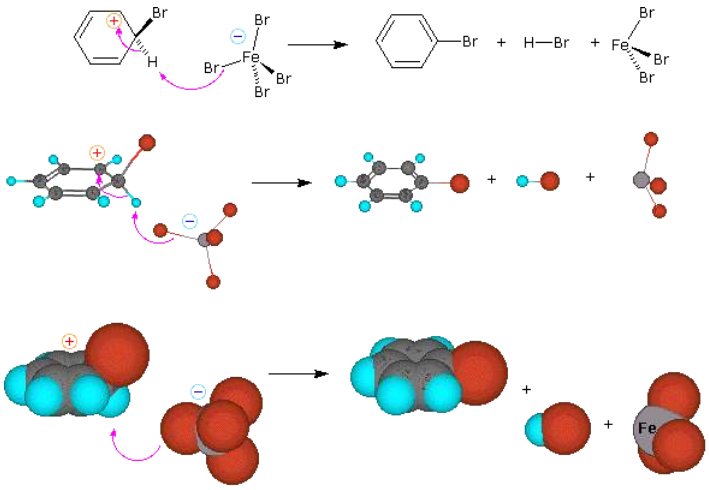


Ferric bromide and other Lewis acids enhance the electrophilic strength of bromine by forming a complex anion, in this case $FeBr_4^{\ominus}$. At the same time, this complexation creates the strongly electrophilic bromine cation, which reacts with nucleophiles.

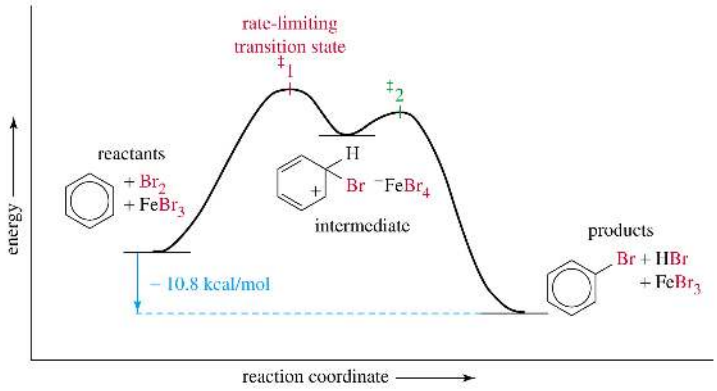
Step 2: Pi electrons of benzene react with the bromine cation to form the sigma comoplex, resonance stabilized benzenonium intermediate. This step is the rate determining step.



Step 3: Deprotonation of the benzenonium intermediate (sigma complex) to restore aromaticity.

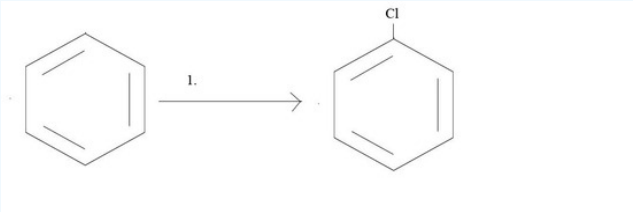


The reaction energy diagram below shows Steps 2 and 3 of the mechanism since these steps involve benzene.

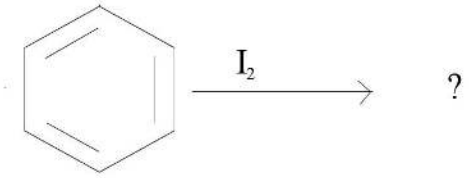


Exercises

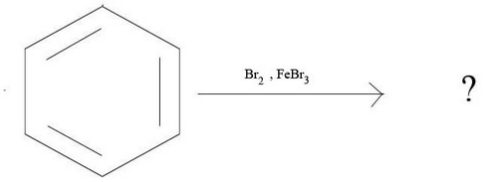
1. What reagents would you need to get the given product?



2. What product would result from the given reagents?



3. What is the major product given the reagents below?



4. Draw the formatin of Cl^+ from $AlCl_3$ and Cl_2

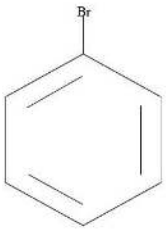
5. Draw the mechanism of the reaction between Cl^+ and a benzene.

Answer

1. Cl_2 and $AlCl_3$ or Cl_2 and $FeCl_3$

2. No Reaction

3.



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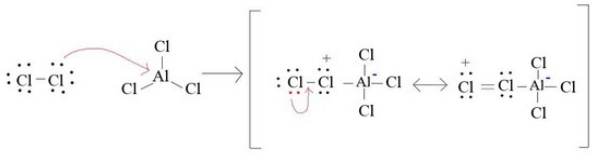

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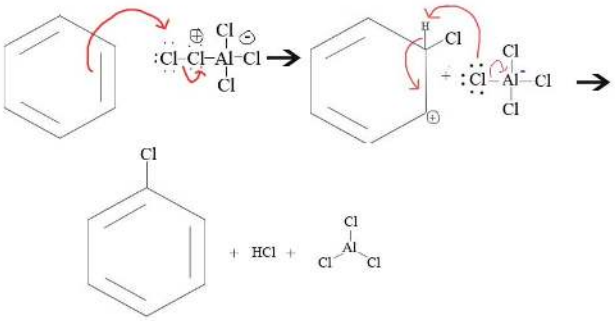

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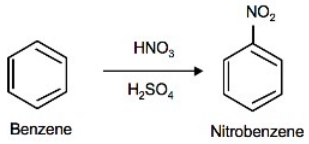
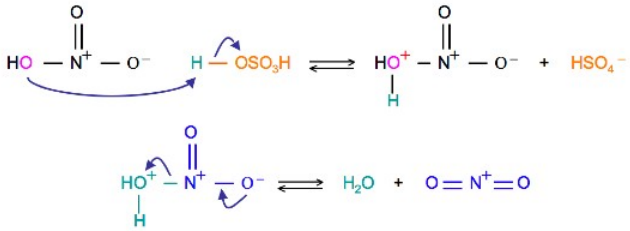
17.3: Nitration of Benzene (an EAS Reaction)

Nitration of Benzene

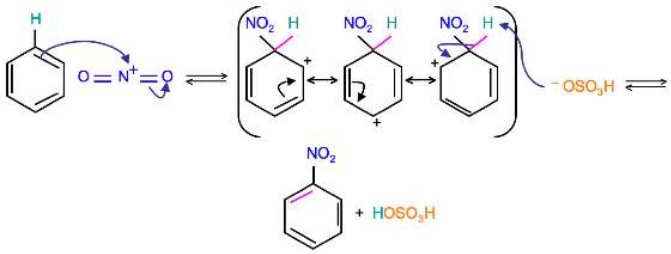
Sulfuric acid catalyzes the nitration of benzene. It is important to note the chemical formula for the nitrate group bonded to benzene is -NO_2. The chemical formula and name are assigned from an organic chemistry perspective which does not align with the inorganic perspective.



Step 1: Nitric acid (HNO_3) is protonated by sulfuric acid which causes the loss of a water molecule and formation of a nitronium ion, a strong electrophile.



Steps 2 and 3: Two pi electrons from benzene form a sigma bond with the nitronium ion to create the sigma complex. Bisulfate deprotonates the sigma complex to restore the aromatic ring as shown below.



Exercise

6. Draw an energy diagram for the nitration of benzene. Draw the intermediates, starting materials, and products. Label the transition states.

Answer

6.

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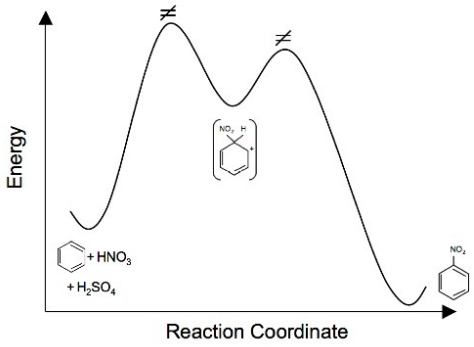

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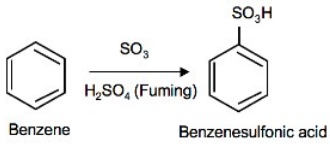
17.4: Sulfonation of Benzene (an EAS Reaction)

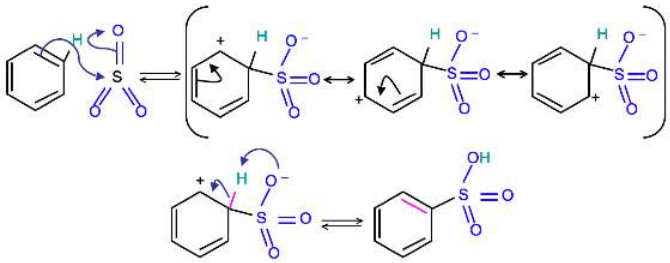
Sulfonation of Benzene

Sulfonation is a reversible reaction that produces benzenesulfonic acid by adding sulfur trioxide and fuming sulfuric acid. It is important to note that the chemical formula of the sulfonic group is $-SO_3H$. The reaction is reversed by adding hot aqueous acid to benzenesulfonic acid to produce benzene.



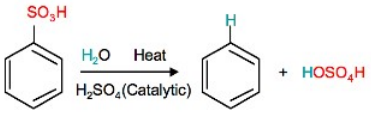
Mechanism

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 reacts with the sulfur of sulfur trixoxide to form the sigma complex. A subsequent proton transfer occurs to produce benzenesulfonic acid. All three steps are shown together in the mechanism below.

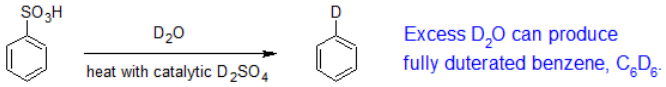


Reverse Sulfonation

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.

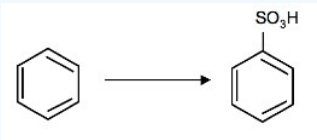


The reversibility of the sulfonation reaction creates an opportunity to prepare deuterated benzene. Isotopically labeled reagents can be useful in determining reaction mechanisms since the C-D bond is stronger than the C-H bond.



Exercise

7. What is/are the required reagent(s)for the following reaction:



8. What is the product of the following reaction:

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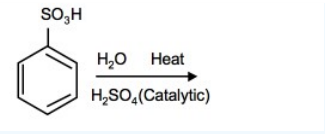


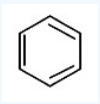
9. Why is it important that the nitration of benzene by nitric acid occurs in sulfuric acid?

10. Write a detailed mechanism for the sulfonation of benzene, including all resonance forms.

Answer

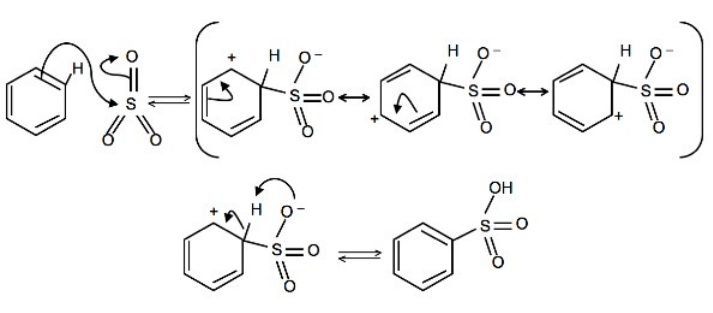
7. SO_3 and H_2SO_4 (fuming)

8.



9. 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.

10.



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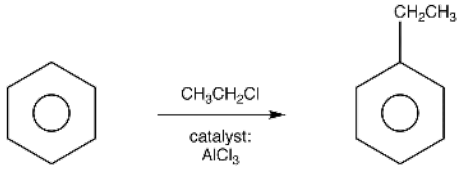
17.5: Alkylation and Acylation of Benzene - The Friedel-Crafts EAS Reactions

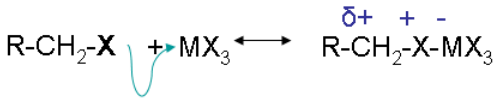
Friedel-Crafts Alkylation

The Fridedel-Crafts Alkylation reaction froms alkyl benzenes from alkyl halides. The usefulness of this reaction is limited, because it can be difficult to stop the reaction at a single alkylation. Additionally, a carbocation intermediate is produced in Step 1 which brings the potential for carbocation rearrangements (ominous theme music).

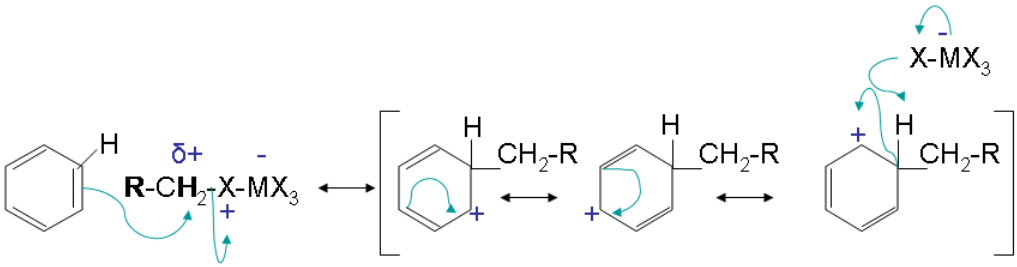


The mechanism takes place as follows:

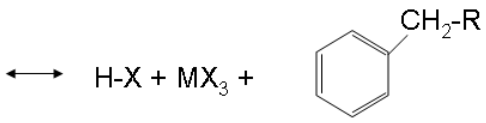
Step 1: A carbocation is created to form the electrophile. This steps activates the haloalkane. Secondary and tertiary halides only form the free carbocation in this step.



Step 2: The pi electrons from benzene react with the electrophile to form the resonance stabilized alkylbenzenium ion.



Step 3: Any Lewis Base reacts picks up the hydrogen from the allkylbenzenium ion to reform the aromatic ring.

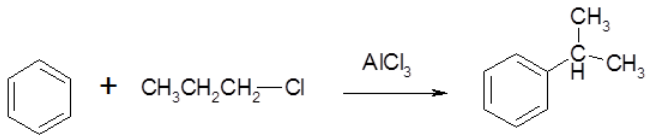


The finish step shown above is the two products.

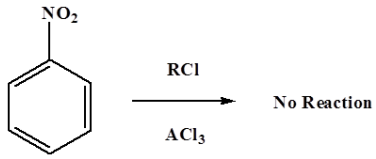
The reactivity of haloalkanes increases as you move up the periodic table and increase polarity. This means that an RF haloalkane is most reactive followed by RCl then RBr and finally RI. This means that the Lewis acids used as catalysts in Friedel-Crafts Alkylation reactions tend have similar halogen 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.



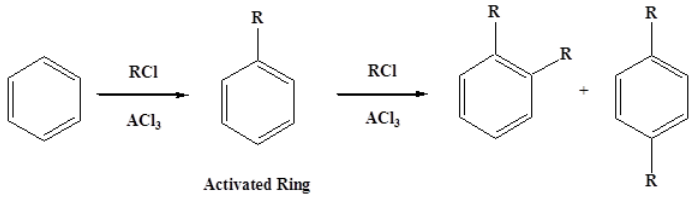
Also, the reaction will only work if the ring you are adding a substituent to is not deactivated. Friedel-Crafts fails when used with compounds such as nitrobenzene and other strong deactivating systems.



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.

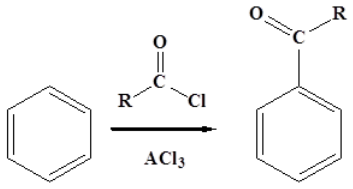
The positive charge strongly deactivates the benzene ring

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

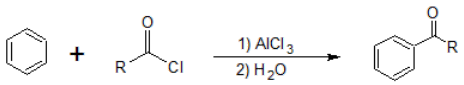
This problem does not occur during Friedel-Crafts Acylation because an acyl group is deactivating. The prevents further acylations.



Dectivated Ring

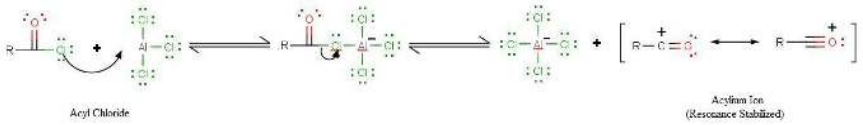
Friedel-Crafts Acylation

There is an additional reaction step for Fridel-Crafts Acylation. The acyl group of the product complexes with the aluminum chloride. Water is added to isolate the acyl benzene final product.

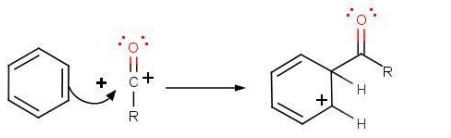


1st Reaction

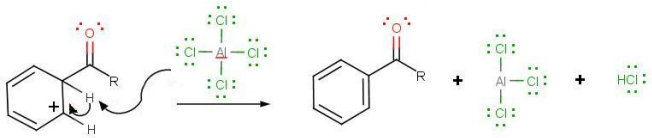
Mechanism Step 1: Acylium ion formation



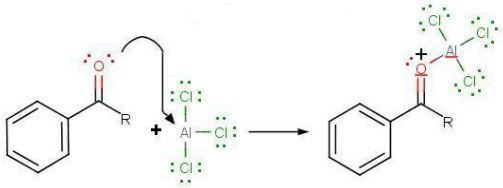
Mechanism Step 2: Pi electrons of benzene react with the acylium ion to form the sigma complex, resonance stabilized acylbenzenium intermediate:



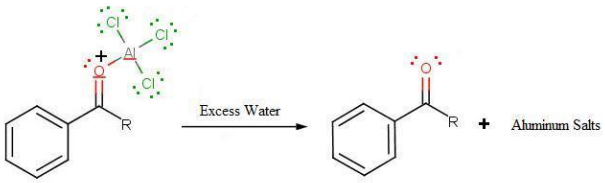
Mechanism Step 3: Deprotonation of the sigma comlex to restore aromaticity.



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. The product forms a complex with aluminum chloride as shown below.



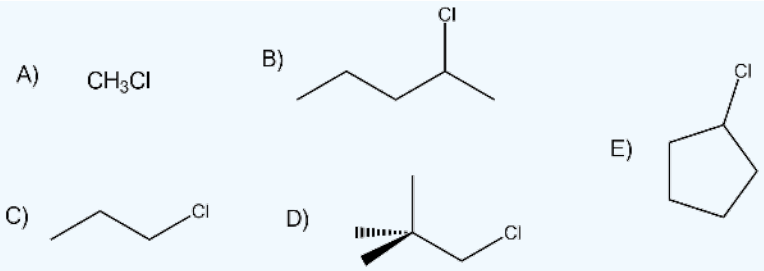
2nd Reaction: Water is added to liberate the final product as the acylbenzene:



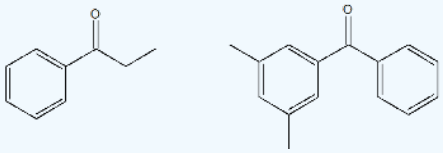
Friedel-Crafts Acylations offer several synthetic advantages over Friedel-Crafts Alkylation. These advantages provide greater control over the production of reaction products. The acylium ion is stabilized by resonance, so no carbocation rearrangement occurs. Additionally, acyl groups are deactivating with for EAS reactions, so the product does not undergo further reactions. However, Friedel-Crafts Acylations do not work with nitrobenzenes or other deactivated benzene rings. The concept of deactivated will be more fully explored in the next two sections of this chapter.

Exercise

11. Which of the following will NOT undergo a rearrangement in a Friedel-Crafts reaction?



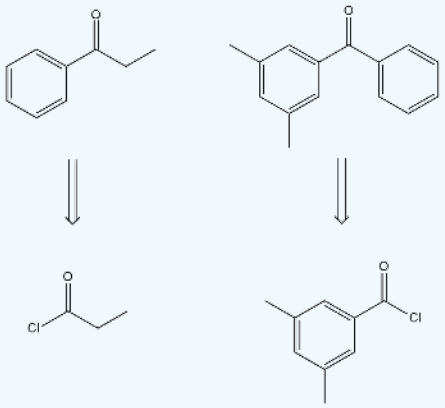
12. Suggest an acyl chloride that was used to make the following compounds:



Answer

11. A, B, and E will not undergo a rearrangement.

12.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
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17.6: Substituent Effects on the EAS Reaction

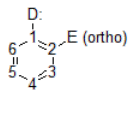
Important Note:

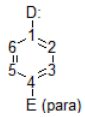
Recognizing substituents as Electron Donating or Withdrawing is a useful skill for evaluating reaction mechanisms. For Electrophilic Aromatic Substitution (EAS) reactions, the rate determining step is the formation of a positively charged sigma complex. In future reactions, the intermediate may have a negative charge. While the electron donating and withdrawing properties of a substituent are inherent within the substituent, their effect on the stability of an intermediate and the reaction rate depends on the charge of the intermediate.

Substituents and their Directing Effects in EAS Reactions

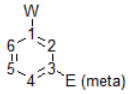
Electron donating groups (D) direct the reaction to the ortho- or para-position, which means the electrophile substitutes for the hydrogen on carbon 2 or carbon 4 relative to the donating group. The withdrawing group directs the reaction to the meta position, which means the electrophile substitutes for the hydrogen on carbon 3 relative to the withdrawing group. The halogens are an exception to this pattern. The halogens are a deactivating group that direct ortho or para substitution.

Donating groups direct the Electrophile (E) to the ortho- and para-positions.





Withdrawing groups direct the Electrophile (E) to the meta-postion.



Examples of electron donating groups in the relative order from the most activating group to the least activating:

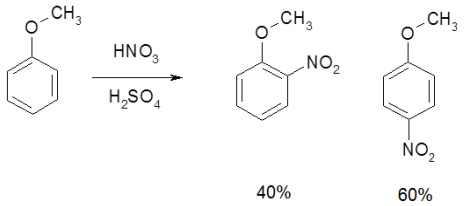
$-NH_2$, $-NR_2$ > -OH, -OR> -NHCOR> $-CH_3$ and other alkyl groups with R as alkyl groups (C_nH_{2n+1})

Examples of electron withdraing groups in the relative order from the most deactivating to the least deactivating:

$-NO_2$, $-CF_3$> -COR, -CN, $-CO_2R$, $-SO_3H$ > Halogens with R as alkyl groups (C_nH_{2n+1})

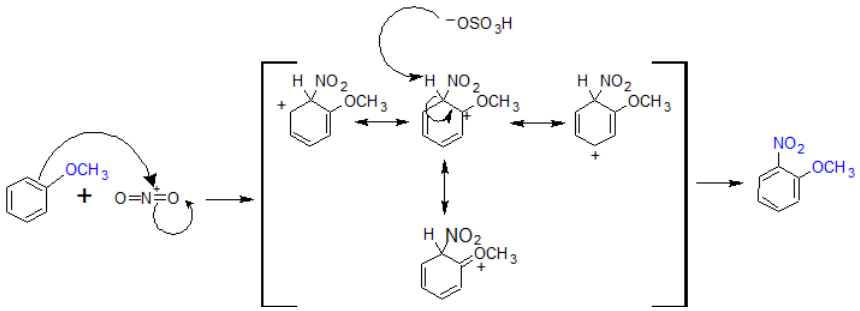
ortho-, para-Directors via Resonance

Groups that donate electrons through resonance are ortho-, para-directors for EAS reactions. Methoxybenzene (anisole) will be used to demonstrate the ortho-, para-direction of substituents that stabilize the sigma complex through resonance. The nitronium ion ($O=N^+=O$) will be used to represent the Electrophile (E+).

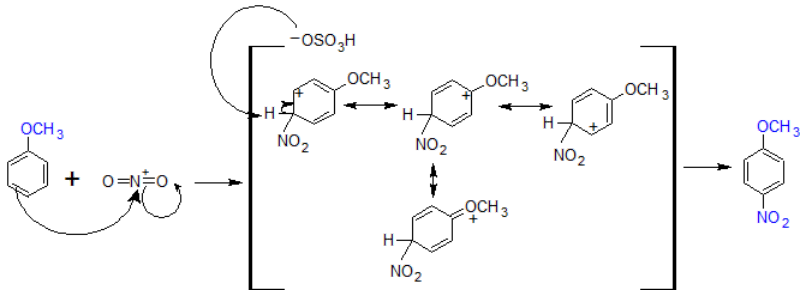


The ortho- and para-directed mechanisms for the nitration of anisole are shown below. When the nitro group adds at the ortho or para position, the stability of the sigma complex is increased by the presence of a fourth resonance form . The greater the stability of the sigma complex causes the ortho and para products for form faster than meta. Generally, the para-product is favored over the ortho-product because of steric effects even though there are two ortho- positions.

Mechanism for ortho-directed product formation

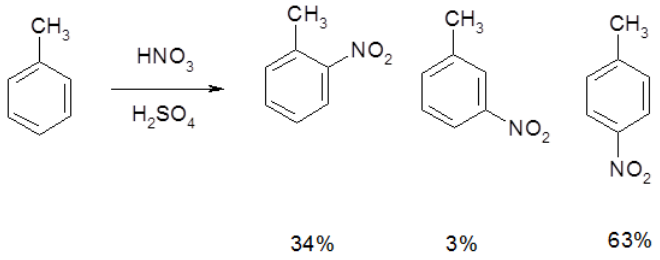


Mechanism for para-directed product formation



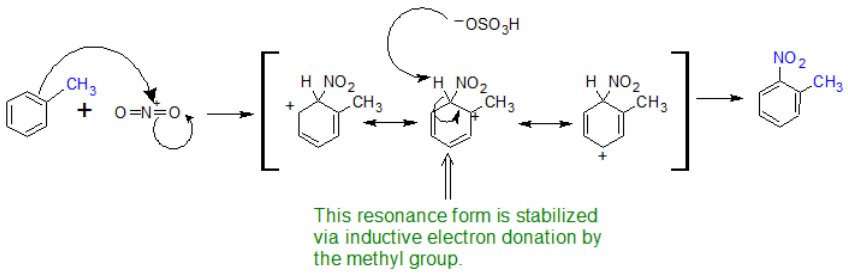
ortho-, para-Directors via Induction

Alkyl groups are ortho-, para-directors for EAS reactions. Toluene will be used to demonstrate the ortho-, para-direction of substituents that stabilize the sigma complex through induction. The nitronium ion ($O=N^+=O$) will be used to represent the Electrophile (E^+). Since the inductive effect is weaker than resonance, we can see that a small percentage of the meta product is also isolated.

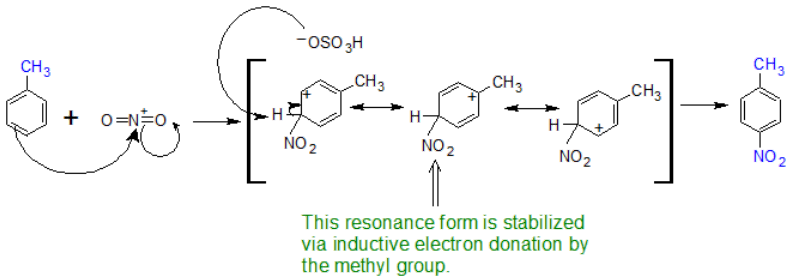


Looking at the stability of the resonance structures of the sigma complex in the reaction mechanism for nitration of toluene explains why the ortho- and para- substitutions are the major products. When the nitro group adds at the ortho or para position, the methyl group stabilizes the transition state through induction electron donation which favors the formation of the ortho- and para-products. As seen with the resonance directed products, the para product is favored because of steric effects even though there are two ortho- positions.

Mechanism for ortho-directed product formation



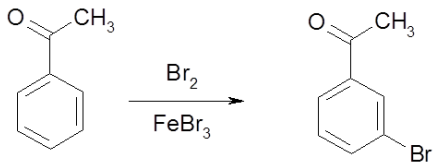
Mechanism for para-directed product formation



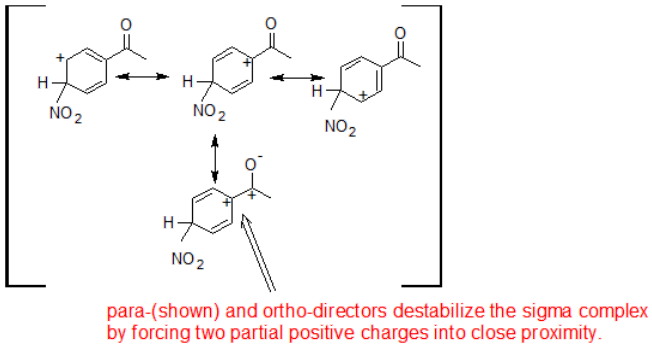
meta Directors - the Electron Withdrawing Groups

Electron withdrawing groups destabilize the sigma complex and deactivate benzene rings to EAS reactions. For electron withdrawing groups, all of the sigma complexes are destabilized. The meta-position is the least destabilized and produces the largest percentage of the reaction products.

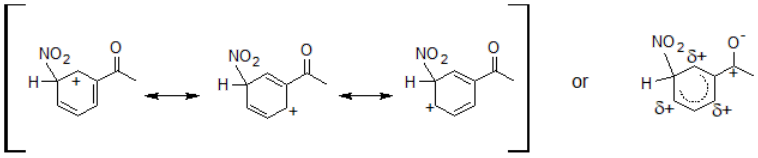
Acetophenone will be used to demonstrate the reactivity of meta-directors using the sigma complexes below. Acyl groups are resonance deactivators.



Ortho and para reactions produce a resonance structure that places the arenium cation next to an additional cation at the carbonyl carbon. This close proximity of partial positive charges destabilizes the sigma complex and slows down ortho and para reaction.



By default the meta product forms faster because the destabilizing effects are reduced through greater physical separation of the partial positive charges.



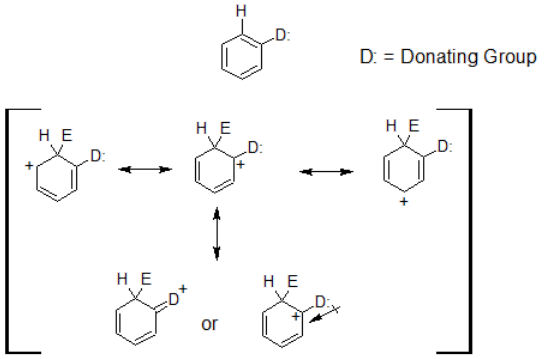
Substituents and Electrophilic Aromatic Substitution (EAS) Reaction Rates

Since sigma complex formation is the rate determining step of EAS reactions, benzene derivatives are divided into two groups based on how the substituent stabilizes or destabilizes the positively charged sigma complex. The EAS reaction of a substituted ring with an activating group is faster than benzene. On the other hand, a substituted ring with a deactivated group is slower than

benzene. Activating groups speed up the EAS reaction by either resonance or inductive electron donation (typically R groups). For resonance, unpaired electrons can be donated to stabilize the positive charge of the sigma complex in the transition state. Stabilizing the intermediate, speeds up the reaction by lowering the activating energy. Inductive electron donation by R groups is an analogous, yet weaker effect than resonance. Inductive electron donation helps to stabilize the sigma complex and speed up (activate) the reaction. Deactivating groups withdraw the electrons away from the carbocation of the sigma complex causing destabilization and increasing the activation energy which slows down (deactivates) the reaction.

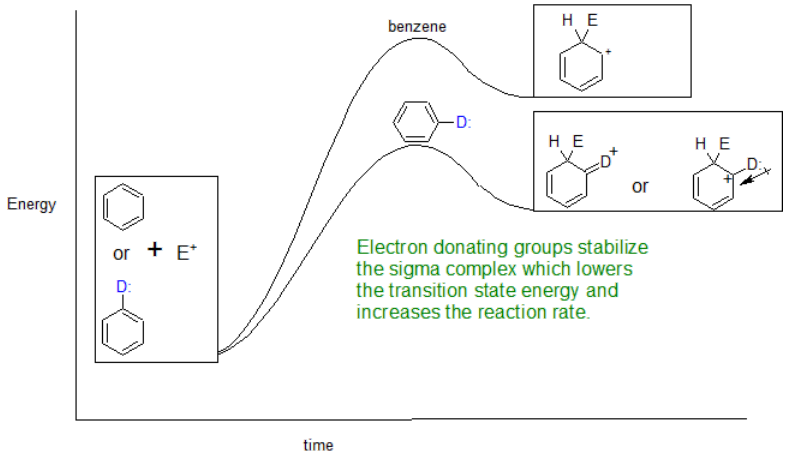
- **Activated rings**: the substituents on the ring **donate** electrons and increase EAS reaction rates
  - Examples of electron donating groups in the relative order from the most activating group to the least activating:

    $-NH_2$, $-NR_2$ > -OH, -OR> -NHCOR> $-CH_3$ and other alkyl groups with R as alkyl groups (C_nH_{2n+1})



The electron donating group (D:) activates the ring with an additional resonance form or inductive donation effect to stabilize the + charge of the sigma complex.

The reaction energy diagram illustrating the substituent effect of electron donating groups (D:) on EAS reaction rates is shown below.

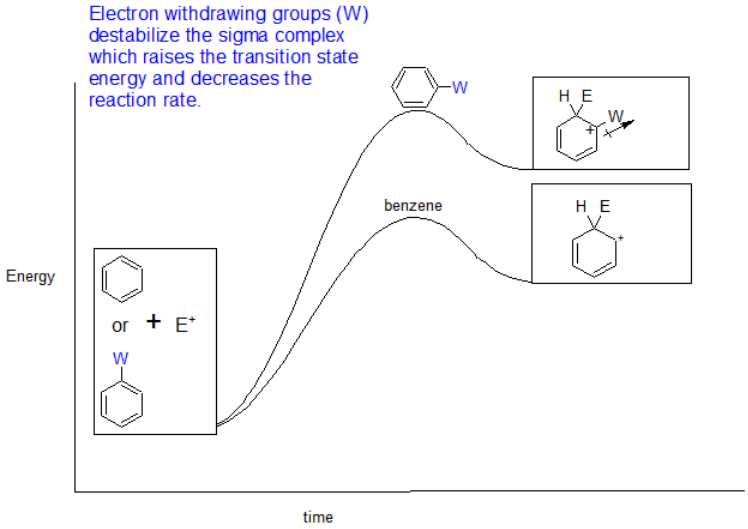


- **Deactivated rings**: the substituents on the ring **withdraw** electrons and decrease EAS reaction rates
  - Examples of electron withdraing groups in the relative order from the most deactivating to the least deactivating:

    $-NO_2$, $-CF_3$> -COR, -CN, $-CO_2R$, $-SO_3H$ > Halogens with R as alkyl groups (C_nH_{2n+1})

The electron withdrawing group (W) deactivates the ring by destabilizing the sigma complex. Note the proximity of the + and δ+ charges.

The reaction energy diagram illustrating the substituent effect of electron withdrawing groups (W) on EAS reaction rate is shown below.



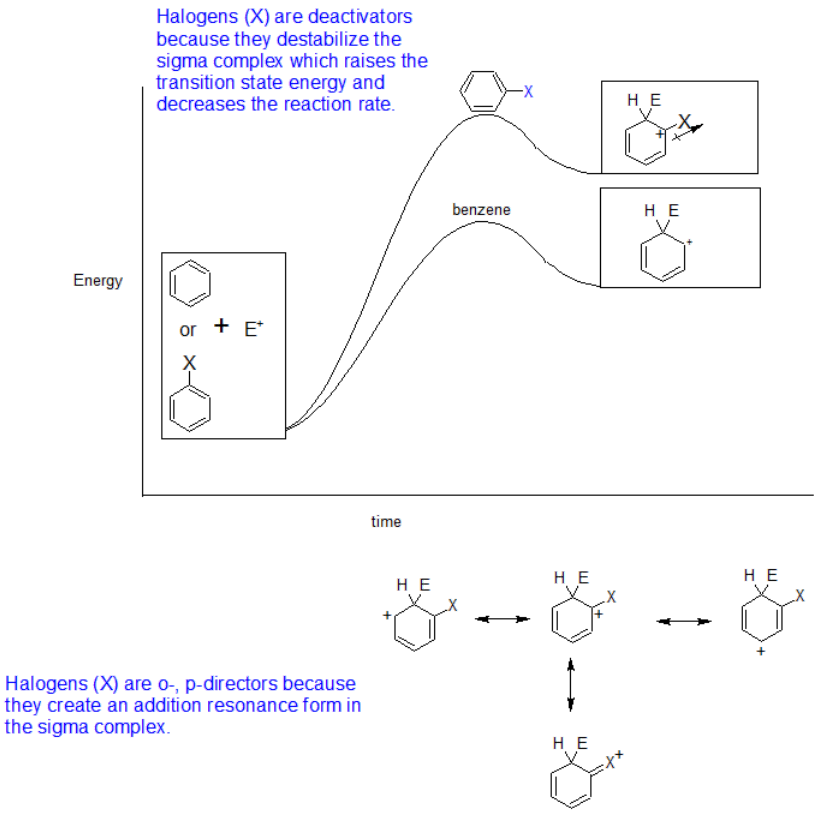
- **The Halogen Paradox: Deactivators that are ortho, para-directors**

Halogens deactivate rings to subsequent EAS reactions. 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.

$$F > Cl > Br > I$$

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 electronegatvie halogen is the least reactive ring (more deactivating substituent). The size of the halogen also effects the reactivity of the benzene ring - as the size of the halogen increases, the reactivity of the ring decreases.

However, the lone pair electrons on the halogen atoms are still available for resonance delocalization in the sigma complex causing ortho-, para-direction of the electrophile. The reaction energy diagram below resolves these contradictory aspects of EAS reactions of halogenated benzene derivatives.



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.

Outside Links

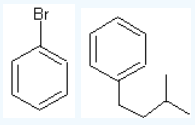
- http://en.Wikipedia.org/wiki/Activating_group
- http://en.Wikipedia.org/wiki/Deactivating_group
- http://www.columbia.edu/itc/chemistry/c3045/client_edit/ppt/PDF/12_12_14.pdf

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

Exercises

13. Predict the direction of the electrophile substition on these rings:



14. Which nitration product is going to form faster?

nitration of aniline or nitration of nitrobenzene?

15. Predict the product of the following two sulfonation reactions:

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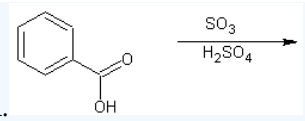
A. 

16. Classify these two groups as activating or deactivating groups:

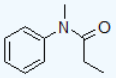
A. alcohol

B. ester

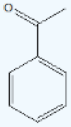
17. By which effect does trichloride effect a monosubstituted ring?

18. Trichloromethylbenzene has a strong concentration of electrons at the methyl substituent. Comparing this compound with toluene, which is more reactive toward electrophilic substitution?

19. The following compound is less reactive towards electrophilic substitution than aniline? Explain.



20. Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para reactions.

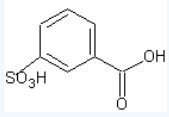


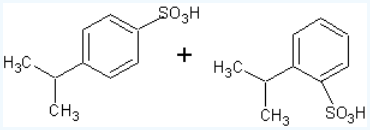
Answer

13. The first substitution is going to be ortho and/or para substitution since we have a halogen subtituent. The second substition is going to be ortho and/or para substitution also since we have an alkyl substituent.

14. 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 substiuent. As described above $NH_2$is an activating group which speeds up the reaction and NO_2 is deactivating group that slows down the reaction.

15.

A. the product is 

B. the product is 

16.

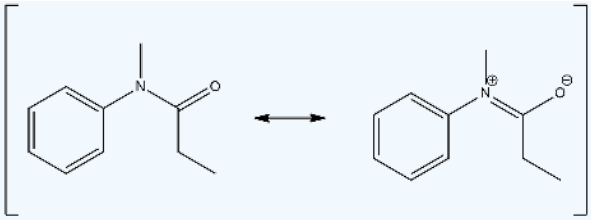
A. alcohol is an activating group.

B. ester is a deactivating group.

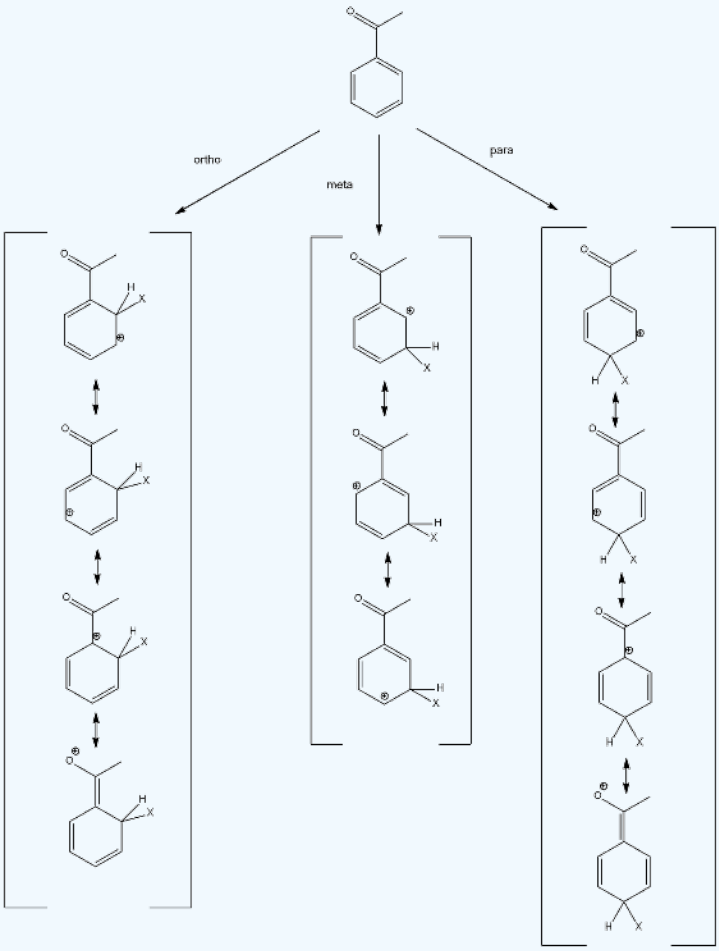
17. Trichloride deactivate a monosubstitued ring by inductive effect.

18. The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

19. As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



20.



16.6 Trisubstituted Ben

Exercises

Questions

Q16.5.1

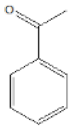
(Trichlorometyl)benzene has a strong concentration of electrons at the methyl substituent. Comparing this toluene, which is more reactive toward electrophilic substitution?

Q16.5.2

The following compound is less reactive towards electrophilic substitution than aniline? Explain.

Q16.5.3

Consider the intermediates of the following molecule during an electrophilic substitution. Draw resonance structures for ortho, meta, and para attacks.



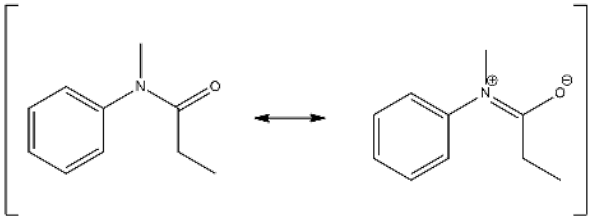
Solutions

S16.5.1

The trichloromethyl group is an electron donor into the benzene ring, therefore making it more stable and therefore more reactive compared to electrophilic substitution.

S16.5.2

As seen in resonance the electron density is also localized off of the ring, thereby deactivating it compared to aniline.



S16.5.3

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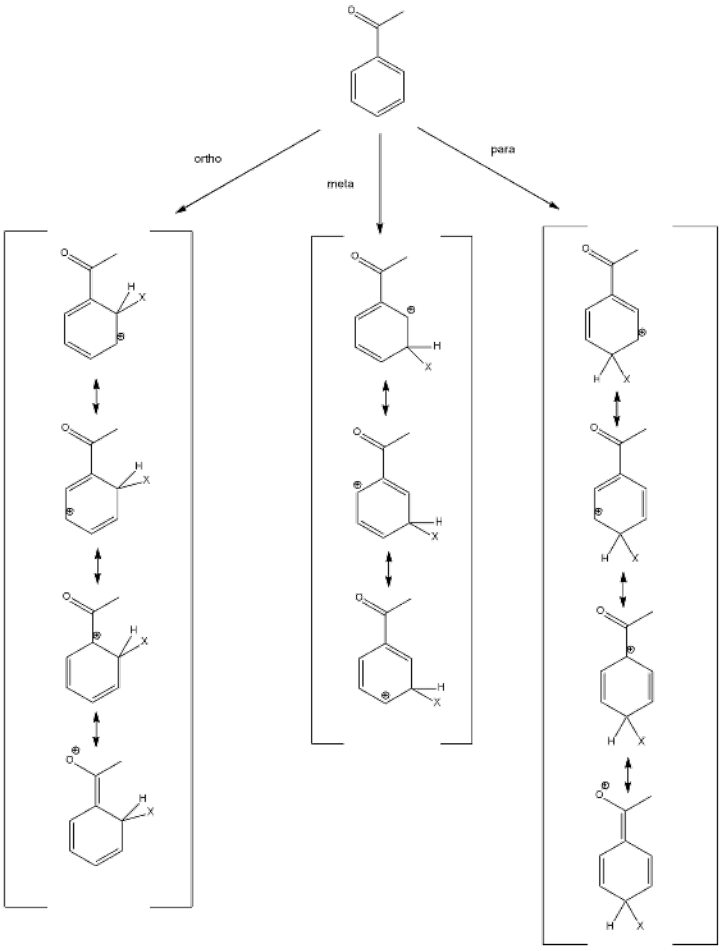

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Lana Alawwad (UCD)

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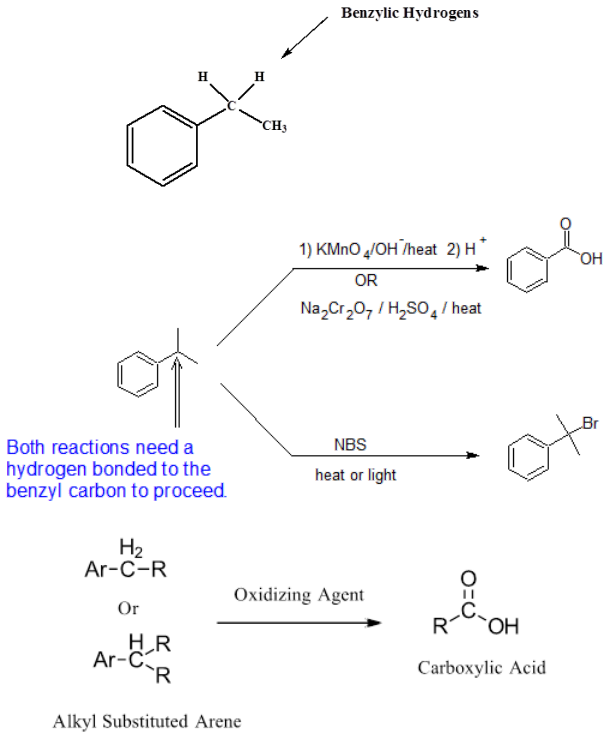
17.7: Side-Chain Reactions of Benzene Derivatives

Oxidation of Alkyl Side Chains

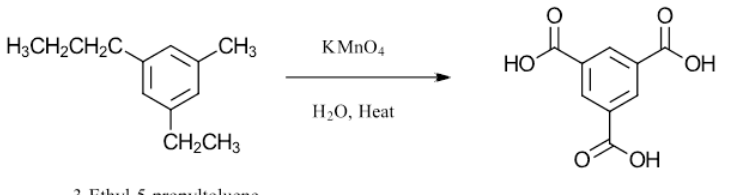
There is another reaction which occurs at the atom directly attached to an aromatic ring. This is known as "side chain oxidation." When a compound which has an alkyl group directly attached to an aryl group is treated with a strong oxidizing agent like potassium permanganate ($KMnO_4$) or Jones Reagent (CrO_3/H_2SO_4), the benzylic carbon is oxidized to a carboxylic acid group which remains attached to the aryl group. Any other carbon-carbon bonds in the alkyl group are broken. For the oxidation reaction, the number of carbon atoms in the alkyl side chain does not matter, However, the benzylic carbon must have at least one benzylic hydrogen attached. Thus, tertiary carbons attached to an aromatic ring are not affected by these reactions. It should be noted that during this reaction an ortho/para directing alkyl group is converted to a meta directing carboxylic.

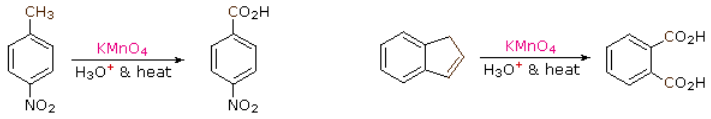


Add tertiary no reaction

Two other examples of this reaction are given below, and illustrate its usefulness in preparing substituted benzoic acids.

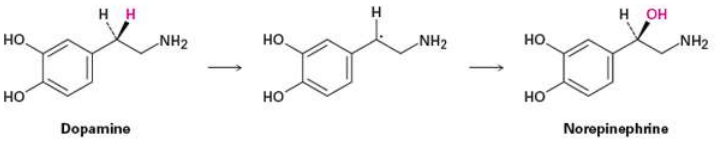
Add straing chain and tertirary.

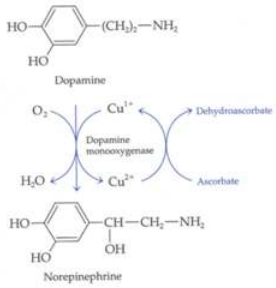




The mechanism of this reaction is obscure, but the fact that it specifically requires that there be a benzylic C-H bond suggests that breaking this bond is essential. Any intermediate that might be formed by breaking this bond will be stabilized by resonance with the aryl group, which provides an explanation for the specificity of attack at the benzylic position. Such reactions also occur in a biological context. Enzymes oxidize alkyl side chains on aromatic rings as part of making such compounds soluble enough to be eliminated.

Analogous side-chain oxidations occur in various biosynthetic pathways. The neurotransmitter norepinephrine, for instance, is biosynthesized from dopamine by a benzylic hydroxylation reaction. The process is catalyzed by the copper-containing enzyme dopamine -monooxygenase and occurs by a radical mechanism. A copper–oxygen species in the enzyme first abstracts the *pro*-R benzylic hydrogen to give a radical, and a hydroxyl is then transferred from copper to carbon.





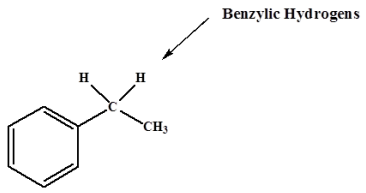
Bromination of the Benzylic Carbon

The bromination reaction is the N-bromosuccinamide (NBS) radical, substitution reaction previously studied. As with the oxidation reaction, one benzylic hydrogen is needed so that it can be substituted with bromine. Examples of both reactions are shown below.

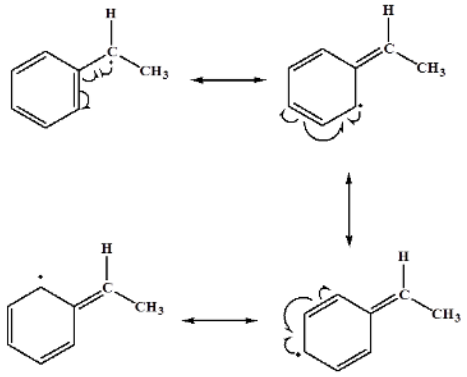
The brominating reagent, N-bromosuccinimide (NBS), has proven useful for achieving allylic or benzylic substitution in CCl_4 solution at temperatures below its boiling point (77 ºC). One such application is shown in the second equation. the allylic bromination with NBS is analagous to the alkane halogenation reaction (Section 10.3) since it also occurs as a radical chain reaction. The NBS serves as the source for the bromine, which is used in the initiation step to create a bromine radical that then abstracts a proton from the allylic position in the propagation step. The radical created then reacts with the NBS to to become bromiated and the cycle continues until it is terminated.

The predominance of allylic substitution over other positions comes down to bond dissociation energies. The relative bond dissociation energies are shown in the table at the top of this section. The C-H bond that we are focusing on as the point of difference for each of the energies shows that the allylic C-H bond has a strength of about 88 kcal/mol. This means that the allylic radical created is more stable than a typical alkyl radical with the same substitution by about 9 kcal/mol. Therefore, this radical is the most likely one to form and thus react.

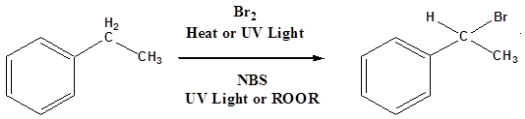
The benzylic C-H bonds weaker than most sp^3 hybridized C-H. This is because the radical formed from homolysis is resonance stabilized.



Resonance stabilization of the benzylic radical

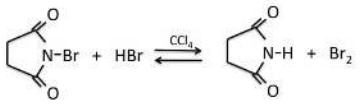


Because of the weak C-H bonds, benzylic hydrogens can form benzylic halides under radical conditions.



NBS as a Bromine Source

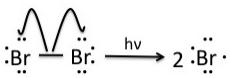
NBS (N-bromosuccinimide) is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts with trace amounts of HBr to produce a low enough concentration of bromine to facilitate the allylic bromination reaction.



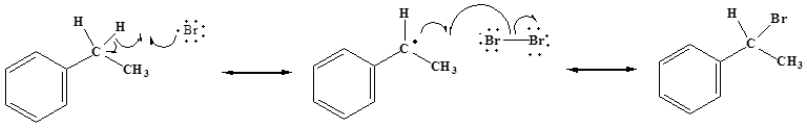
Allylic Bromination Mechanism

Step 1: Initiation

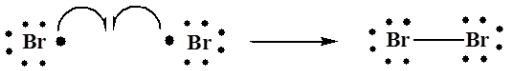
Once the pre-initiation step involving NBS produces small quantities of Br_2, the bromine molecules are homolytically cleaved by light to produce bromine radicals.



Step 2 and 3: Propagation

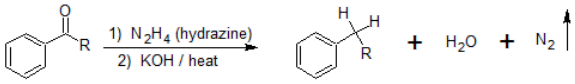


Step 4: Termination



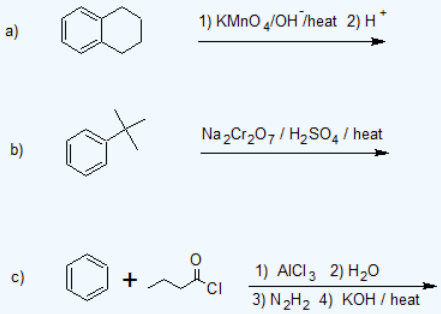
Acyl Side Chain Reductions

Since there are several limitations to the Friedel-Crafts alkylation that are not observed with the Friedel-Crafts acylation, reduction of the acyl side chain to an alkyl side chain is a useful reaction for multiple step synthesis. The Wolff-Kishner reaction reduces the carbon groups (aldehydes and ketones) to alkanes and is not limited to acyl groups bonded to benzene rings. This acyl reduction reaction is also useful because acyl groups are deactivating, meta-directors, and alkyl groups are activating, ortho-, para-directors which adds flexibility to multiple step synthesis strategies.



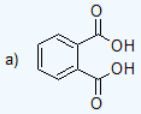
Exercise

21. Draw the bond-line structures for the product(s) of the following reactions.

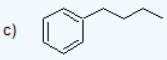


Answer

21.



b) No reaction because there are no benzylic hydrogens.



This compond cannot be synthesized by
F-C Alkylation because of carbocation rearrangment.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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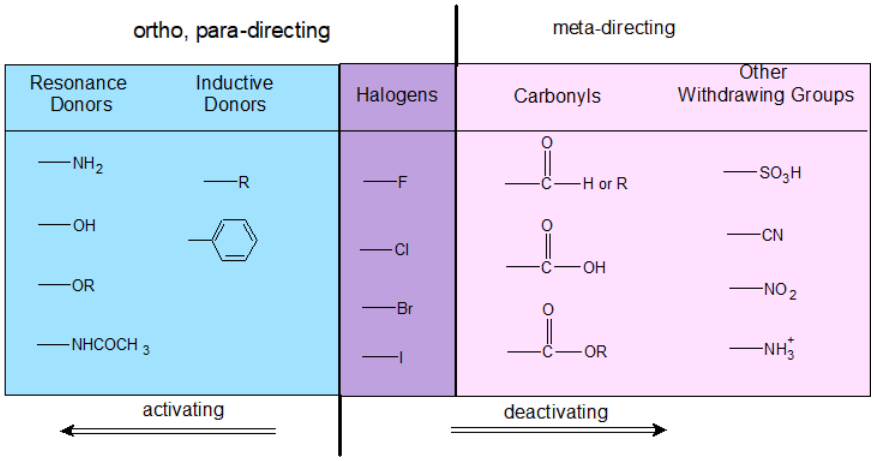
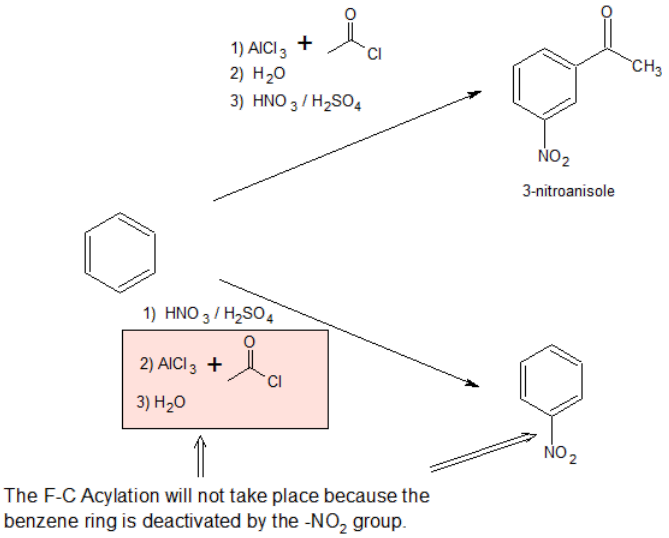
17.8: Synthetic Strategies for Di-substituted Benzenes

Synthetic Considerations

To develop multiple step syntheses for di-substituted benzene derivatives, the regiochemistry of the substituents will determine the order of the reactions. The directing effects of the benzene substituents are summarized below.

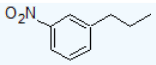


The limitations of the Friedel-Crafts reactions must also be considered. Friedel-Crafts alkylation and acylation reactions can only occur on benzene rings or benzene rings with ortho-, para-directors (activated rings or rings with halogens). Even though both acyl and nitro groups are meta-directors, benzene would need to be acylated before it is nitrated. To synthesize 3-nitroanisole [1-(3-nitrophenyl)ethan-1-one], the top reaction sequence is needed. The bottom reaction sequence will not produce the desired product as shown in the two synthetic pathways below.

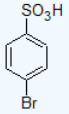


Exercise

22. Starting with benzene and using any synthetic reagents, propose a multiple step synthesis for each of the following compounds.

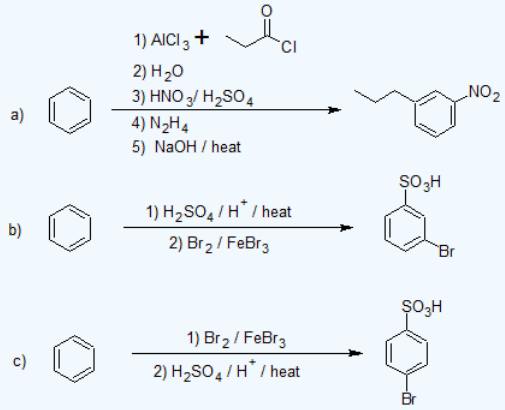
a) 

b)

c) 

Answer

22.



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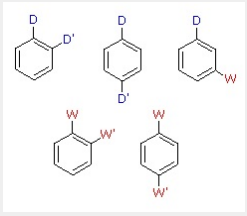
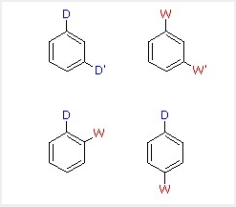
17.9: Trisubstituted Benzenes - Effects of Multiple Substituents

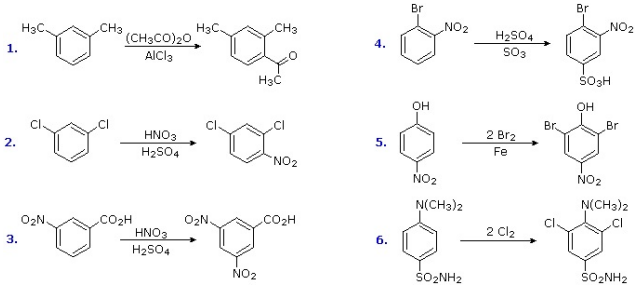
Orientational Interaction of Substituents

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

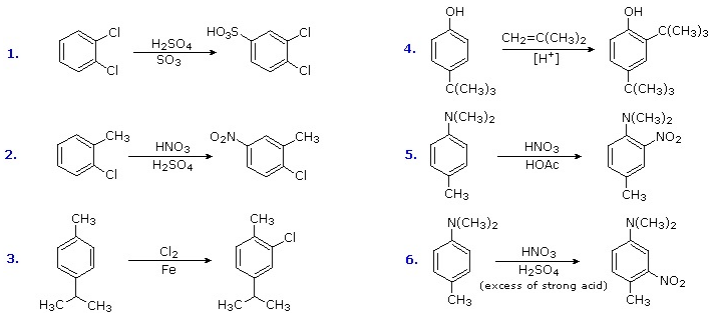
The products from substitution reactions of compounds having a reinforcing orientation of substituents are easier to predict than those having antagonistic substituents. For example, the six equations shown below are all examples of reinforcing or cooperative directing effects operating in the expected 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 six.

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.

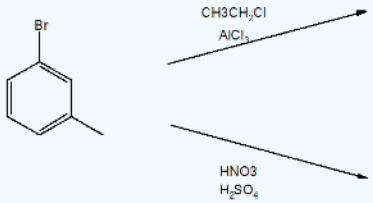


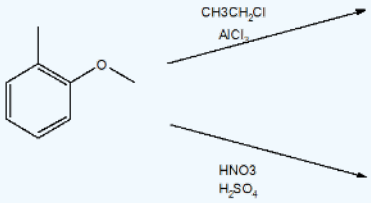
In a tertiary (3°) alcohol, the carbon atom holding the -OH group is attached directly to three alkyl groups, which may be any combination of same or different. Examples:

2-methylpropan-2-ol 2-methylbutan-2-ol

Exercise

23. Predict the products of the following reactions:





Answer

23.

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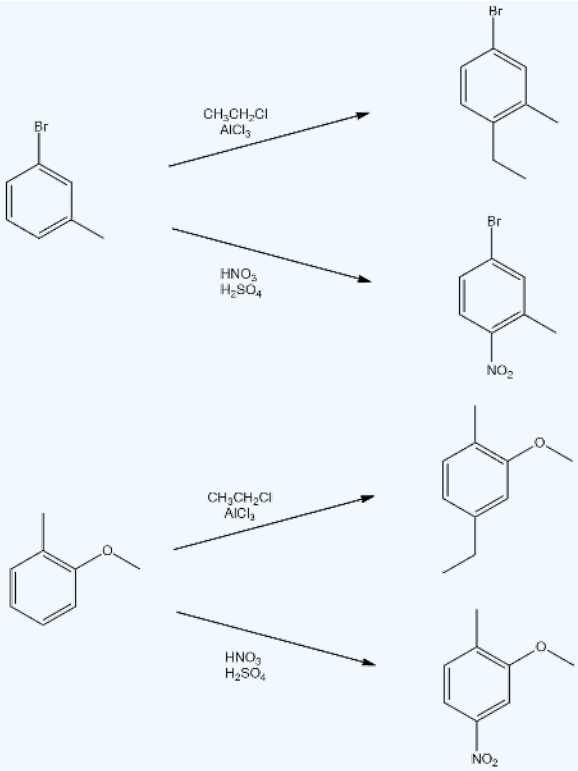

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17.10: Nucleophilic Aromatic Substitution - The Addition-Elimantion Mechanism

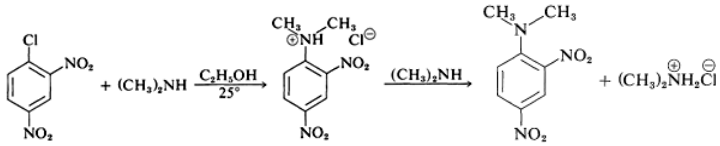
A Nucleophilic Aromatic Displacement Reactions of Aryl Halides

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 reaction with 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 $N0_2$, and
b. when very strongly basic nucleophilic reagents are used.

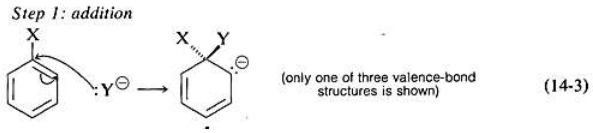
Addition-Elimination Mechanism of Nucleophilic Substitution of Aryl Halides

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:

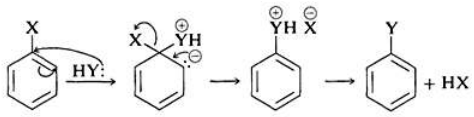


In general, the reactions of activated aryl halides closely resemble the S_N2-displacement reactions of aliphatic halides. The same nucleophilic reagents are effective (e.g., CH_3O^-, HO^-, and RNH_2); the reactions are second order overall (first order in halide and first order in nucleophile); and for a given halide the stronger the nucleophile, 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 that are closely analogous to those described for alkenyl and alkynyl halides. The first step involves the nucleophile $Y:^-$ reacting with the carbon bearing the halogen substituent to form an intermediate carbanion (Equation 14-3). 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).



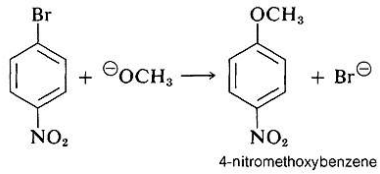
In the second step, loss of an anion, X^- or Y^-, regenerates an aromatic system. If X^- is lost, the overall reaction is nucleophilic displacement of X by Y. In the case of a neutral nucleophilic reagent, Y or HY, the reaction sequence would be the same except for the necessary adjustments in the charge of the intermediate:



Why is this reaction pathway generally unfavorable for the simple aryl halides? The answer is that the anionic intermediate is too high in energy to be formed at any practical rate. Not only has the anion lost the aromatic stabilization of the benzene ring, but its formation results in transfer of negative charge to the ring carbons, which themselves are not very electronegative:

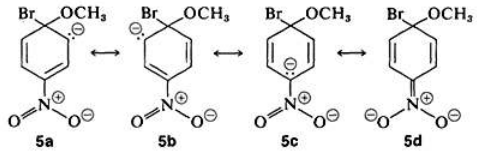
However, when strongly electron-attracting groups are located on the ring at the ortho-para positions, the intermediate anion is stabilized by delocalization of electrons from the ring carbons to more favorable locations on the substituent groups. As an

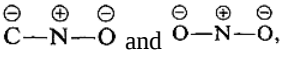
example, consider the displacement of bromine by $^{-}OCH_3$ in the reaction of 4-bromonitrobenzene and methoxide ion:



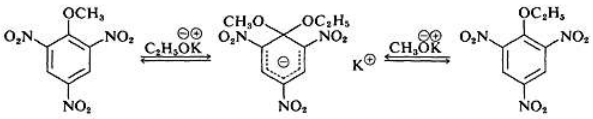
4-nitromethoxybenzene

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 the charge is transferred from the ring carbons to the electronegative oxygen of the nitro substituent:



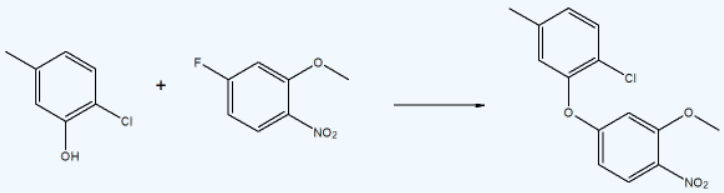
Substituents in the meta positions have much less effect on the reactivity of an aryl halide because delocalization of electrons to the substituent is not possible. No formulas can be written analogous to 5c and 5d in which the negative charges are both on atoms next to positive nitrogen,  and ,

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:



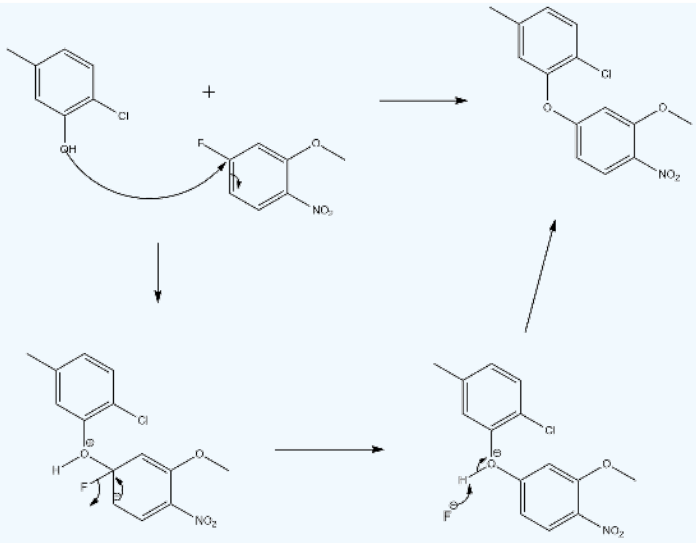
Exercise

24. Propose a mechanism for the following reaction:



Answer

24.



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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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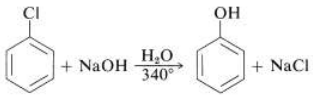
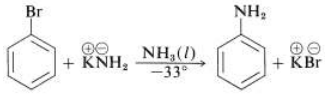
17.11: NAS Reactions - the Elimination-Addition (Benzyne) Mechanism

Elimination-Addition Mechanism of Nucleophilic Aromatic Substitution via Benzyne (Arynes)

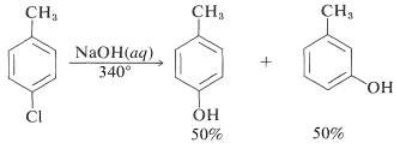
The reactivities of aryl halides, such as the halobenzenes, are exceedingly low toward nucleophilic reagents that normally effect displacements with alkyl halides and activated aryl halides. Substitutions do occur under forcing conditions of either high temperatures or very strong bases. For example, 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):



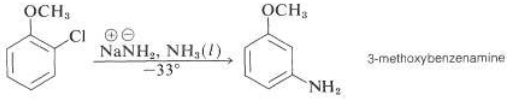
In addition, aryl chlorides, bromides, and iodides can be converted to areneamines **$ArNH_2$** by the conjugate bases of amines. In fact, the reaction of potassium amide with bromobenzene is extremely rapid, even at temperatures as low as **−33°** with liquid ammonia as solvent:



However, displacement reactions of this type differ from the previously discussed displacements 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:

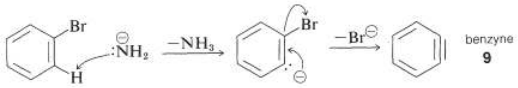


Even more striking is the exclusive formation of 3-methoxybenzenamine in the amination of 2-chloromethoxybenzene. Notice that this result is a violation of the principle of least structural change (Section 1-1H):



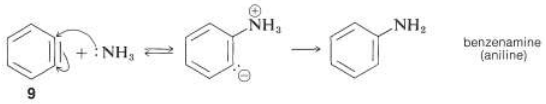
The mechanism of this type of reaction has been studied extensively, and much evidence has accumulated in support of a stepwise process, which proceeds first by base-catalyzed *elimination* of hydrogen halide (**HX**) from the aryl halide - as illustrated below for the amination of bromobenzene:

Elimination



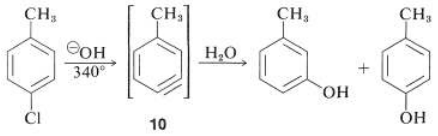
The product of the elimination reaction is a highly reactive intermediate **9** called **benzyne**, or **dehydrobenzene**, which differs from benzene in having two less hydrogen and an extra bond between two ortho carbons. Benzyne reacts rapidly with any available nucleophile, in this case the solvent, ammonia, to give an addition product:

Addition



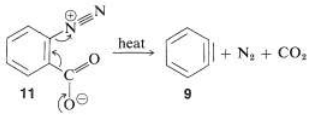
9

The rearrangements in these reactions result from the reaction 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:



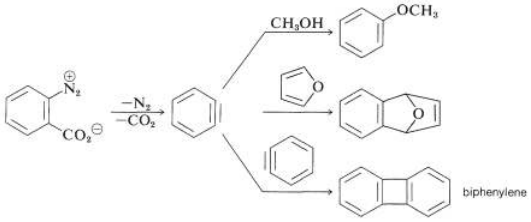
10

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:



11 9

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:

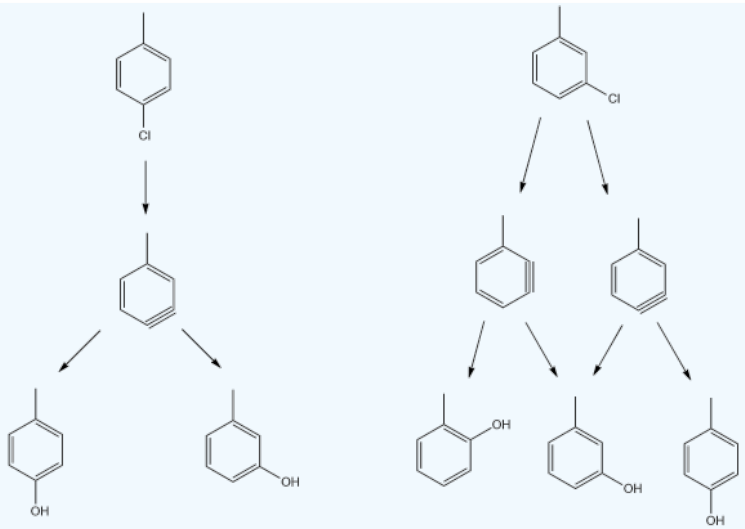


Exercise

25. 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

25. 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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John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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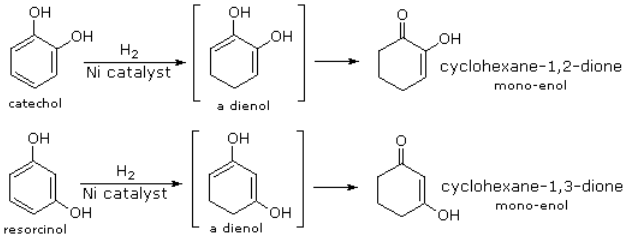
17.12: Reduction of Aromatic Compounds

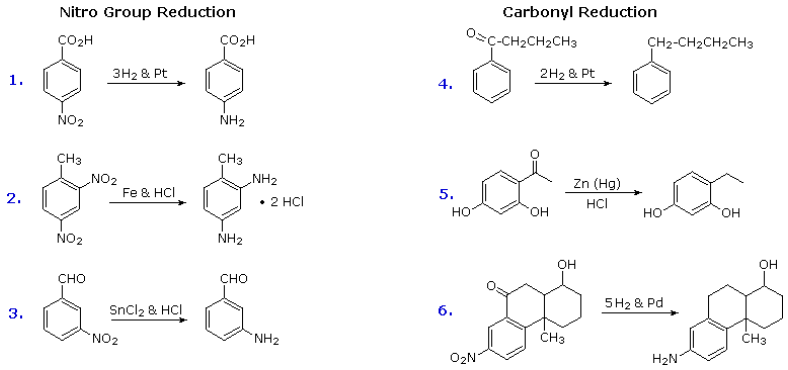
Reduction of Aromatic Compounds

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.



Reduction of Nitro Groups and Aryl Ketones Substituents on Benzene Rings

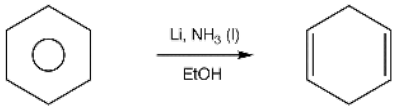
Electrophilic nitration and Friedel-Crafts acylation reactions introduce deactivating, meta-directing substituents on an aromatic ring. The attached atoms are in a high oxidation state, and their reduction converts these electron withdrawing functions into electron donating amino and alkyl groups. Reduction 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).



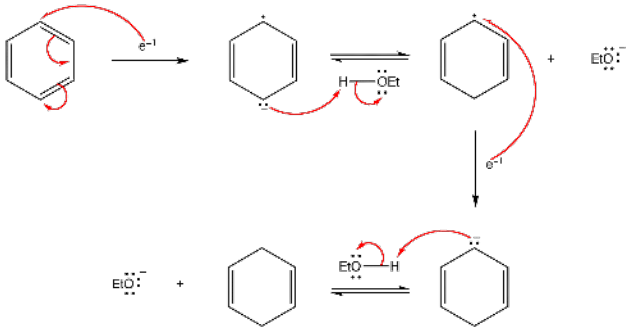
Several alternative methods for reducing nitro groups to amines are known. These include zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most cases.

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.

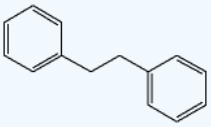


Mechanism:



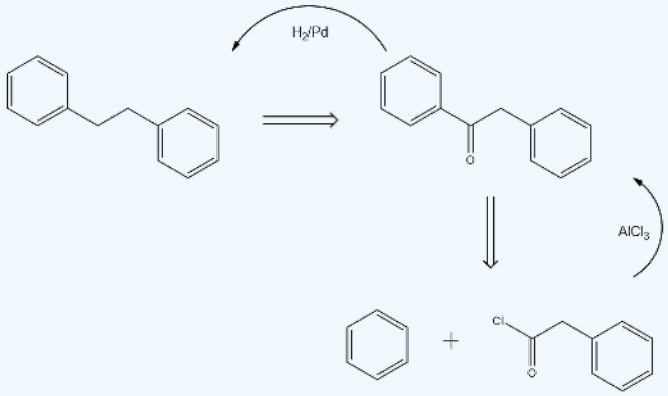
Exercise

26. How would you make the following from benzene and an acid chloride?



Answer

26.



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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Mario Morataya (UCD)
- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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17.13: Additional Exercises

18-1 Draw the resonance structures for benzaldehyde to show the electron-withdrawing group.

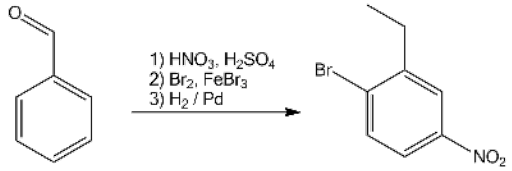
18-2 Draw the resonance structures for methoxybenzene to show the electron-donating group.

18-3 How would make the following compounds from benzene?

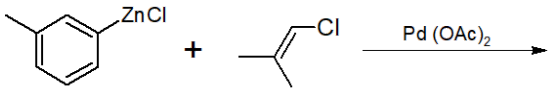
A) *m*-bromonitrobenzene

B) *m*-bromoethylbenzene

18-4 There is something wrong with the following reaction, what is it?



18-5 Choose the correct answer.



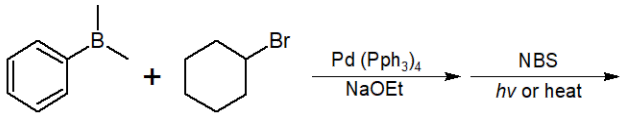
a) 1-methyl-3-(2-methylprop-1-en-1-yl)benzene

b) 2-chloro-4-methyl-1-(2-methylprop-1-en-1-yl)benzene

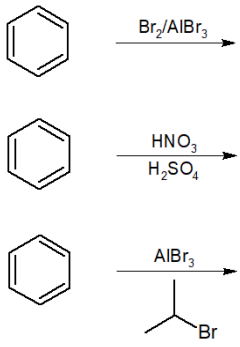
c) 1-chloro-3-(2-methylprop-1-en-1-yl)benzene

d) 1-(1-chloroethenyl)-3-methylbenzene

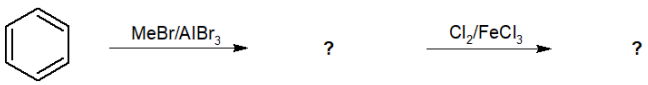
18-6 Predict the final product of the following reaction chain.



18-7 Provide the final product for the following reactions.



18-8 For the following reaction chain, provide the intermediate and final product(s).



18-9 Give the IUPAC name for the final product(s) of the previous problem, **18-8**.

18-10 For the following reaction chain, provide the intermediate and final product(s).

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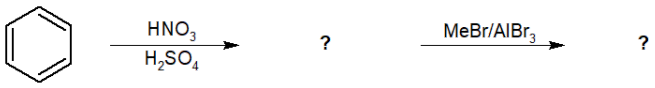
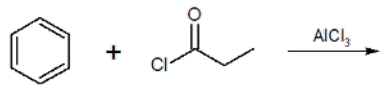
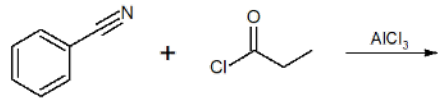


18-11 Give the final product of the following reactions.

a)

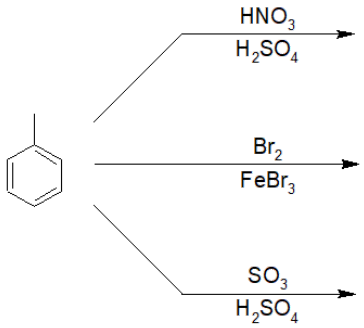


b)

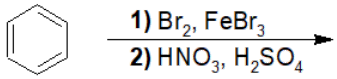


Halogenation, Nitration, and Sulfonation of Benzene

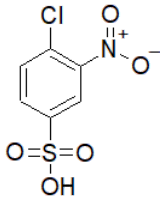
18-12 Predict the products of the following reactions.



18-13 Give the IUPAC nomenclature and structure of the product of the following reaction.



18-14 Choose the correct answer that describes the best route of synthesis of the following molecule.



a) Chlorination, sulfonation, nitration

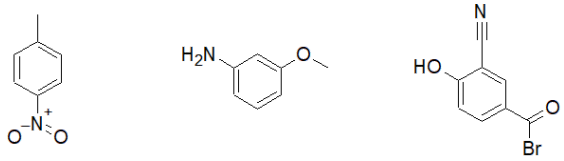
b) Sulfonation, nitration, chlorination

c) Nitration, sulfonation, chlorination

Activating, Ortho-, Para-Directing Substituents

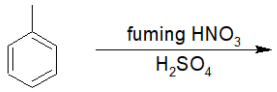
18-15 For the following compounds, point to the position(s) on the ring that are most likely to have a substituent added.

a) b) c)

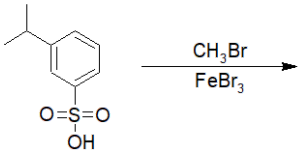


18-16 Predict the major product of the following reactions.

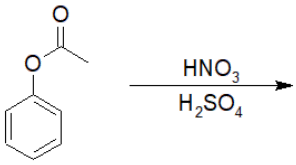
a)



b)



18-17 Provide the correct IUPAC nomenclature and structure of the product of the following reaction.

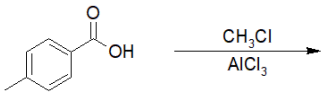


Deactivating, Meta-Directing Substituents

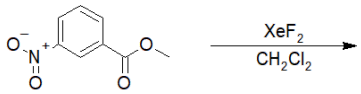
18-18 Predict the products of the following reactions.

a)

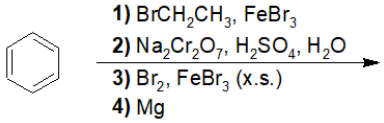
b)



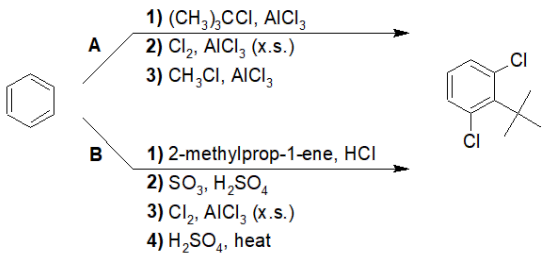
c)



18-19 Predict the product of the following reaction.

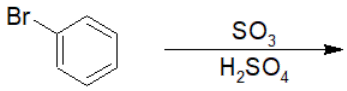


18-20 Choose the pathway that will lead to the product formed on the right.



Halogen Substitutes: Deactivating, but Ortho, Para-Directing

18-21 Choose the correct IUPAC nomenclature of one of the products of the following reaction.



a) 3-bromobenzene-1-sulfonic acid

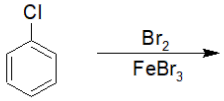
b) 4-bromobenzene-1-sulfonic acid

c) 5-bromobenzene-1,3-disulfonic acid

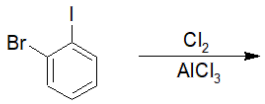
d) 4-bromophenyl hydrogen sulfate

18-22 Predict the products of the following reactions.

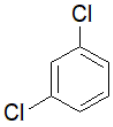
a)



b)



18-23 Propose a route of synthesis for the following compound, starting with chlorobenzene (assume any desired intermediate compounds can be isolated for use in subsequent steps).

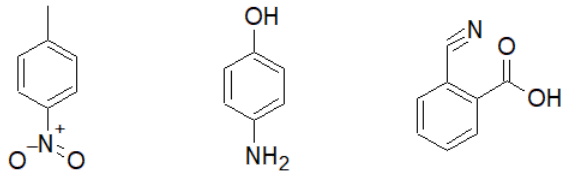


1,3-dichlorobenzene

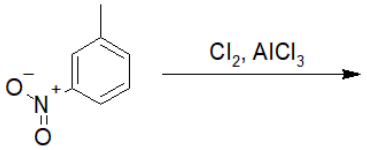
Effects of Multiple Substituents on Electrophilic Aromatic Substitution

18-24 For the following compounds, identify which substituent is the stronger activating group and predict the position(s) of a subsequent electrophilic aromatic substitution.

a) **b)** **c)**

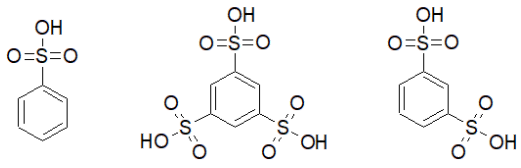


18-25 Predict all possible singly chlorinated products of the following reaction.

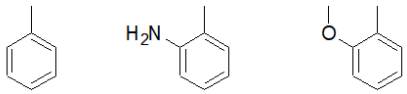


18-26 Rank the following compounds in order from slowest to fastest to go through an electrophilic aromatic substituent reaction.

a)



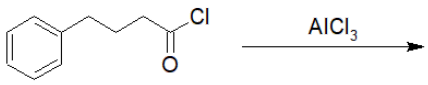
b)



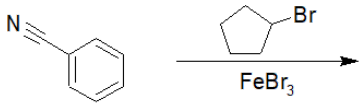
Friedel-Crafts Alkylation/Acylation

18-27 Predict the products of the following reactions.

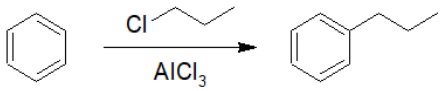
a)



b)

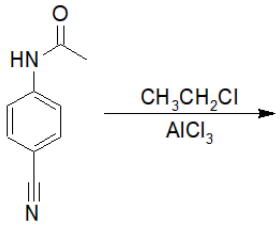


18-28 Explain whether or not the following reaction is the best way to synthesize propylbenzene and if not, propose a better route of synthesis.



propylbenzene

18-29 Choose the correct answer and if a product is formed, provide the structure of the product.



a) No reaction

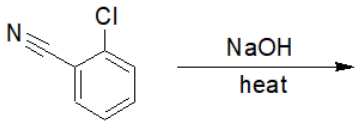
b) 4-amino-2-methylbenzonitrile

c) 4-amino-2-ethylbenzonitrile

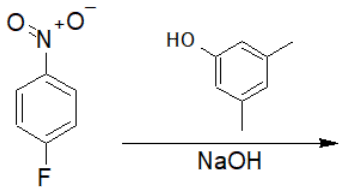
d) N-(4-cyano-2-ethylphenyl)acetamide

Nucleophilic Aromatic Substitution

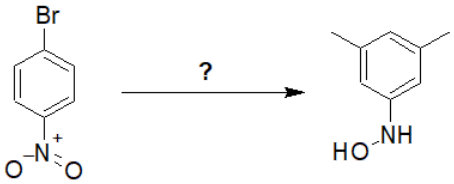
18-30 Predict the product of the following reaction and provide the correct IUPAC nomenclature.



18-31 Predict the product of the following reaction.

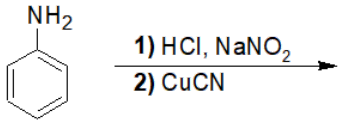


18-32 Suggest a route of synthesis to make *N*-hydroxy-3,5-dimethylaniline from 1-bromo-4-nitrobenzene.

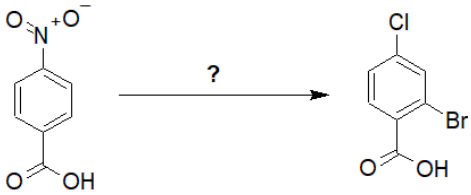


Aromatic Substitutions Using Organometallic Reagents

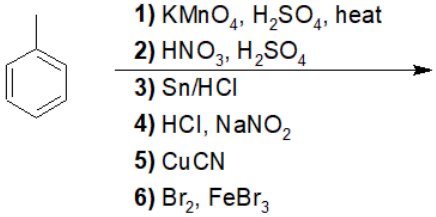
18-33 Provide the structure and IUPAC nomenclature of the product of the following reaction.



18-34 Suggest a route of synthesis to make 2-bromo-4-chlorobenzoic acid from 4-nitrobenzoic acid.



18-35 Choose the correct IUPAC nomenclature for the product of the following reaction.



a) 2-bromo-5-nitrobenzoic acid

b) 2-bromo-5-cyanobenzoic acid

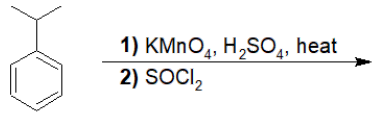
c) 3-cyano-5-nitrobenzoyl bromide

d) 3-bromo-5-cyanobenzoic acid

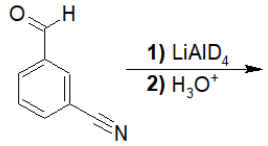
Side-Chain Reactions of Benzene Derivatives

18-36 Predict the products of the following reactions.

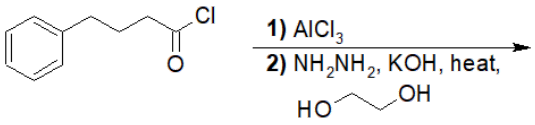
a)



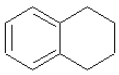
b)



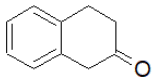
18-37 Choose the correct structure of the product of the following reaction.



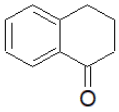
a)



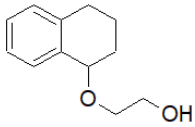
b)



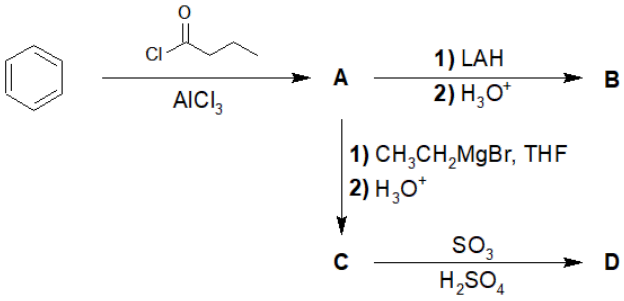
c)



d)



18-38 Provide the intermediate and final products of the following reactions.



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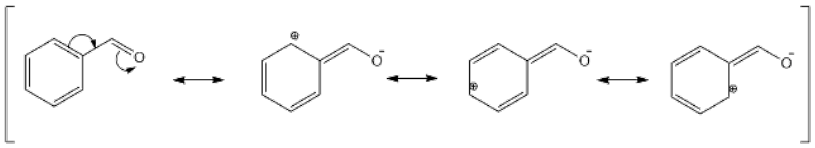
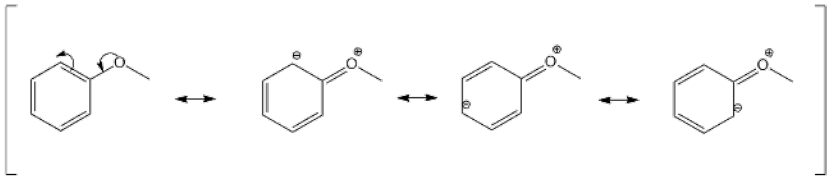
17.14: Solutions to Additional Exercises

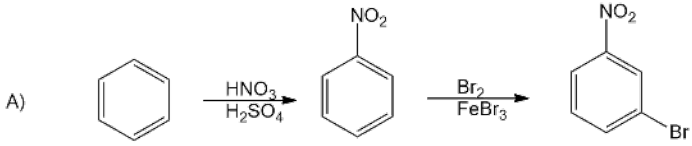
18-1

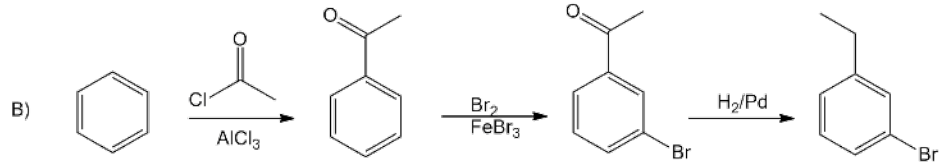


18-2



18-3 This is just one possible way to synthesize it.

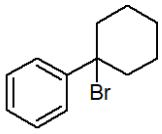




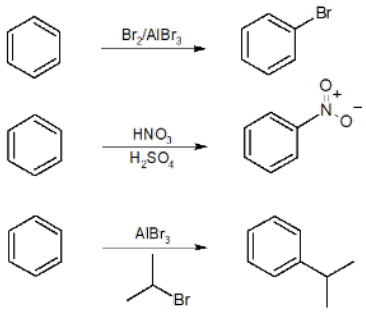
18-4 The bromine should be in the meta position. Right now it is in the ortho position, from perhaps having the ethyl group present first and then the having it substituted there. BUT the ethyl group is last to form, and the aldehyde and nitro groups would both encourage a meta substitution.

18-5 Answer: A

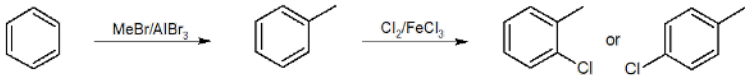
18-6



18-7

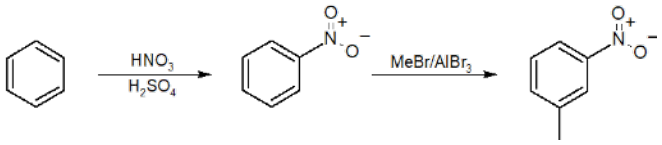


18-8

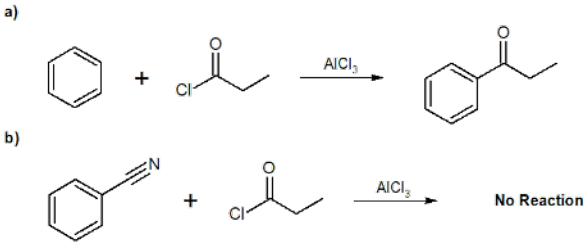


18-9 1-chloro-2-methylbenzene and 1-chloro-4-methylbenzene

18-10

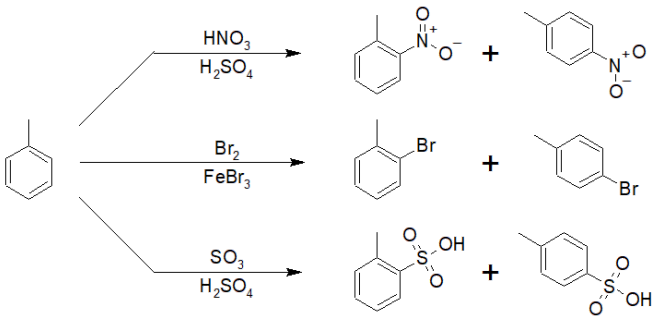


18-11

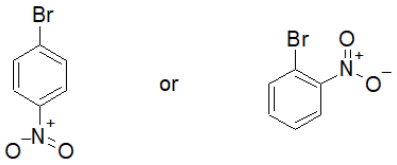


Halogenation, Nitration, and Sulfonation of Benzene

18-12:



18-13:



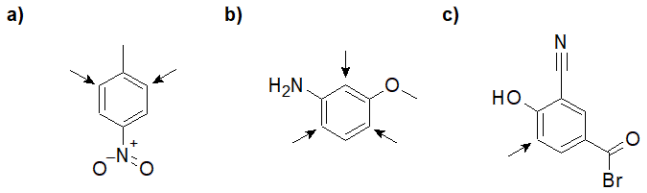
1-bromo-4-nitrobenzene **1-bromo-2-nitrobenzene**

18-14:

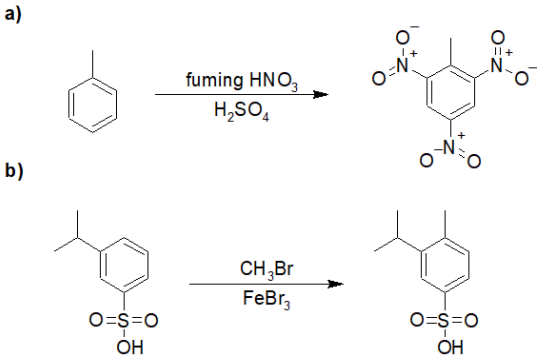
Answer: A

Activating, Ortho-, Para-Directing Substituents

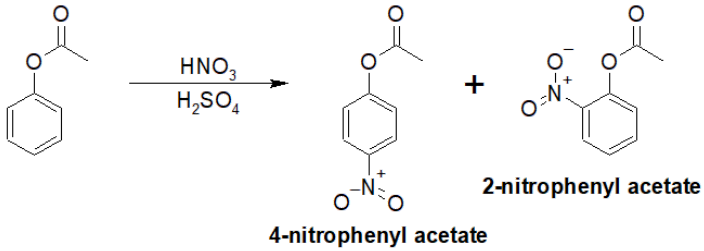
18-15:



18-16:

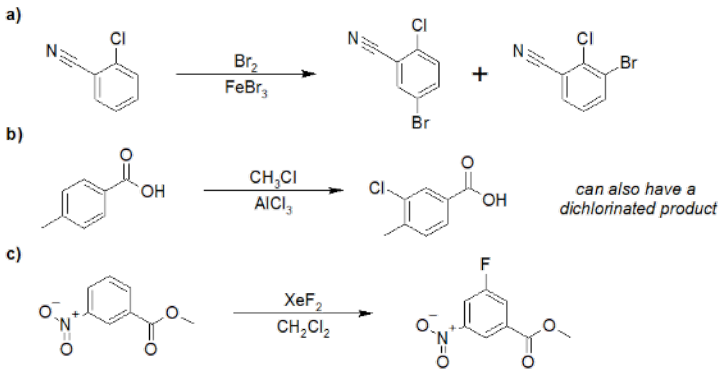


18-17:



Deactivating, Meta-Directing Substituents

18-18:



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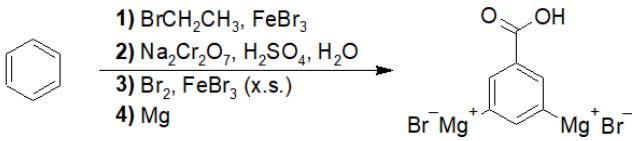

18-20:

Answer: B

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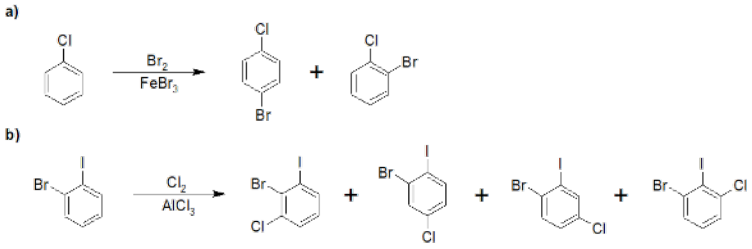
Halogen Substitutes: Deactivating, but Ortho, Para-Directing

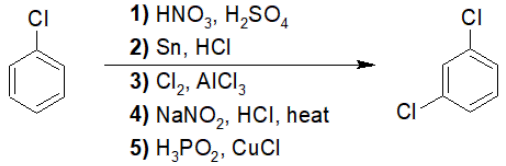
18-21:

Answer: B

18-22:

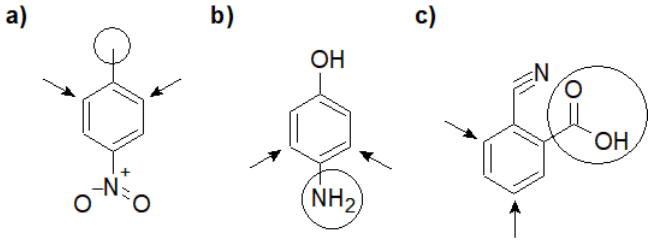


18-23:

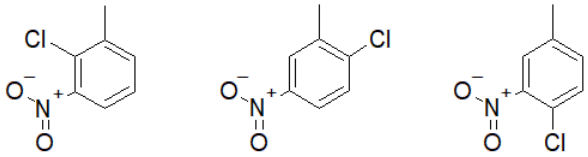


Effects of Multiple Substituents on Electrophilic Aromatic Substitution

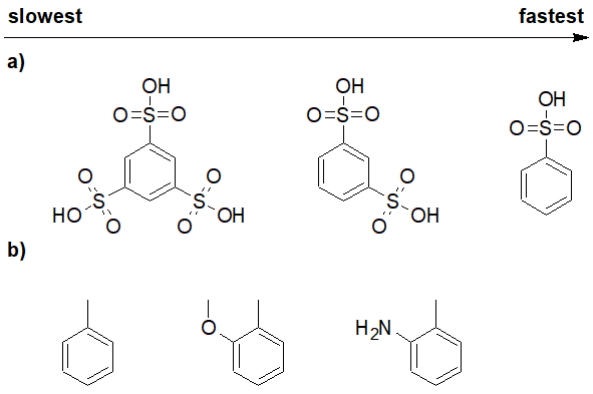
18-24:



18-25:



18-26:



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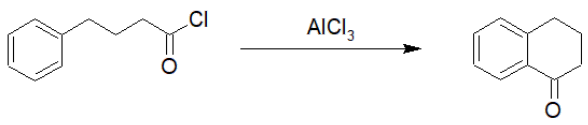
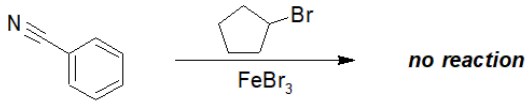
Friedel-Crafts Alkylation/Acylation

18-27:

a)



b)



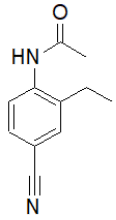
no reaction

18-28:

Friedel-Crafts alkylation using 1-chloropropane is not the best way to synthesize propylbenzene. You will end up with (propan-2-yl)benzene as your main product due to a hydride shift occurring during an intermediate step. A better route of synthesis may be Friedel-Crafts acylation using propanoyl chloride to make 1-phenylpropan-1-one, followed by a Clemmensen reduction to obtain the final product.

18-29:

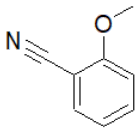
Answer: D



***N*-(4-cyano-2-ethylphenyl)acetamide**

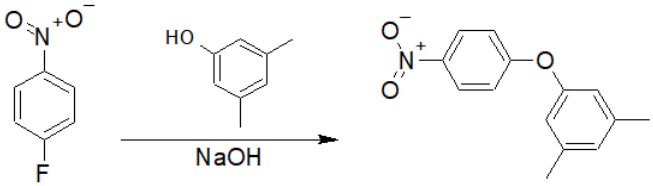
Nucleophilic Aromatic Substitution

18-30:



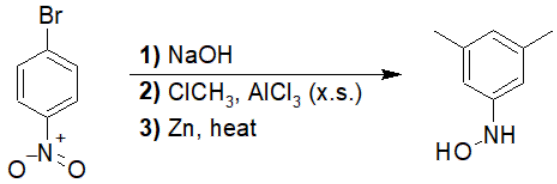
2-methoxybenzonitrile

18-31:



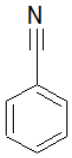
18-32:

Possible route of synthesis:



Aromatic Substitutions Using Organometallic Reagents

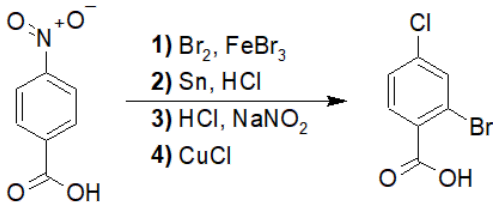
18-33:



benzonitrile

18-34:

Possible route of synthesis:



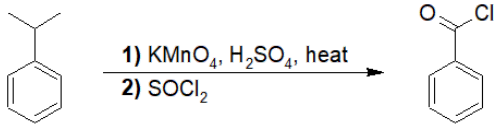
18-35:

Answer: D

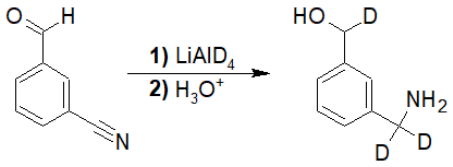
Side-Chain Reactions of Benzene Derivatives

18-36:

a)



b)



18-37:

Answer: A

18-38:

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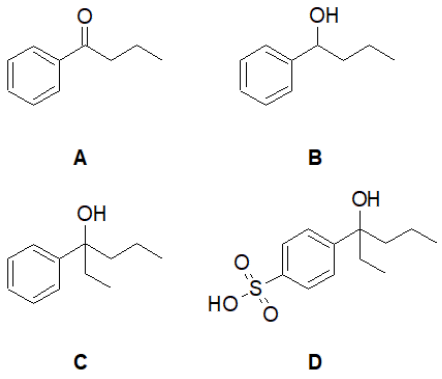

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CHAPTER OVERVIEW

18: Ketones and Aldehydes
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of aldehydes and ketones (section 19.1)
- determine the structure of aldehydes and ketones from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 19.2)
- predict the products and specify the reagents to synthesize aldehydes and ketones for reactions studied to date (section 19.3)
- predict the products and specify the reagents to synthesize aldehydes and ketones for new reactions (section 19.4)
- write the general mechanism for nucleophilic addition reactions with aldehydes and ketones (sections 19.5 to 19.11, 19.13, & 19.15)
- predict the relative reactivity of carbonyl compounds to nucleophilic addition reactions (sections 19.5 to 19.13, & 19.15)
- predict the relative equilibrium constant & rates of hydration for aldehydes and ketones (section 19.6)
- show the general mechanism for the Wittig reaction (section 19.13)
- predict the products and specify the reagents for oxidation and reduction reactions of aldehydes and ketones (section 19.14 and 19.15)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis including the use of acetals/ketals as protecting groups (sect 19.12)

Please note: IUPAC nomenclature and important common names of aldehydes and ketones were explained in Chapter 3.

Topic hierarchy

18.1: Carbonyl Compound Structure and Properties
18.2: Spectroscopy of Ketones and Aldehydes
18.3: Review of Ketone and Aldehyde Synthesis
18.4: 19.4 New Synthesis of Aldehydes and Ketones
18.5: Nucleophilic Addition Reactions of Ketones and Aldehydes
18.6: Nucleophilic Addition of Water (Hydration)
18.7: Nucleophilic Addition of Cyanide and Acetylide
18.8: Nucleophilic Addition of Grignards
18.9: Nucelophilic Addition of Amines (Imine and Enamine Formation)
18.10: Nucleophilic Addition of Hydrazine (Wolff-Kishner Reaction)
18.11: Nucelophilic Addition of Alcohols (Acetal Formation)
18.12: Acetals as Protecting Groups
18.13: Nucelophilic Addition of Phosphorus Ylides (The Wittig Reaction)
18.14: Oxidation of Aldehydes
18.15: Reductions of Ketones and Aldehydes
18.16: Additional Exercises
18.17: Solutions to Additional Exercises

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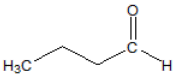
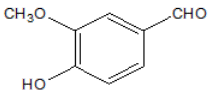
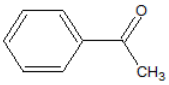
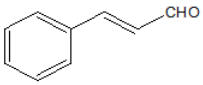
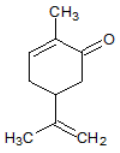
18.1: Carbonyl Compound Structure and Properties

The Carbonyls: the Aldehyes and Ketones

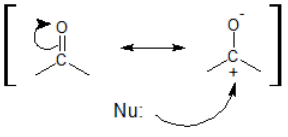
While there are several functional groups that include a carbonyl structural feature, the term "carbonyls" is used to describe aldehydes and ketones.

Aldehydes and ketones share a great deal of chemical reactivity so it makes sense to talk about these two functional groups within the same chapter. Aldehydes and ketones are both polar molecules that are H-bond acceptors. Following the "4 to 6 Rule", aldehydes and ketones with short carbon chains are soluble in water. Aldehydes and ketones are typically liquids with densities of approximately 0.8 g/mL. Aldehydes and ketones are prevalent in common household substances as shown in the table below.

Compound	Structure	Odor	Uses
Butyraldehyde		buttery	foods
Vanillin		vanilla	foods & perfumes
Acetophenone		pistachio	ice cream
Trans-Cinnamaldehyde		cinnamon & drugs	candy, food,
(-) carvone		spearmint	candy & food
(+) carvone	seed	caraway	food

Aldehydes and Ketones are Electrophiles

The carbon of the carbonyl group is electrophilic because of resonance as shown below.



The δ+ and trigonal planar molecular shape make carbonyl carbons good electrophiles.

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18.2: Spectroscopy of Ketones and Aldehydes

IR Spectra

The carbonyl stretching vibration band C=O of saturated aliphatic ketones appears:

C=O stretch

- aliphatic ketones 1715 cm^{-1}
- alpha, beta-unsaturated ketones 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.

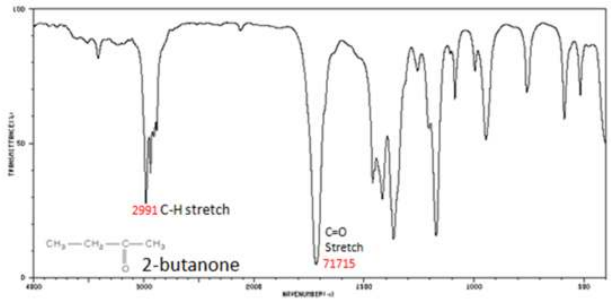


Figure 8. Infrared Spectrum of 2-Butanone

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}
- alpha, beta-unsaturated aldehydes 1710-1685 cm^{-1}

Figure 9. shows the spectrum of butyraldehyde.

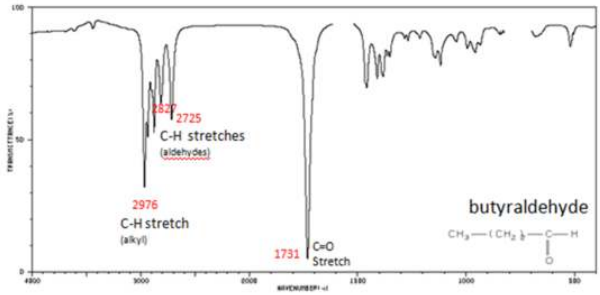
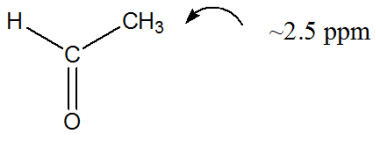


Figure 9. Infrared Spectrum of Butyraldehyde

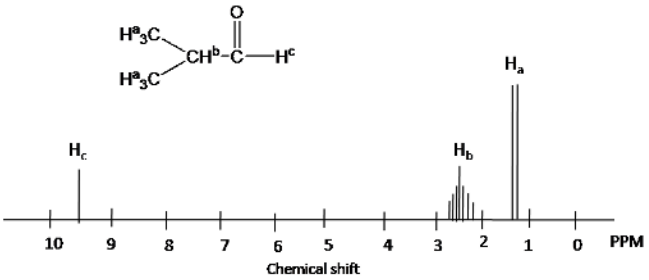
NMR Spectra

Hydrogens attached to carbon adjacent to the sp^2 hybridized carbon in aldehydes and ketones usually show up 2.0-2.5 ppm.



Aldehyde hydrogens are highly deshielded and appear far downfield as 9-10 ppm.

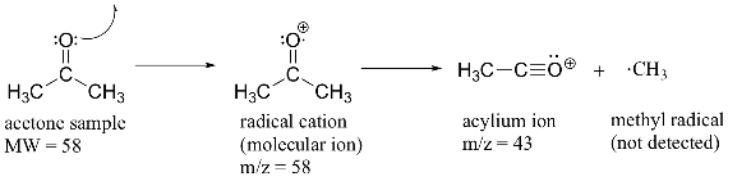
Chemical shift of each protons is predicted by ^1H chemical shift ranges (H_a): chemical shift of methyl groups (1.1 ppm). (H_b) The chemical shift of the -CH- group move downfield due to effect an adjacent aldehyde group: (2.4 ppm). The chemical shift of aldehyde hydrogen is highly deshielded (9.6 ppm).



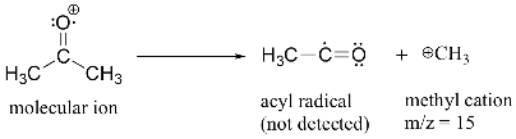
4) Splitting pattern is determined by (N+1) rule: Ha is split into two peaks by H_b(#of proton=1). H_b has the septet pattern by H_a (#of proton=6). H_c has one peak.(Note that H_c has doublet pattern by H_b due to vicinal proton-proton coupling.)

Mass Spectra

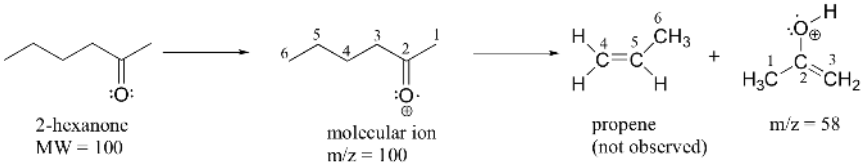
Much of the utility in electron-ionization MS comes from the fact that the radical cations generated in the electron-bombardment process tend to fragment in predictable ways. Detailed analysis of the typical fragmentation patterns of different functional groups is beyond the scope of this text, but it 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.



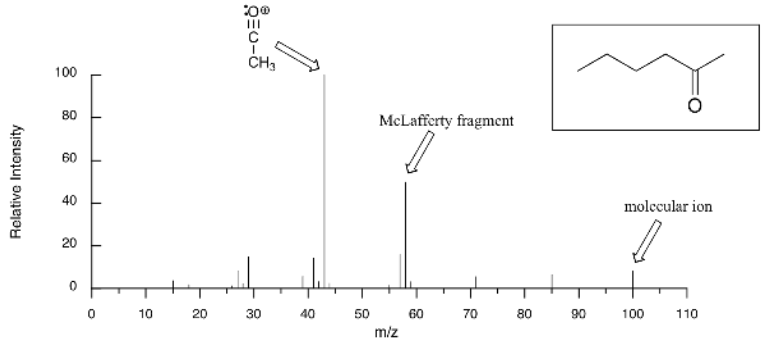
After the parent peak and the base peak, the next largest peak, at a relative abundance of 23%, is at m/z = 15. This, as you might expect, is the result of formation of a methyl cation, in addition to an acyl radical (which is neutral and not detected).



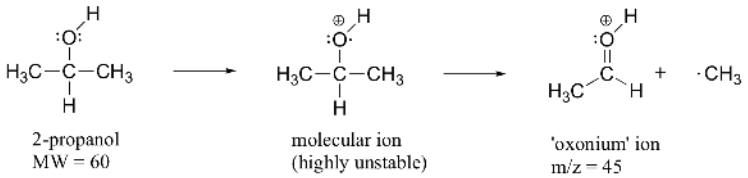
A common fragmentation pattern for larger carbonyl compounds is called the **McLafferty rearrangement**:

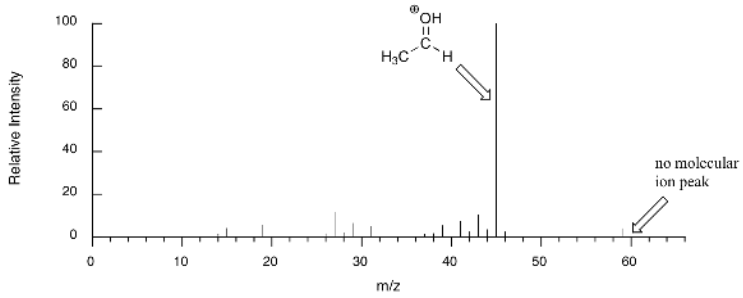


The mass spectrum of 2-hexanone shows a 'McLafferty fragment' at m/z = 58, while the propene fragment is not observed because it is a neutral species (remember, only cationic fragments are observed in MS). The base peak in this spectrum is again an acylium ion.



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.



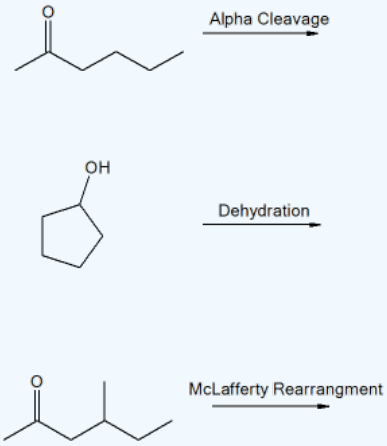


Other functional groups have predictable fragmentation patterns as well. By carefully analyzing the fragmentation information that a mass spectrum provides, a knowledgeable spectrometrist can often ‘put the puzzle together’ and make some very confident predictions about the structure of the starting sample.

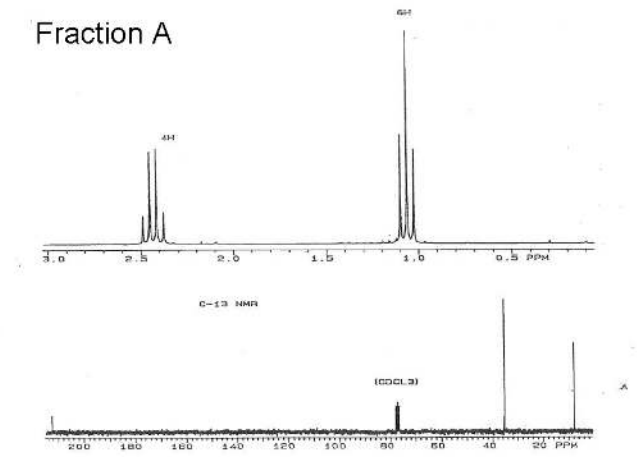
Click here for examples of compounds listed by functional group, which demonstrate patterns which can be seen in mass spectra of compounds ionized by electron impact ionization.

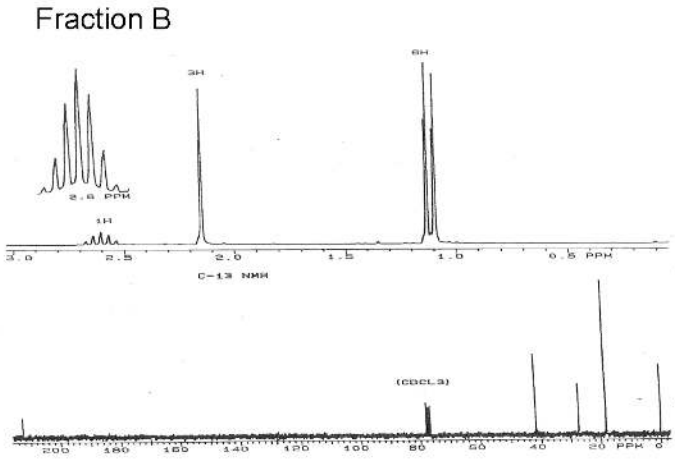
Exercise

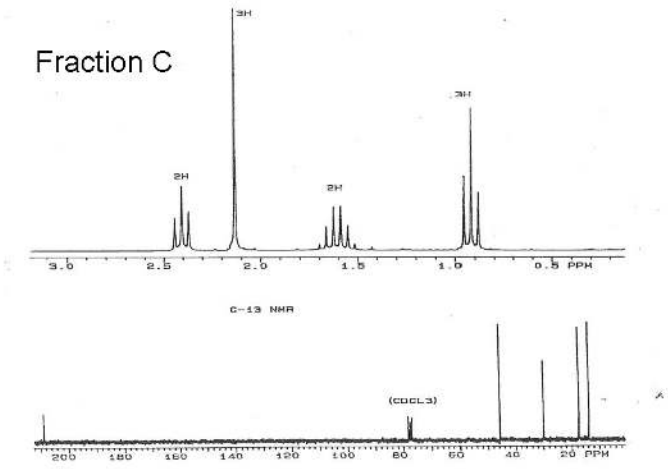
1. a) What are the masses of all the components in the following fragmentation reactions?



b) 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.







Answer

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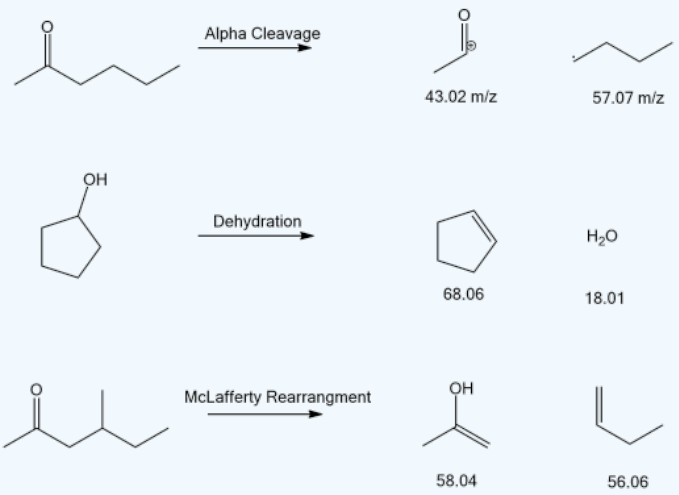
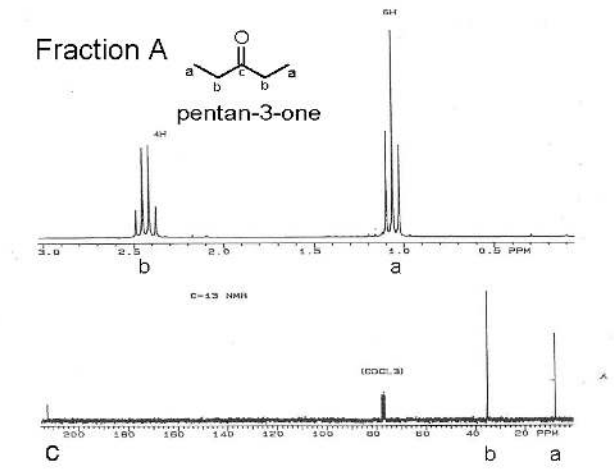
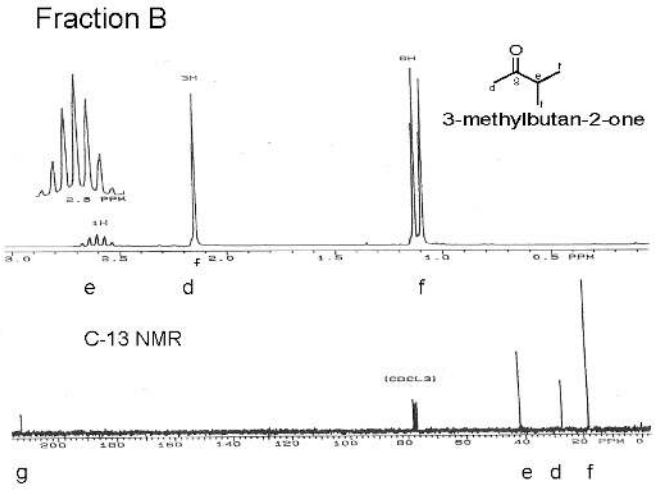
1. a)

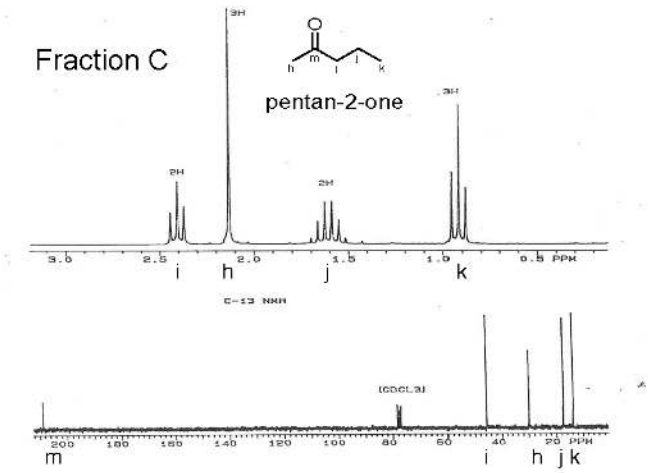


b)

https://chem.libretexts.org/@go/page/183091


Fraction A
pentan-3-one
6H
4H
b
a
C-13 NMR
(CDCL3)
c
b
a


Fraction B
3-methylbutan-2-one
3H
6H
1H
e
d
f
C-13 NMR
(CDCL3)
g
e
d
f


Fraction C
pentan-2-one
3H
2H
2H
3H
i
h
j
k
C-13 NMR
(CDCL3)
m
i
h
j
k

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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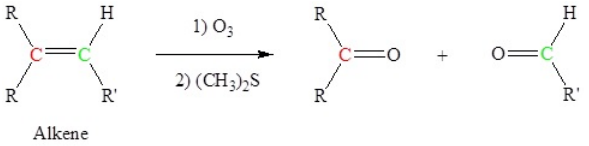
18.3: Review of Ketone and Aldehyde Synthesis

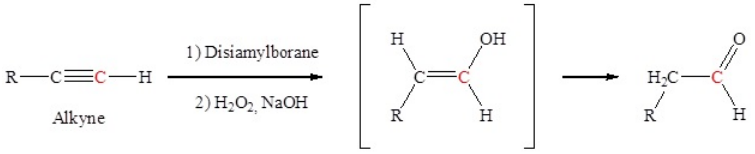
So far this text has discussed aldehyde and ketone synthesis from the ozolysis of alkenes, hydration of alkynes, oxidation of alcohols, and Friedel-Crafts acylation of benzene rings.

Alkenes can be cleaved using ozone (O_3) to form aldehydes and/or ketones



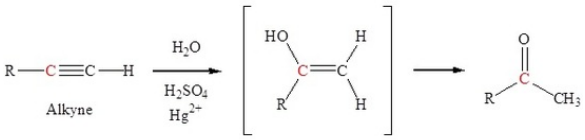
Hydration of an alkyne to form aldehydes

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.

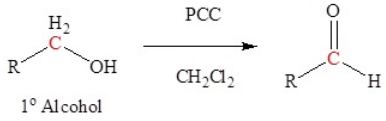


Hydration of an alkyne to form ketones

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.

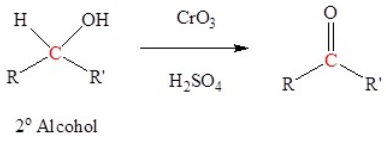


Oxidation of 1° alcohols with PCC to form aldehydes

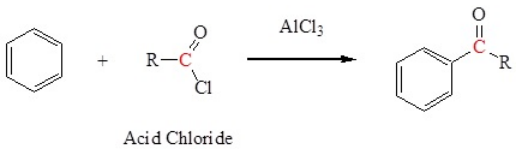


Oxidation of 2° alcohols to form ketones

Typically uses Jones reagent (CrO_3 in H_2SO_4) but many other reagents can be used

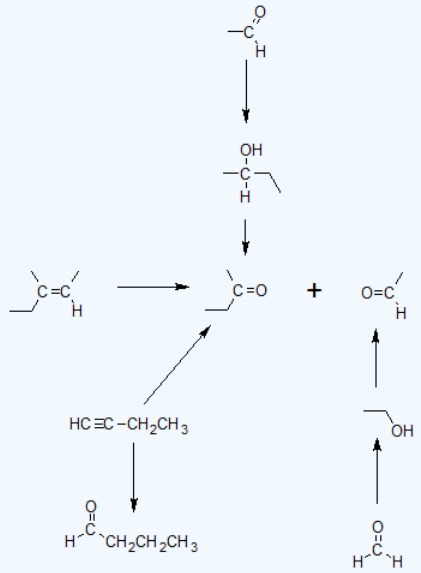


Friedel-Crafts acylation to form a ketone



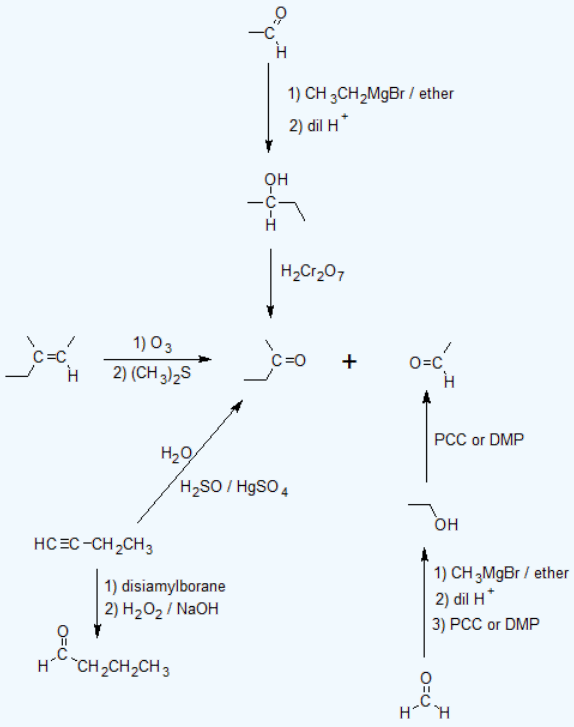
Exercise

2. Specify the reagents to complete the reaction map below.



Answer

2.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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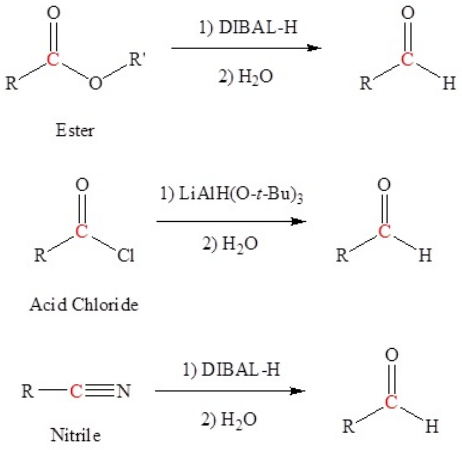
18.4: 19.4 New Synthesis of Aldehydes and Ketones

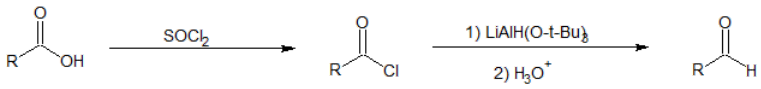
Ester, Acid Chloride, and Nitrile Reduction to form Aldehydes

The reduction of esters, acid chlorides, and nitriles require reducing agents that are derivatives of lithium aluminum hydride ($LiAlH_4$). For esters and nitriles, $LiAlH_4$ is modified into the organometallic reagent diisobutyl aluminum hydride which can be represented as DIBAL or DIBAL-H or DIBAH or DIBALH. To reduce acid chlorides, t-butoxide groups are combined with $LiAlH_4$ to form lithium tritert-butoxy aluminum hydride.



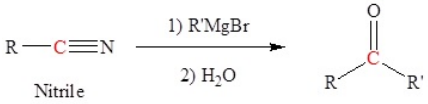
Carboxylic Acids can be converted to Aldehydes

Carboxylic acids cannot be reduced directly to aldehydes. Carboxylic acids can be converted to acid chlorides using thionyl chloride which can then be reduced to aldehydes using $LiAlH(O\text{-}t\text{-}Bu)_3$.



Grignard reagents react with Nitriles to form Ketones

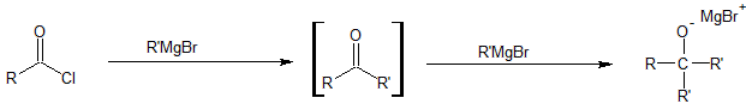
Nitriles can also be used to synthesize ketones when they react with Grignards as shown below.



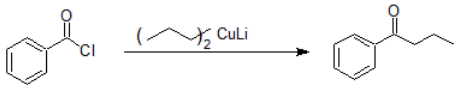
Organocuprate reagents react with Acid Chlorides to form Ketones

Organocuprate reagents are the least reactive of the organometallic reagents studied so far. While we learned to synthesize alcohols by reacting Grignard reagents with aldehydes and ketones, organocuprates will not react with aldehydes and ketones.

Grignard reagents will keep reacting with the product of the acid chloride reaction.

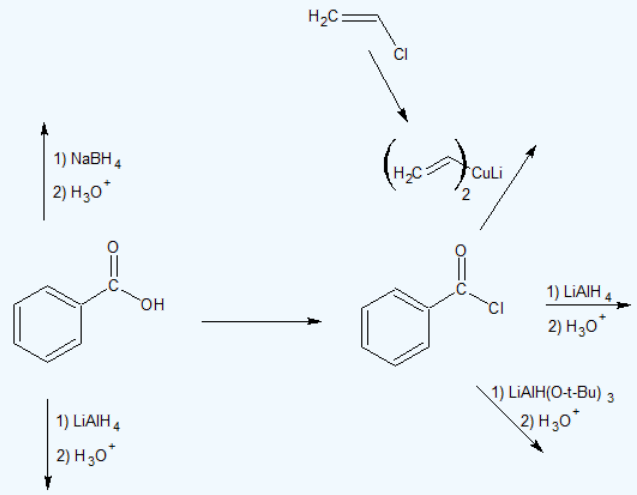


Organocuprate reactions with acid chlorides stop at the ketone as shown below.



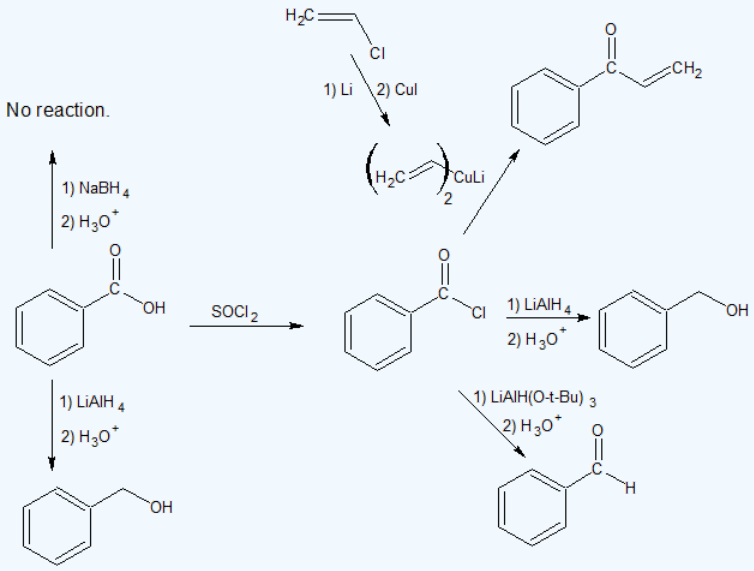
Exercise

3. Complete the reaction map below.



Answer

3.



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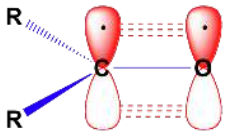
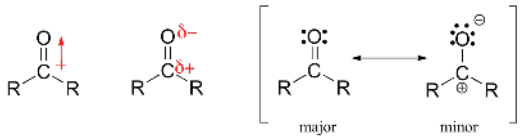
18.5: Nucleophilic Addition Reactions of Ketones and Aldehydes

Carbonyls are Electrophiles

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 soverlaps 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' pbond with a 2p orbital on the oxygen.

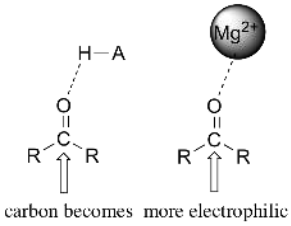


The carbon-oxygen double bond is polar: oxygen is more electronegative than carbon, so electron density is higher on the oxygen side of the bond and lower on the carbon side. Recall that bond polarity can be depicted with a dipole arrow, or by showing the oxygen as holding a partial negative charge and 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.

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.

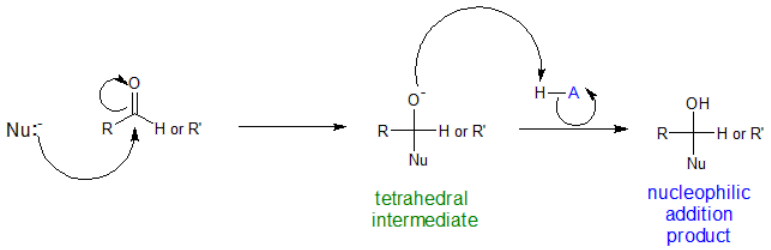


The same effect can also be achieved if a Lewis acid, such as a magnesium ion, is located near the carbonyl oxygen.

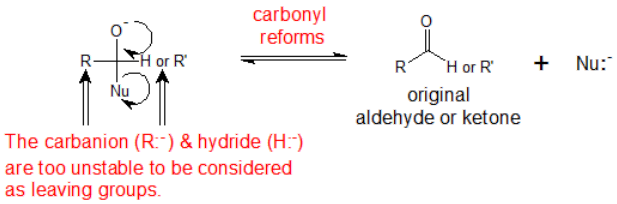
Nucelophilic Addition to a Carbonyl

When a nucleophile reacts with the carbonyl carbon of an aldehyde or ketone, there is no leaving group – the incoming nucleophile simply 'pushes' the electrons in the pi bond up to the oxygen. After the carbonyl has reacted with the nucleophile, the negatively charged oxygen has the capacity to act as a nucleophile. The nucleophile can be charged or neutral. However, most commonly the oxygen acts as a base, abstracting a proton from a nearby acid group in the solvent or enzyme active site. The nucelophiiles studied in this chapter are water (H_2O), cyanide (CN^-), Grignard reagent (RMgX), amines (and ammonia), hydrazine (N_2H_4), alcohols (ROH), and phosphorus ylides ($R_3P{=}CRH$).

The generic mechanism for a strong nucleophile generally occurs under basic conditions as shown below.

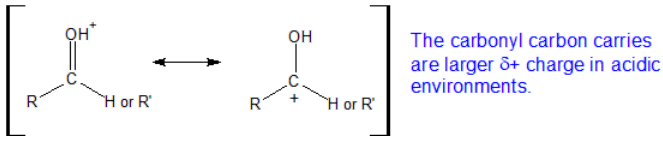


A closer look at the tetrahedral intermediate shows us that if the carbonyl reforms, then the original aldehyde or ketone is reformed.

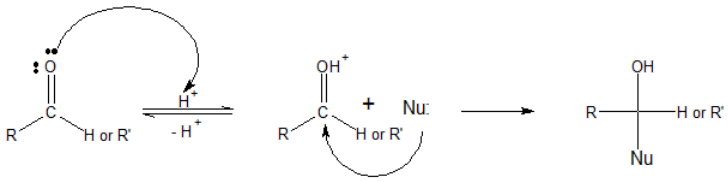


It is possible for the nucleophile to repeatedly add and leave the carbonyl group. Protonation of the tetrahedral intermediate to form the nucleophilic additon product is favored by the low activation energy of proton transfer reactions.

For reaction with weak nucleophiles generally occurs under acidic conditions to increase the electrophilicity of the carbonyl group as resonance form below illustrates.

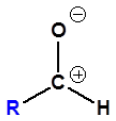


While the net result of the reaction is similar, the mechanism is slightly different due to the order of the proton transfer reactions.

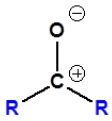


Relative Reactivity of Carbonyl Compounds to Nucleophilic Addition

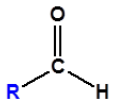
In general aldehydes are more reactive than ketones because of the lack of stabilizing alkly groups. The primary carbocation formed in the in the polarizing resonance structure of an aldehyde (discussed above) is less stable and therefore more reactive than the secondary carbocation formed by a ketone.



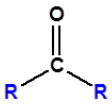
1° Carbocation
(Less Stable, More Reactive)



2° Carbocation
(MoreStable, Less Reactive)



Aldehyde
Less Stabilization
More Reactive



Ketone
Less Stabilization
More Reactive

Exercise

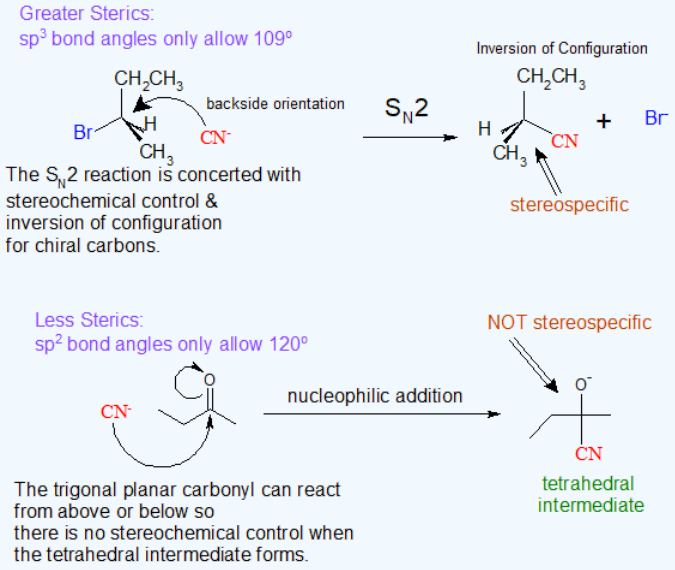
4. Compare the mechanisms of

an S_N2 reaction between 2-bromobutane and cyanide

tetrahedral complex formation between 2-butanone and cyanide.

Answer

4.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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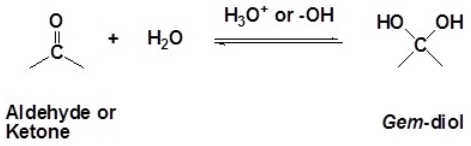
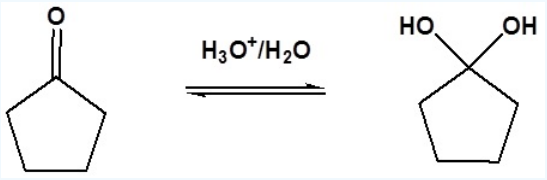
18.6: Nucleophilic Addition of Water (Hydration)

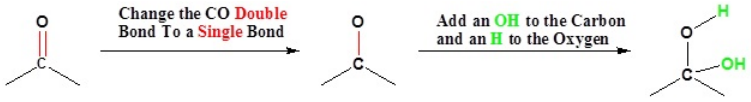
It has been demonstrated that water, in the presence of an acid or a base, adds rapidly to the carbonyl function of aldehydes and ketones establishing a reversible equilibrium with a **hydrate** (geminal-diol or *gem*-diol). The word germinal or gem comes from the Latin word for twin, *geminus*.



Example

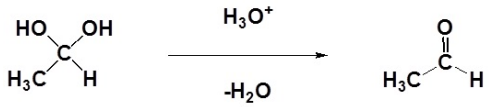


Going from Reactants to Products Simplified



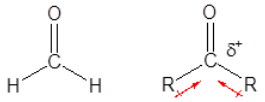
Reversibility of the Reaction

Isolation of *gem*-diols is difficult because the reaction is reversibly. Removal of the water during a reaction can cause the conversion of a gem-diol back to the corresponding carbonyl.

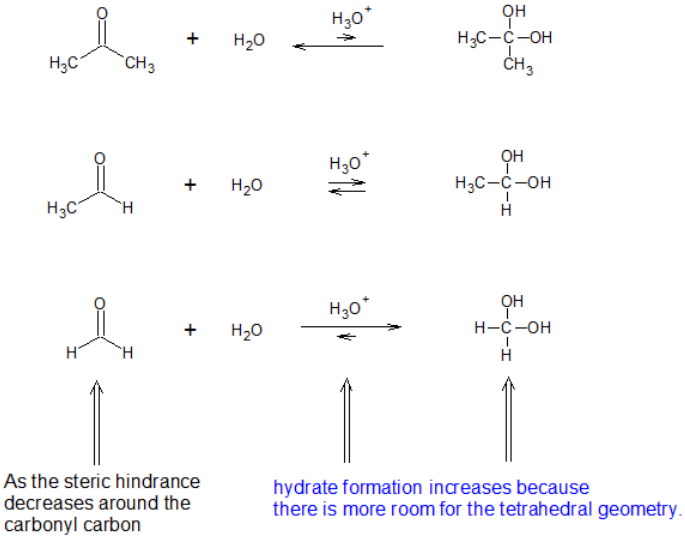


Factors Affecting the *Gem*-diol Equilibrium

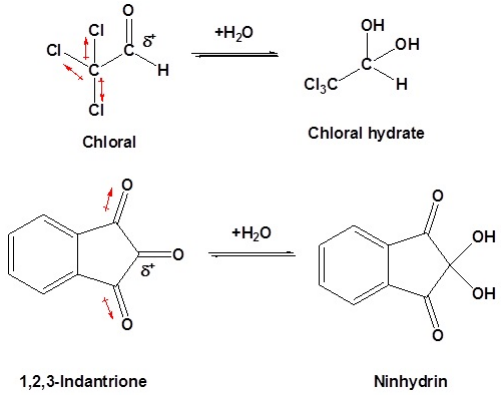
In most cases the resulting *gem*-diol is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde where the weaker pi-component of the carbonyl double bond, relative to other aldehydes or ketones, and the small size of the hydrogen substituents favor addition. 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. Likewise, the addition of strong electron-withdrawing groups destabilizes the carbonyl and tends to form stable *gem*-diols.



The relative equilbrium between the carbonyl and gem-diol builds understanding about steric effects in reaction mechanisms. This relationship is summarized below.



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 resolve finger prints.

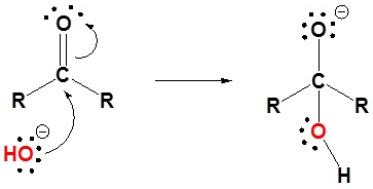


Mechanism of *Gem*-diol Formation

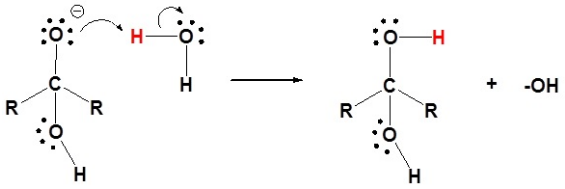
The mechanism is catalyzed by the addition of an acid or base. Note! This may speed up the reaction but is has not effect on the equilibriums discussed above. Basic conditions speed up the reaction because hydroxide is a better nucleophilic than water. Acidic conditions speed up the reaction because the protonated carbonyl is more electrophilic.

Basic conditions

1) Nucleophilic hydroxide reacts with carbonyl carbon

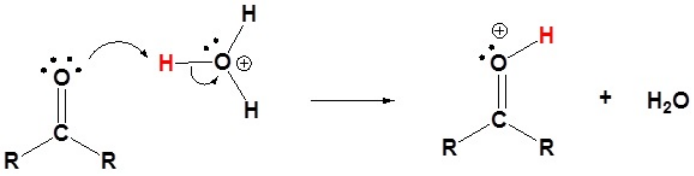


2) Protonation of the alkoxide

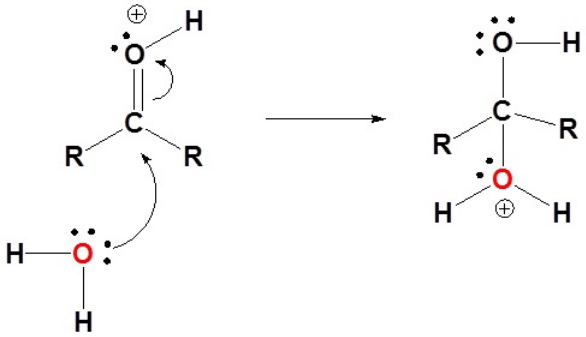


Acidic conditions

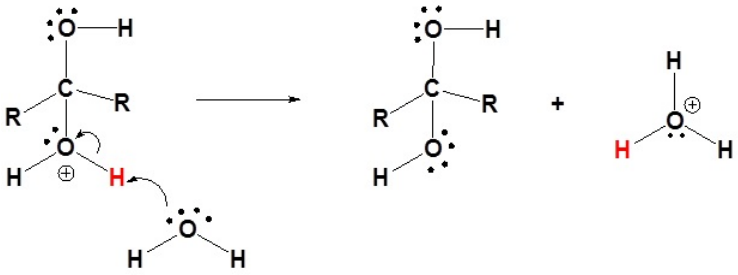
1) Protonation of the carbonyl



2) Nucleophilic water reacts with carbonyl carbon

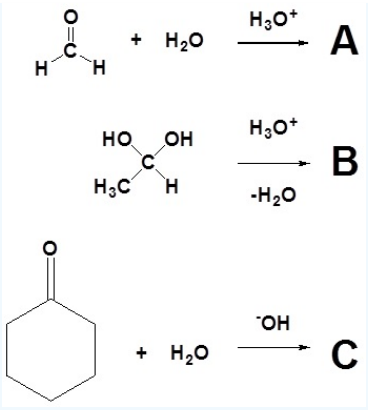


3) Deprotonation

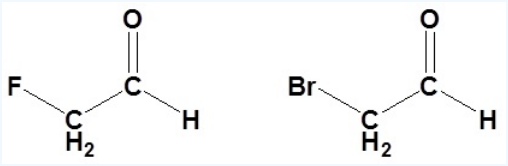


Exercise

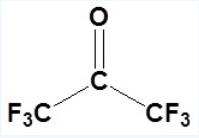
5. Draw the expected products of the following reactions.



6. Of the following pairs of molecules which would you expect to form a larger percentage of *gem*-diol at equilibrium? Please explain your answer.

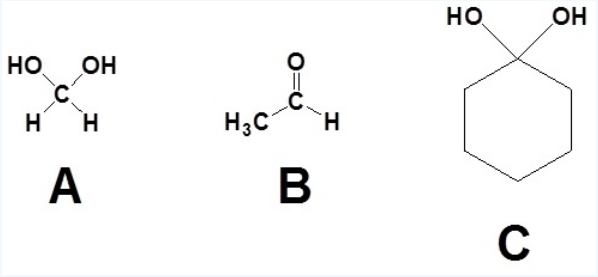


7. Would you expect the following molecule to form appreciable amount of *gem*-diol in water? Please explain your answer.



Answer

5.



6. 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.

7. 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 alkyl group is dominated by the presence of six highly electronegative fluorines.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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18.7: Nucleophilic Addition of Cyanide and Acetylide

Cyanohydrins have the structural formula of $R_2C(OH)CN$. The “R” on the formula represents an alkyl, aryl, or hydrogen. To form a cyanohydrin, a hydrogen cyanide adds reversibly to the carbonyl group of an organic compound thus forming a hydroxyalkanenitrile adducts (commonly known and called as cyanohydrins).

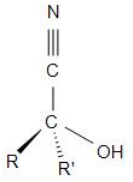
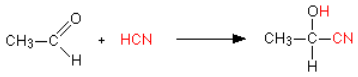


Figure **1:** General structure of a cyanohydrin

The reaction of aldehydes and ketones with hydrogen cyanide

Hydrogen cyanide adds across the carbon-oxygen double bond in aldehydes and ketones to produce compounds known as hydroxynitriles. For example, with ethanal (an aldehyde) you get 2-hydroxypropanenitrile:

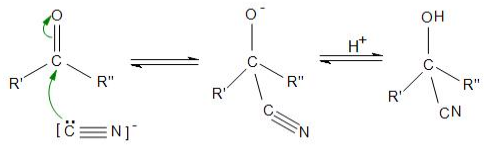


With propanone (a ketone) you get 2-hydroxy-2-methylpropanenitrile:

The reaction isn't normally done using hydrogen cyanide itself, because this is an extremely poisonous gas. Instead, the aldehyde or ketone is mixed with a solution of sodium or potassium cyanide in water to which a little sulphuric acid has been added. The pH of the solution is adjusted to about 4 - 5, because this gives the fastest reaction. The solution will contain hydrogen cyanide (from the reaction between the sodium or potassium cyanide and the sulphuric acid), but still contains some free cyanide ions. This is important for the mechanism.

Mechanism of Cyanohydrin Formation

Acid-catalyzed hydrolysis of silylated cyanohydrins has recently been shown to give cyanohydrins instead of ketones; thus an efficient synthesis of cyanohydrins has been found which works with even highly hindered ketones.



Acetone Cyanohydrins

Acetone cyanohydrins (ACH) have the structural formula of $(CH_3)_2C(OH)CN$. It is an organic compound serves in the production of methyl methacrylate (also known as acrylic).

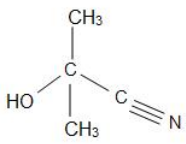


Figure 2: Acetone cyanohydrins

It is classified as an extremely hazardous substance, since it rapidly decomposes when it's in contact with water. In ACH, sulfuric acid is treated to give the sulfate ester of the methacrylamid. Preparations of other cyanohydrins are also used from ACH: for HACN to Michael acceptors and for the formylation of arenas. The treatment with lithium hydride affords anhydrous lithium cyanide.

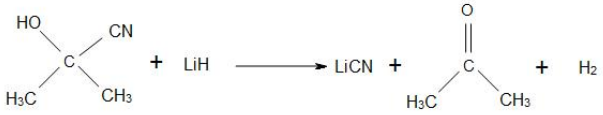
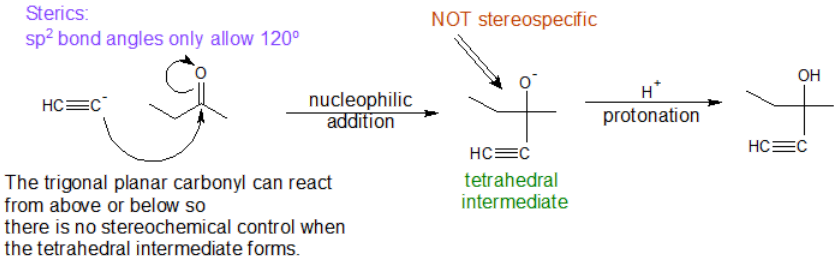


Figure 3: Reduction of Acetone cyanohydrins

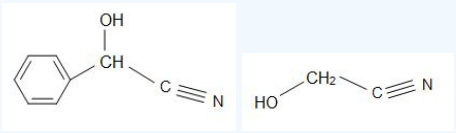
Acetylide Ions (RCC^-)

The reactivity of acetylide ions with aldehydes and ketones follows the mechanism for cyanide. For example, 2-butanone reacts with acetylide as shown in the reaction below.



Exercise

8. Mandelonitrile occurs in pits of some fruits. Glycolonitrile is the simplest cyanohydrin. Their structures are shown below.

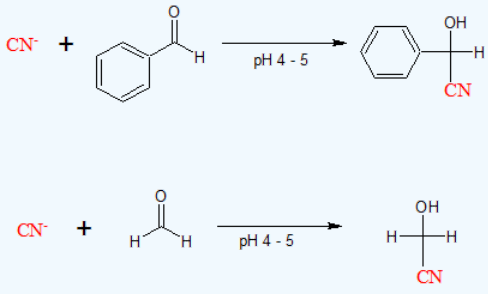


Madelonitrile glycolonitrile

Propose the reactants for mandelonitrile and glycolonitrile.

Answer

8.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

- Jim Clark (Chemguide.co.uk)

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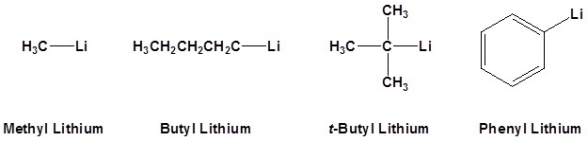
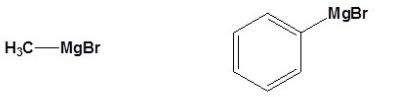
18.8: Nucleophilic Addition of Grignards

Common Organometallic Reagents

The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. 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:-). Some common organometallic reagents are shown below



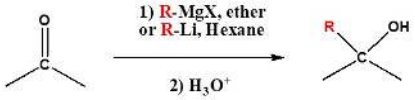
Methyl Lithium | Butyl Lithium | *t*-Butyl Lithium | Phenyl Lithium



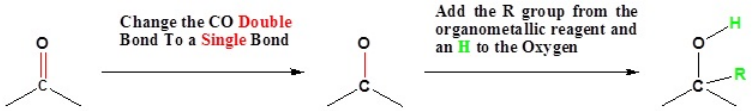
Methyl Magnesium Bromide | Phenylmagnesium Bromide

Reaction of Organometallic Reagents with Various Carbonyls

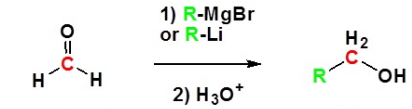
Because organometallic reagents react as their corresponding carbanion, they are excellent nucleophiles. The basic reaction involves the nucleophilic attack of the carbanionic carbon in the organometallic reagent with the electrophilic carbon in the carbonyl to form alcohols.



Both Grignard and Organolithium Reagents will perform these reactions going from Reactants to Products by this simplified pattern:

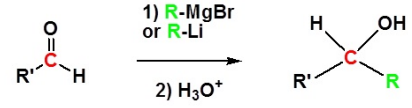


Addition to formaldehyde gives 1° alcohols



Formaldehyde | 1° Alcohol

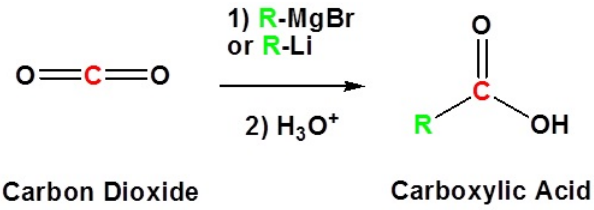
Addition to aldehydes gives 2° alcohols



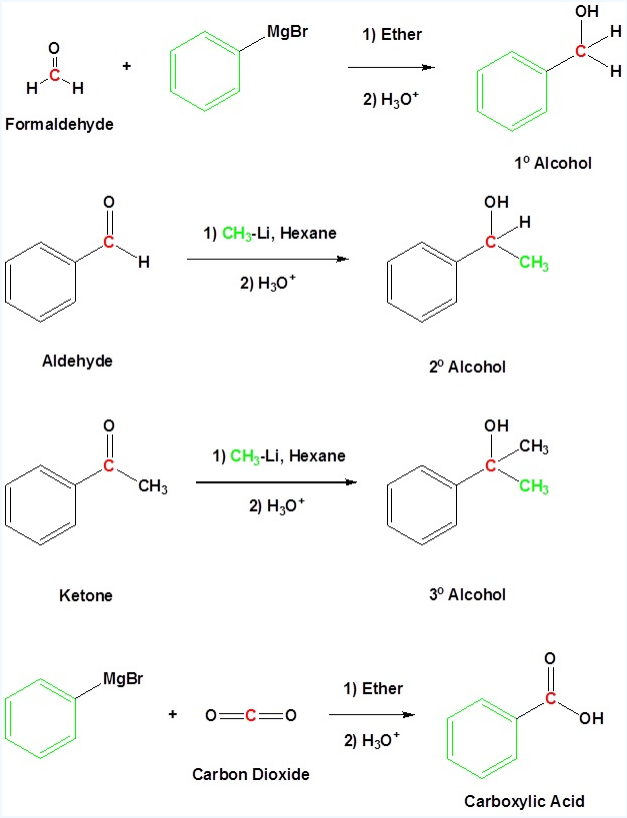
Aldehyde | 2° Alcohol

Addition to ketones gives 3° alcohols

Addition to carbon dioxide (CO_2) forms a carboxylic acid



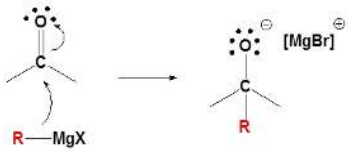
Example



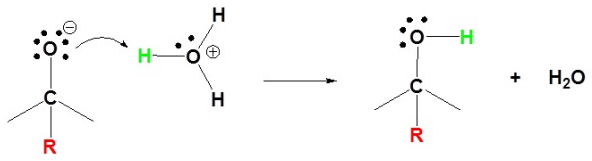
Mechanism for the Addition to Carbonyls

The mechanism for a Grignard agent is shown. The mechanism for an organometallic reagent is the same.

1) Nucleophilic reaction with carbonyl carbon



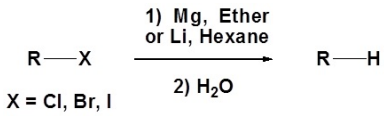
2) Protonation of tetrahedral intermediate



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.

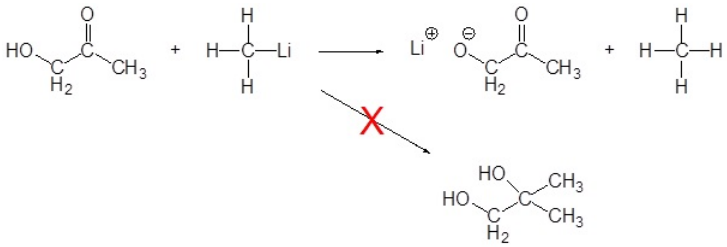
In fact, the reactivity of Grignard reagents and organolithium reagents can be exploited to create a new method for the conversion of halogens to the corresponding hydrocarbon (illustrated below). The halogen is converted to an organometallic reagent and then subsequently reacted with water to from an alkane.



Conjugate base anions of terminal alkynes (acetylide anions) are nucleophiles, and can do both nucleophilic substitution and nucleophilic addition reactions.

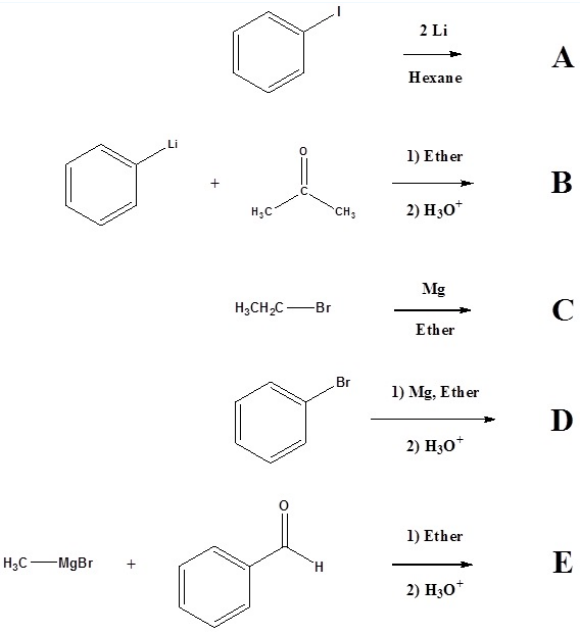
Limitation of Organometallic Reagents

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 react with the carbonyl. A partial list of functional groups which cannot be used are: alcohols, amides, 1° amines, 2° amines, carboxylic acids, and terminal alkynes.

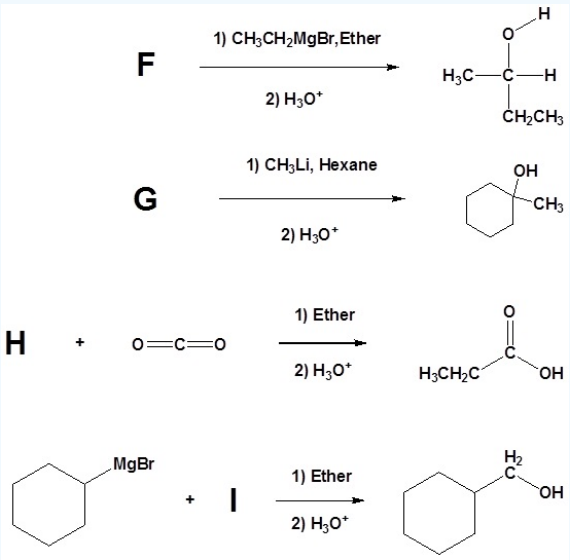


Exercises

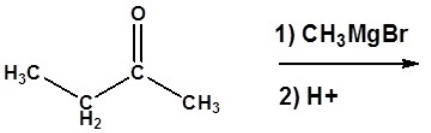
9. Please write the product of the following reactions.



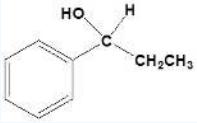
10. Please indicate the starting material required to produce the product.



11. Please give a detailed mechanism and the final product of this reaction

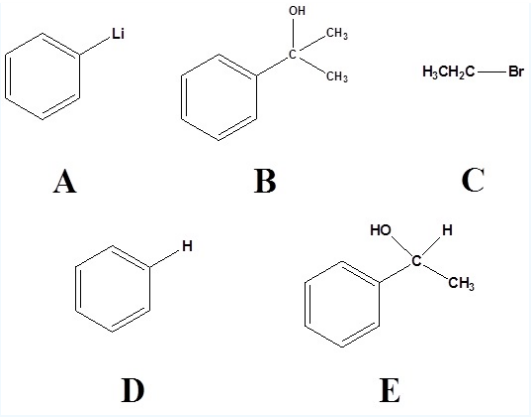


12. Please show two sets of reactants which could be used to synthesize the following molecule using a Grignard reaction.



Answers

9.



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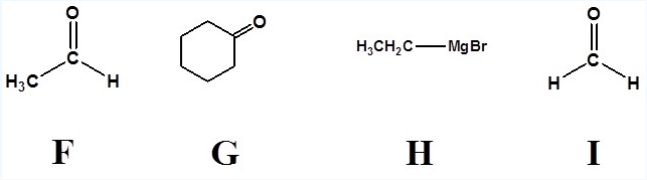
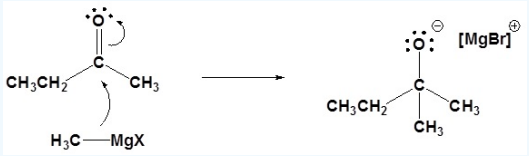
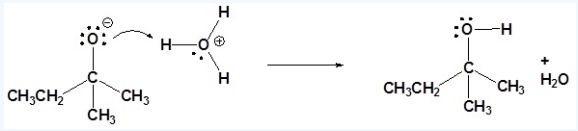


11.

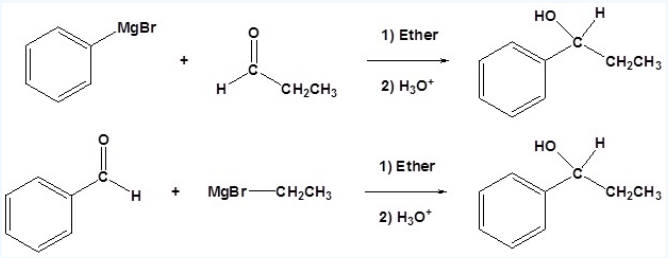
Nucleophilic addition reaction



Protonation



12.



Contributors and Attributions

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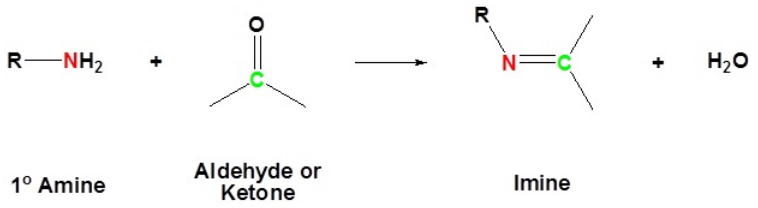
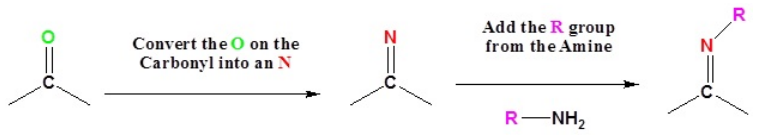
18.9: Nucelophilic Addition of Amines (Imine and Enamine Formation)

Reaction with Primary Amines to form Imines

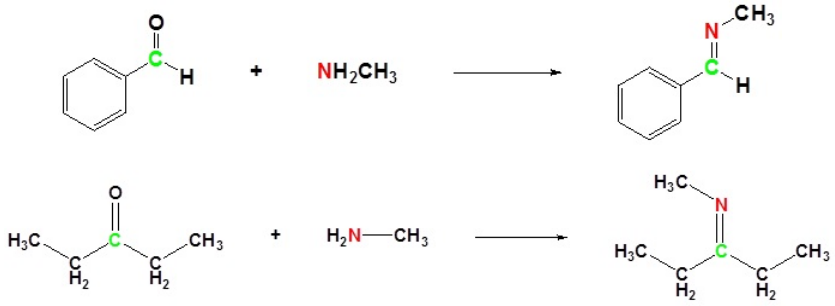
The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. The pH for reactions which form imine 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.



Converting reactants to products simply

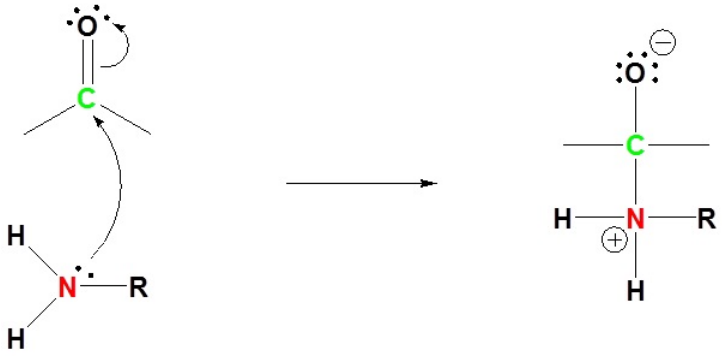


Examples of imine forming reactions



Mechanism of imine formation

1) Nucleophilic addition reaction



2) Proton transfer

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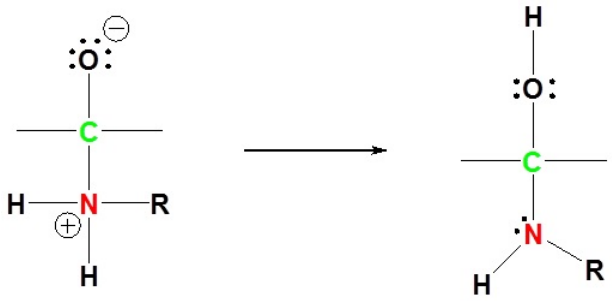
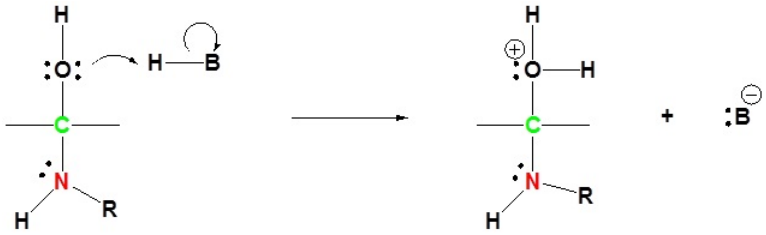
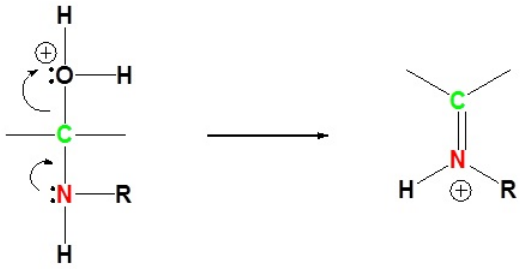


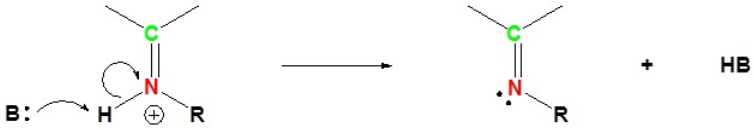
3) Protonation of OH



4) Removal of water

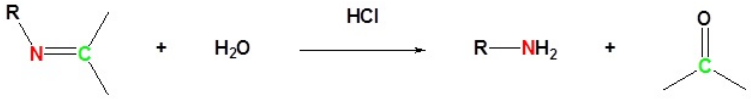


5) Deprotonation to form neutral final product



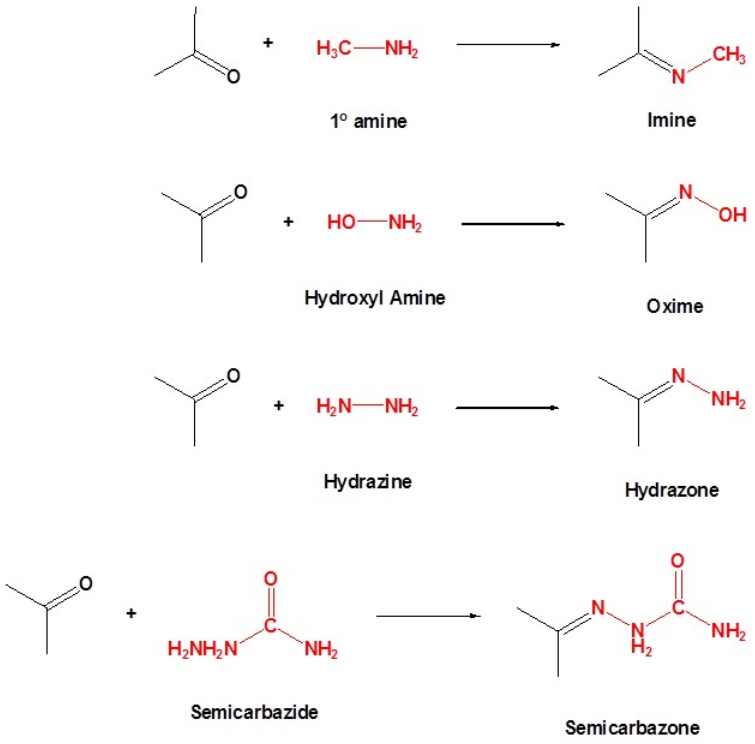
Reversibility of imine forming reactions

Imines can be hydrolyzed back to the corresponding primary amine under acidic aqueous conditons.



Reactions involving other reagents of the type Y-NH_2

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 in the following table, 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 another module.



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 two amino groups ($-NH_2$) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.

Exercise

13. Draw the products of the following reactions.

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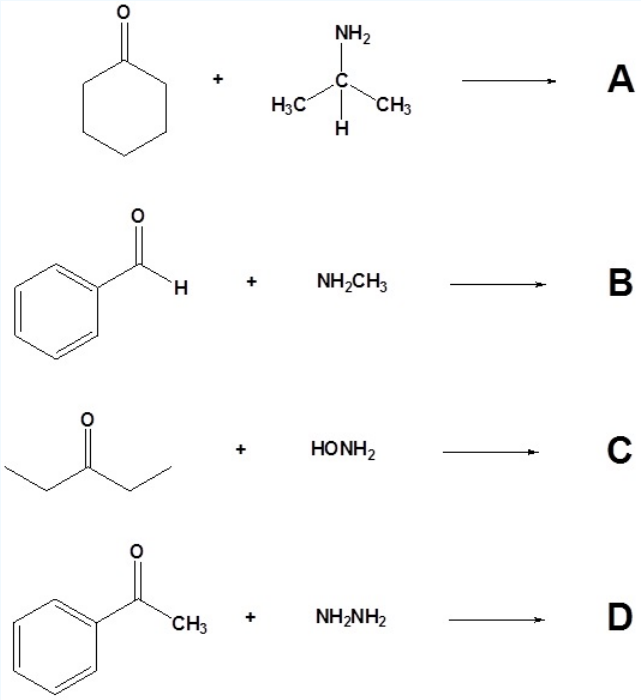
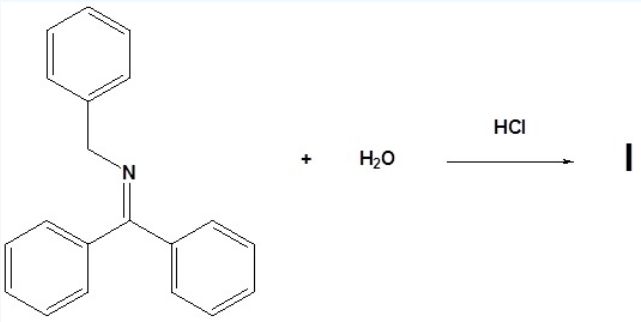
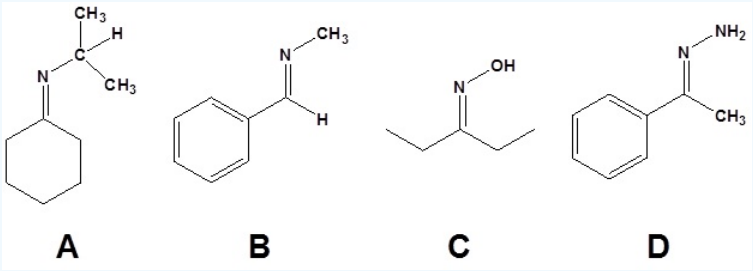


14. Draw the structure of the reactant needed to produce the indicated product.



Answer

13.



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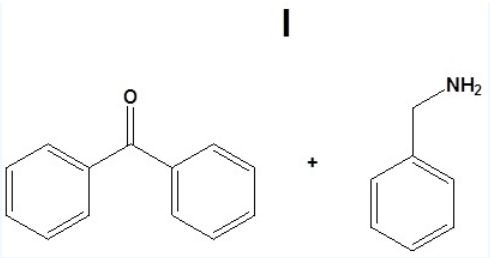


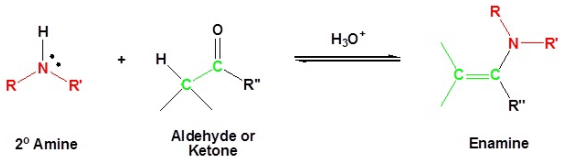
Contributors and Attributions

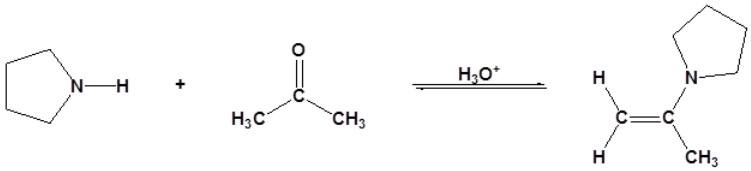
Prof. Steven Farmer (Sonoma State University)

William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

Reaction with Secondary Amines to form Enamines

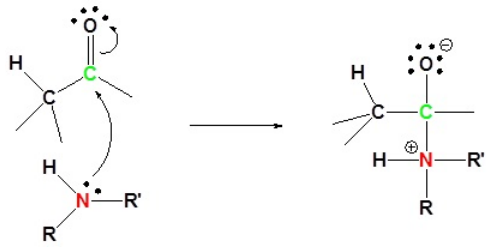
Most aldehydes and ketones react with 2°-amines to give products known as **enamines**. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.



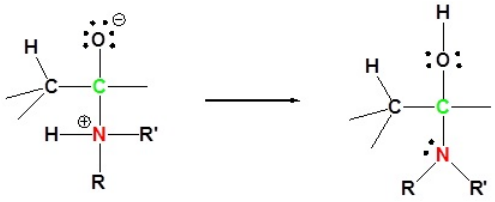


Mechanism

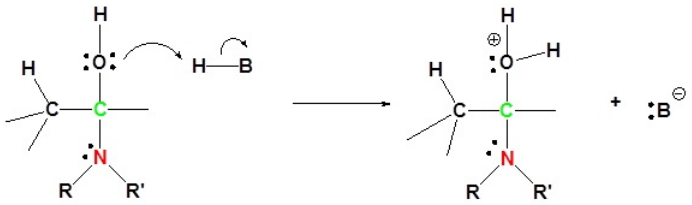
1) Nuleophilic addition reaction



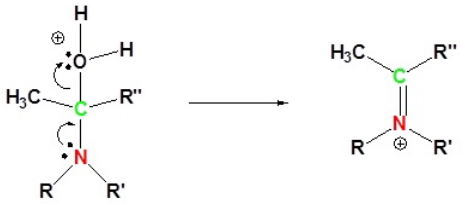
2) Proton transfer



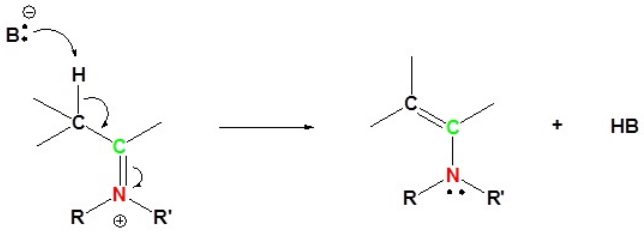
3) Protonation of OH



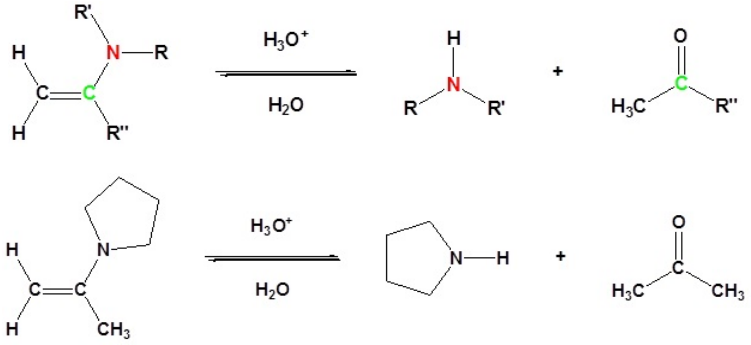
4) Removal of water



5) Deprotonation to neutralize final product

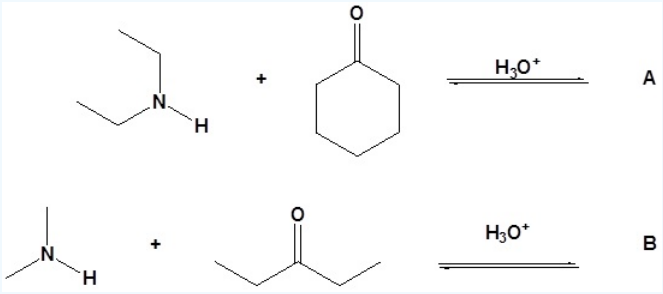


Reversibility of Enamines

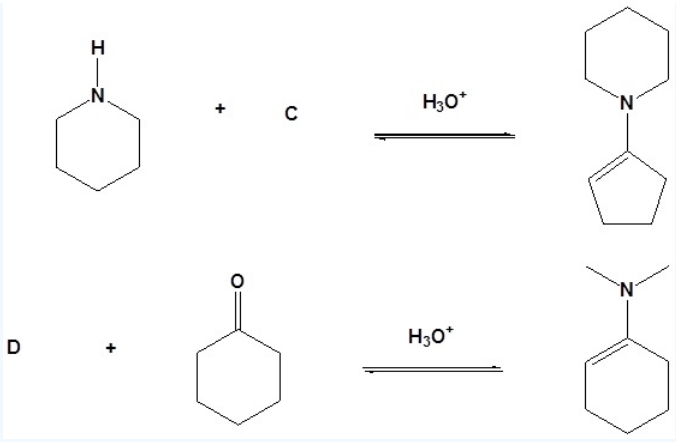


Exercise

15. Draw the products for the following reactions.

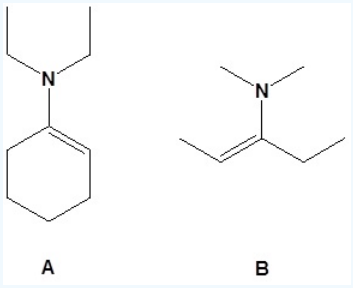


16. Draw the missing reactant to complete each reaction below.

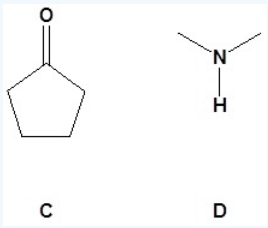


Answer

15.



16.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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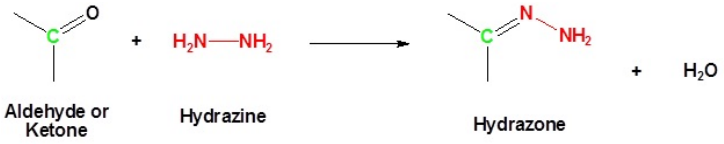
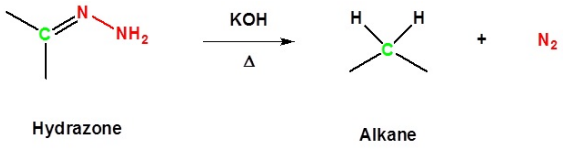
18.10: Nucleophilic Addition of Hydrazine (Wolff-Kishner Reaction)

Aldehydes and ketones can be converted to a hydrazine derivative by reaction with hydrazine. These "hydrazones" can be further converted to the corresponding alkane by reaction with base and heat. These two steps can be combined into one reaction called the Wolff-Kishner Reduction which represents a general method for converting aldehydes and ketones into alkanes. Typically a high boiling point solvent, such as ethylene glycol, is used to provide the high temperatures needed for this reaction to occur. Note! Nitrogen gas is produced as part of this reaction.

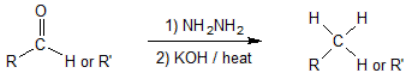
Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone



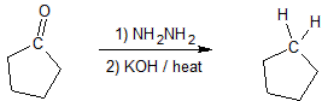
Reaction with a Base and Heat Converts a Hydrazone to an Alkane



Both Reactions Together Produces the Wolff-Kishner Reduction

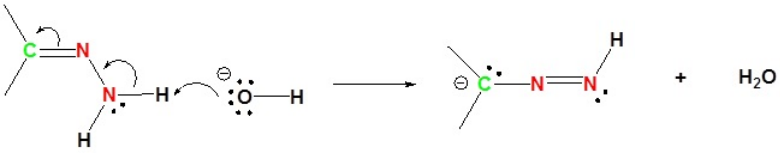


The Wolff-Kishner reaction for cyclopentanone is shown below.

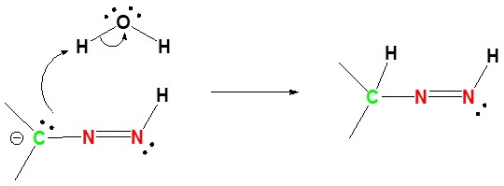


Mechanism of the Wolff-Kishner Reduction

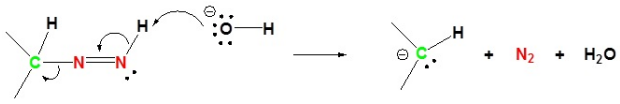
1) Deprotonation of Nitrogen



2) Protonation of the Carbon



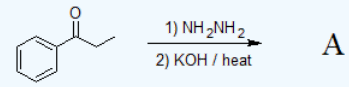
3) Deprotonation of Nitrogen

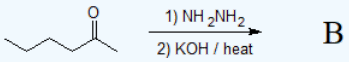


4) Protonation of Carbon

Exercise

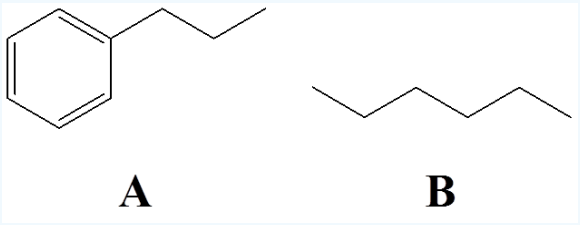
17. Draw the products for the following reactions.





Answer

17.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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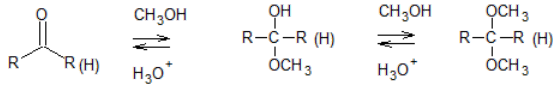
18.11: Nucelophilic Addition of Alcohols (Acetal Formation)

Introduction

It has been demonstrated that water adds rapidly to the carbonyl function of aldehydes and ketones to form geminal-diol. In a similar reaction alcohols add reversibly to aldehydes and ketones to form hemiacetals (h*emi*, Greek, half). This reaction can continue by adding another alcohol to form an acetal. Hemiacetals and acetals are important functional groups because they appear in sugars.



hemiacetal acetal

To achieve effective hemiacetal or acetal formation, two additional features must be implemented. First, an acid catalyst must be used because alcohol is a weak nucleophile; and second, the water produced with the acetal must be removed from the reaction by a process such as a molecular sieves or a **Dean-Stark trap**. The latter is important, since acetal formation is reversible. Indeed, once pure hemiacetal or acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid and an excess of water.

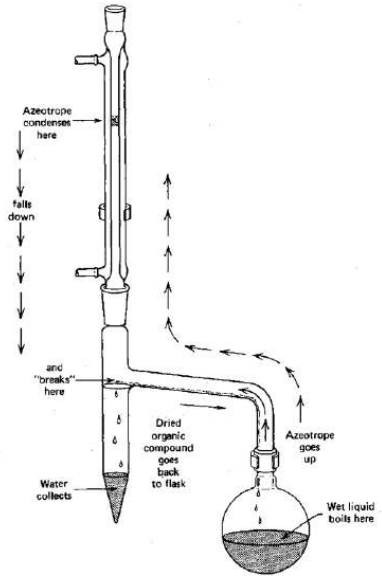
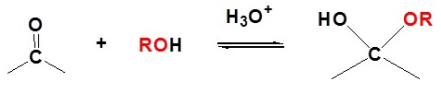


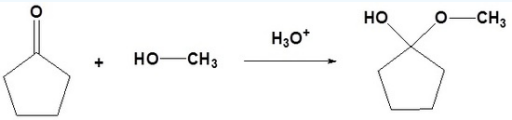
Figure: Dean-Stark Trap for Isolating Hemiacetals and Ketals

Formation of Hemiacetals

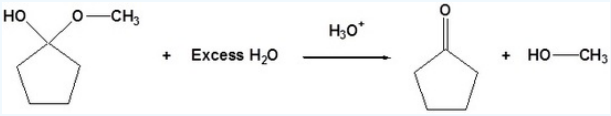


Aldehyde or Ketone **Hemi-Acetal**

Example: Formation of Hemiacetals

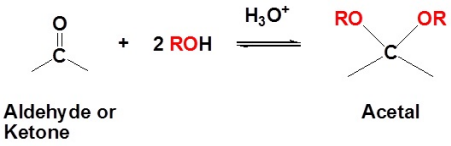


Example: Hemiacetal Reversibility

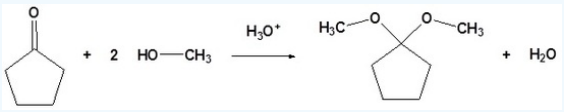


Formation of Acetals

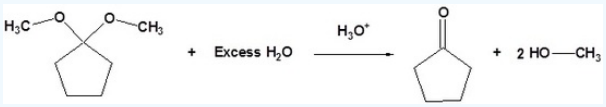
Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents (or an excess amount) of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. It is important to note that a hemiacetal is formed as an intermediate during the formation of an acetal.



Example: Formation of Acetals



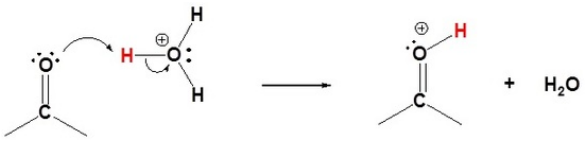
Example: Acetal Reversibility



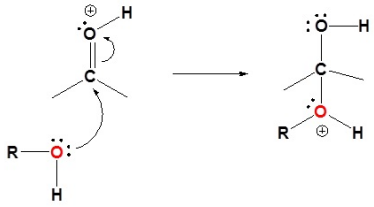
Mechanism for Hemiacetal and Acetal Formation

The mechanism shown here applies to both acetal and hemiacetal formation

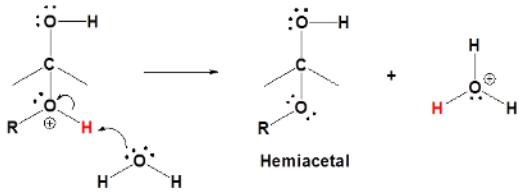
1) Protonation of the carbonyl



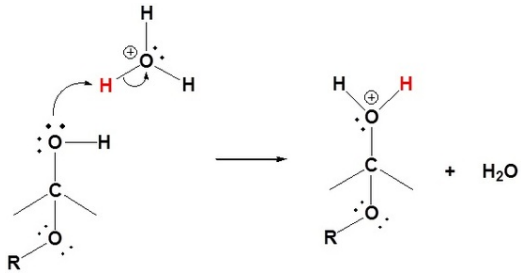
2) Nucleophilic additional reaction by the alcohol



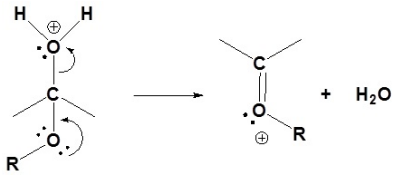
3) Deprotonation to form a hemiacetal



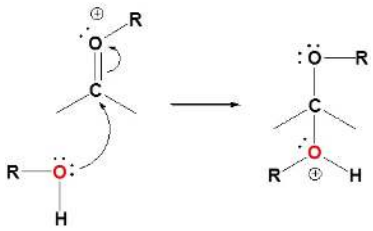
4) Protonation of the alcohol



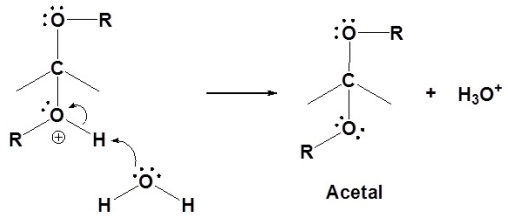
5) Removal of water



6) Nucleophilic addition reaction by the alcohol

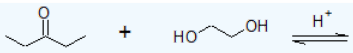


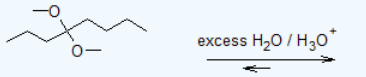
7) Deprotonation by water

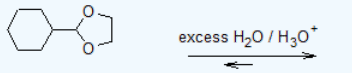


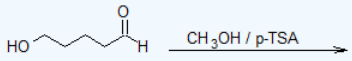
Exercise

18. Draw the products for the following reactions.

a) 

b) 

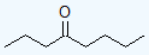
c) 

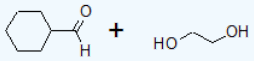
d) 

Answer

18.

a)

b) 

c) 

d)

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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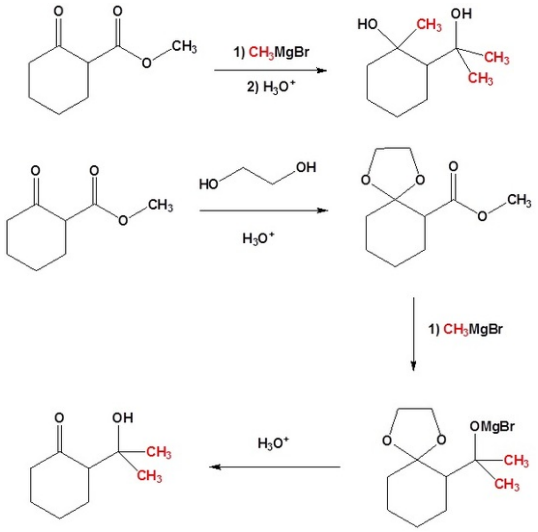
18.12: Acetals as Protecting Groups

Acetals as Protecting Groups

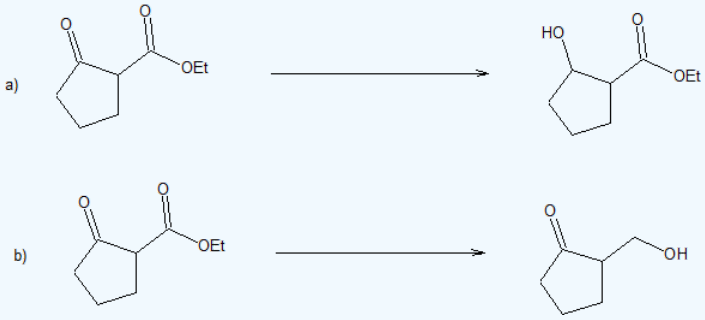
The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general. Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents. 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.

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 esters and ketones.



Exercise

19. Specify the reagents to perform the following chemical transformations.



Answer

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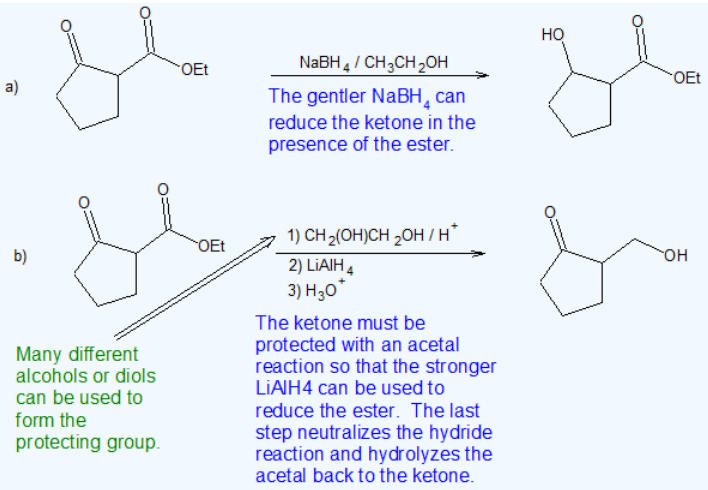

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18.13: Nucelophilic Addition of Phosphorus Ylides (The Wittig Reaction)

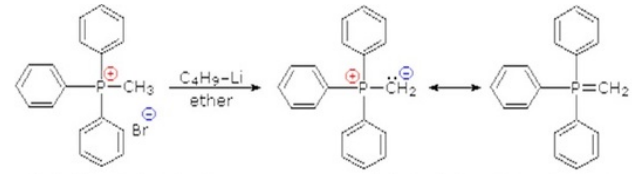
Organophosphorus ylides react with aldehydes or ketones to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. A principal advantage of alkene synthesis by the Wittig reaction is that the location of the double bond is absolutely fixed, in contrast to the mixtures often produced by alcohol dehydration.

Preparation of Phosphorus Ylides

It has been noted that dipolar phosphorus compounds are stabilized by p-d bonding. This bonding stabilization extends to carbanions adjacent to phosphonium centers, and the zwitterionic conjugate bases derived from such cations are known as ylides. An **ylide** is defined as a compound with opposite charges on adjacent atoms both of which have complete octets. For the Wittig reaction discussed below an organophosphorus ylide, also called Wittig reagents, will be used. The ability of phosphorus to hold more than eight valence electrons allows for a resonance structure to be drawn forming a double bonded structure.

An Ylide

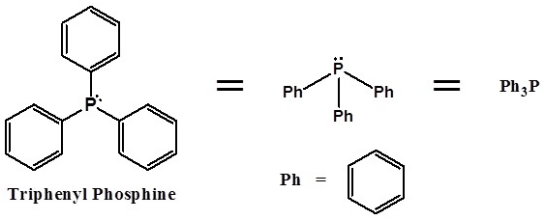
The stabilization of the carbanion provided by the phosphorus causes an increase in acidity (pKa ~35). Very strong bases, such as butyl lithium, are required for complete formation of ylides.



The ylides shown here are all strong bases. Like other strongly basic organic reagents, they are protonated by water and alcohols, and are sensitive to oxygen. Water decomposes phosphorous ylides to hydrocarbons and phosphine oxides, as shown.

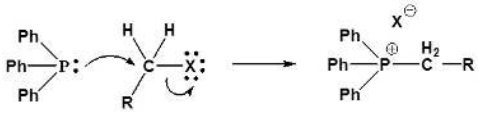
$$R_3P{=}CR'_2 \;+\; H_2O \longrightarrow R_3P{=}O \;+\; R'_2CH_2$$

Although many ylides are commercially available it is often necessary to create them synthetically. Ylides can be synthesized from an alkyl halide and a trialkyl phosphine. Typically triphenyl phosphine is used to synthesize ylides. Because a S_N2 reaction is used in the ylide synthesis 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 synthesis which involves a synthesized Wittig reagent.

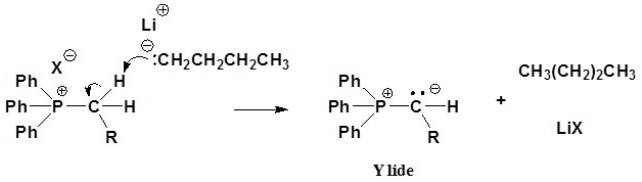


Mechanism of ylide formation

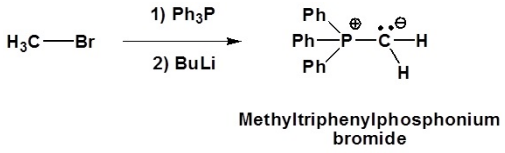
1) S_N2 reaction



2) Deprotonation

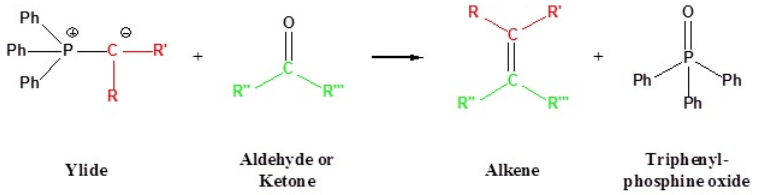


Examples of ylide formation

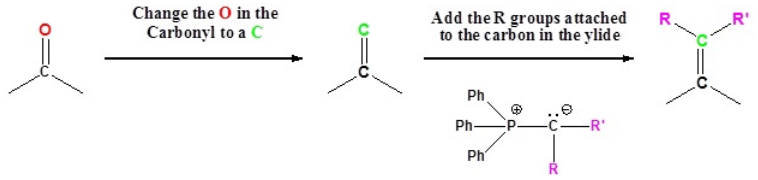


The Wittig Reaction

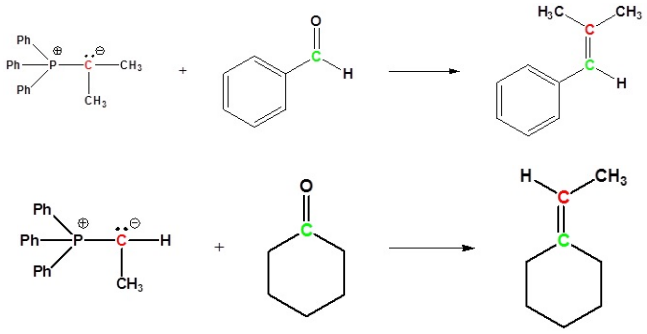
The most important use of ylides in synthesis comes from their reactions with aldehydes and ketones, which are initiated in every case by a covalent bonding of the nucleophilic alpha-carbon to the electrophilic carbonyl carbon. Ylides react to give substituted alkenes in a transformation called the Wittig reaction. This reaction is named for George Wittig who was awarded the Nobel prize for this work in 1979. 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.



Going from reactants to products simplified



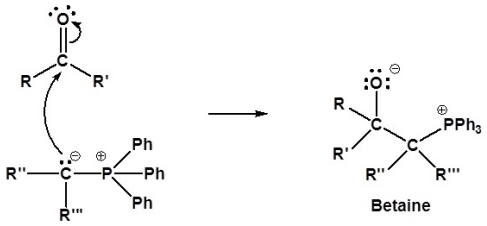
Examples of the Wittig reaction



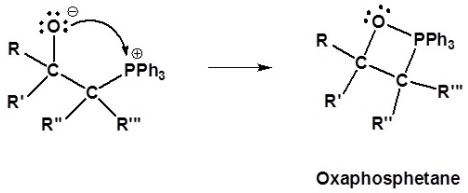
Mechanism of the Wittig reaction

Following the initial carbon-carbon bond formation, two intermediates have been identified for the Wittig reaction, a dipolar charge-separated species called a betaine and a four-membered heterocyclic structure referred to as an oxaphosphatane. Cleavage of the oxaphosphatane to alkene and phosphine oxide products is exothermic and irreversible.

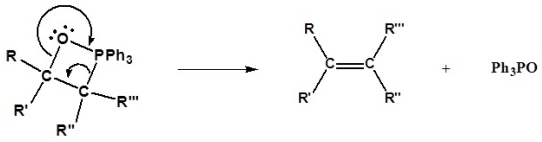
1) Nucleophillic reaction with the carbonyl



2) Formation of a 4 membered ring

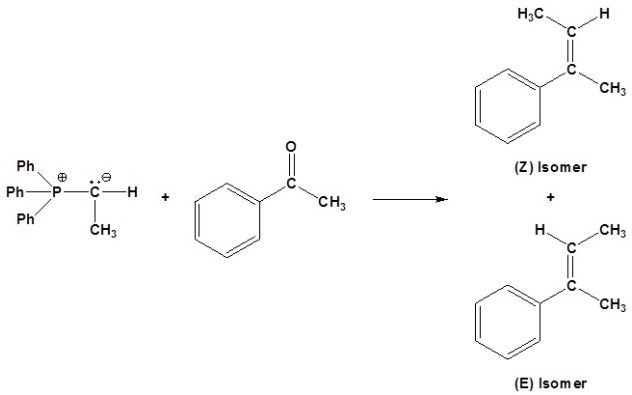


3) Formation of the alkene



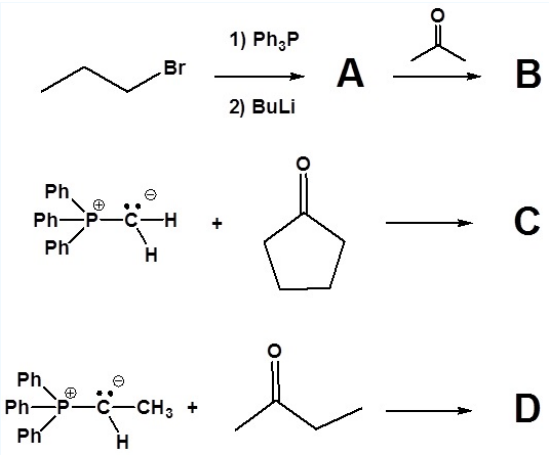
Limitation of the Wittig reaction

If possible both E and Z isomer of the double bond will be formed. This should be considered when planning a synthesis involving a Wittig Reaction.

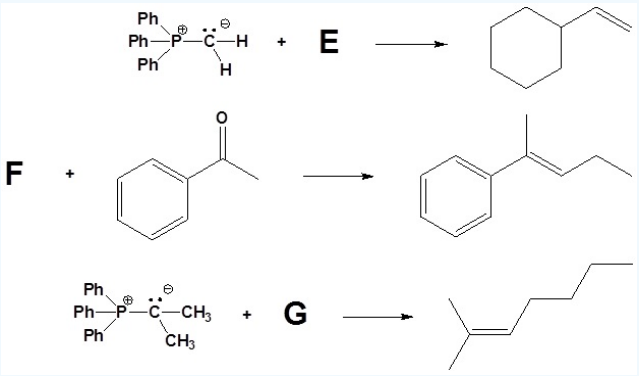


Exercise

20. Draw the products of the following reactions.



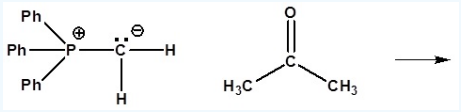
21. Please indicate the starting material required to produce the product.



22. Draw the structure of the oxaphosphetane which is made during the mechanism of the reaction given that produces product **C**.

23. Draw the structure of the betaine which is made during the mechanism of the reaction given that produces product **D**.

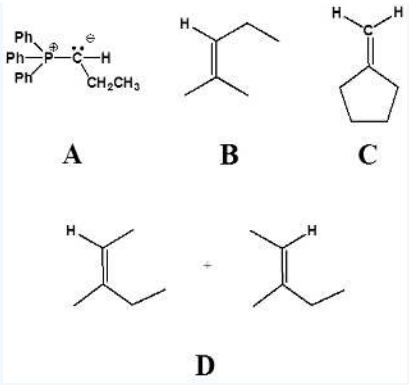
24. Propose a detailed mechanism and the final product of this reaction



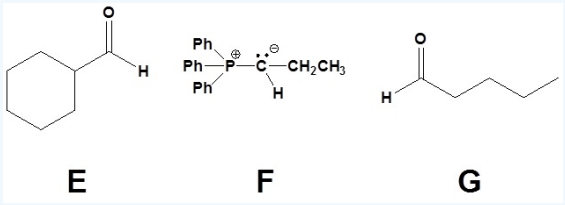
25. It has been shown that reacting and epoxide with triphenylphosphine forms an alkene. Propose a mechanism for this reaction. Review the section on epoxide reactions if you need help.

Answer

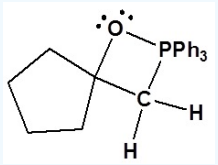
20.



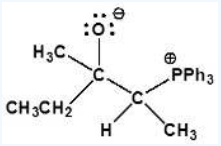
21.



22.

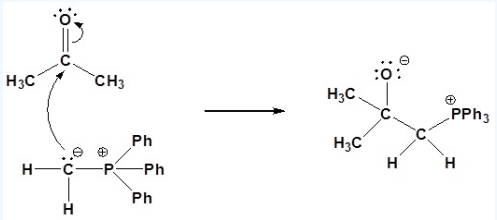


23.

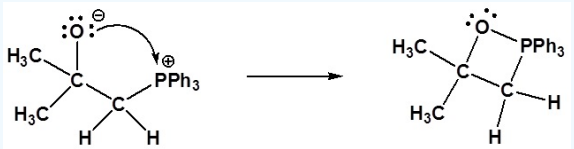


24.

Nucleophillic reaction with the carbonyl



Formation of a 4 membered ring



Formation of the alkene

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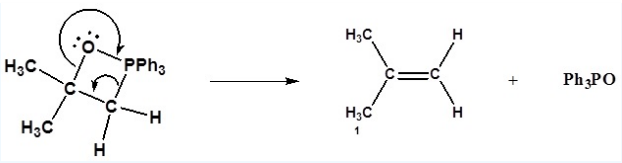
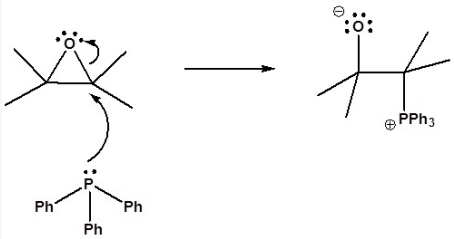
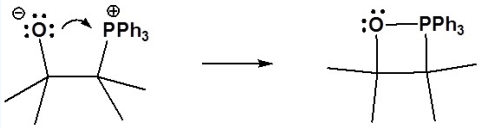


25.

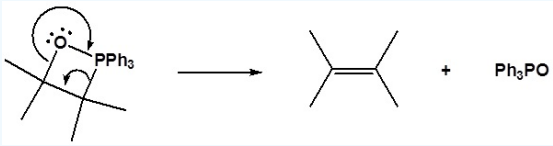
Nucleophillic reaction with the epoxide



Formation of a 4 membered ring



Formation of the alkene



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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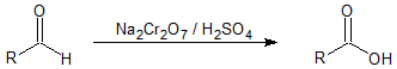
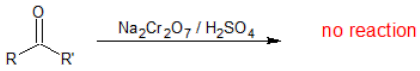
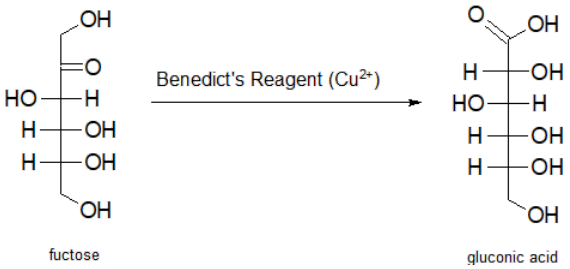
18.14: Oxidation of Aldehydes

Oxidation and Carbonyls

Aldehydes are so easily oxidized that oxidation reactions can be an unwanted side reaction. Isolated ketones cannot be oxidized. The poly-hydroxy ketones of monosaccharides can be oxidized as seen in carbohydrate chemistry.

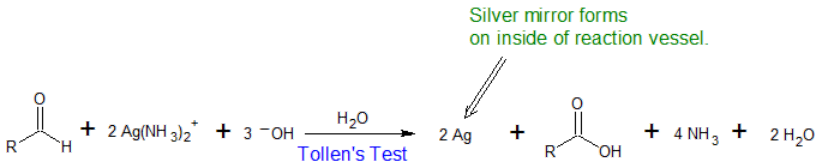


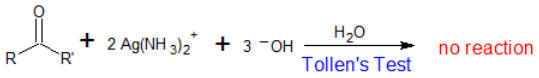




Tollen's Test

The Tollen's Test differentiates between aldehydes and ketones based on one of their few differences in chemical reactivity. Aldehydes can be oxidized and ketones cannot. In the Tollen's Test, silver ions (Ag^+) oxidize aldehydes to carboxylic acids and are reduces to silver metals which can form a beautiful coating on the inside of the reaction flask.





Exercise

26. Draw and name the oxidation products for the following compounds.

a) benzaldehyde

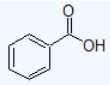
b) acetaldehyde

c) 3-hydroxypentanal

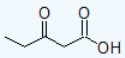
Answer

26.

https://chem.libretexts.org/@go/page/183103

a)  benzoic acid

b) acetic acid

c)  3-oxopentanoic acid

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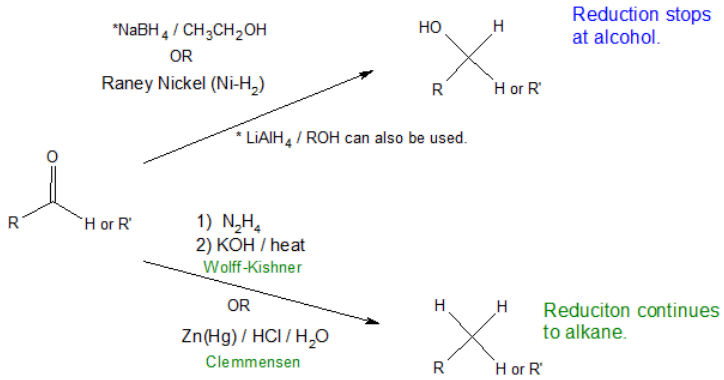
18.15: Reductions of Ketones and Aldehydes

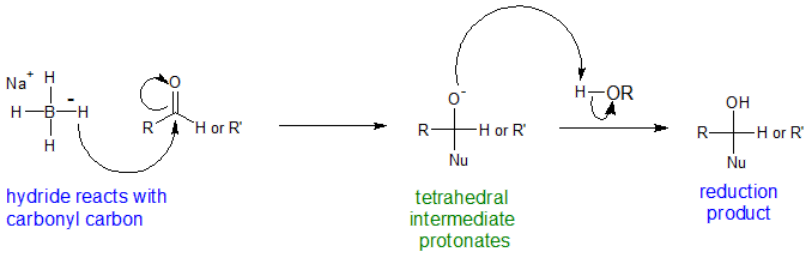
Carbonyl Reduction Reactions

Aldehydes and ketones can be partially reduced to alcohols with sodium borohydride or Raney nickel. Of course, $LiAlH_4$ could be used in stead of $NaBH_4$. However, $LiAlH_4$ is a stronger reducing agent so some benefits of selectivity are lost. Depending on the presence of more than one functional group within a single molecule, reaction selectivity can be useful. Aldehydes and ketones can be fully reduced to alkanes the Wolff-Kishner or Clemmensen Reduction.



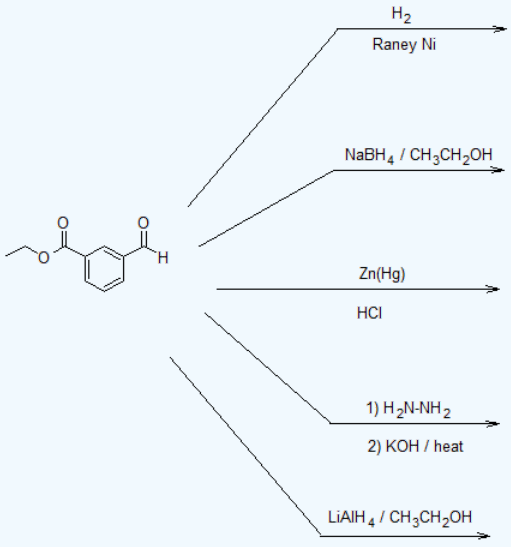
Hydride Reduction Mechanism

The hydride reduction mechanism follows the pattern we have learned for other nucleophilic addition reactions.



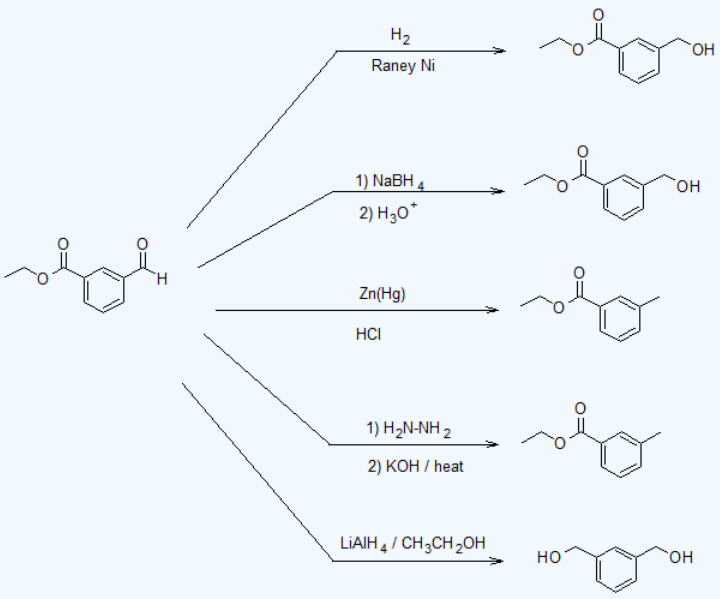
Exercise

27. Complete the reaction map below.



Answer

27.



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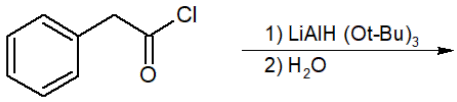
18.16: Additional Exercises

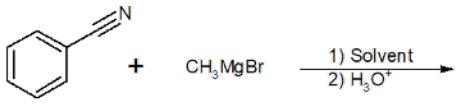
General Review

19-1 Give the product of the following reaction.

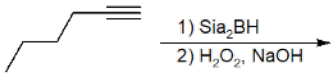


19-2 For each of the following reactions, give the final product.

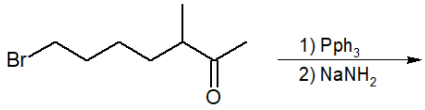
a)



b)

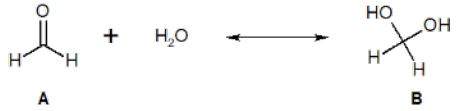


19-3 For the following reaction, give the final product.

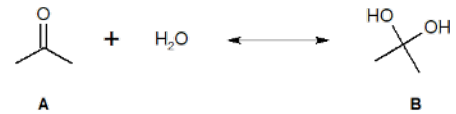


19-4 For the following reactions, identify the side favored at equilibrium.

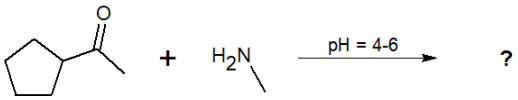
1)



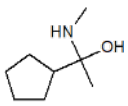
2)



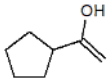
19-5 Identify the correct product of the following reaction.



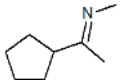
a)



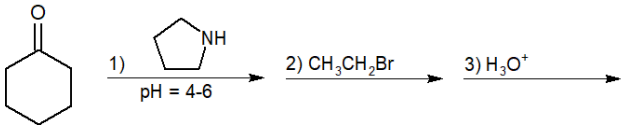
b)



c)

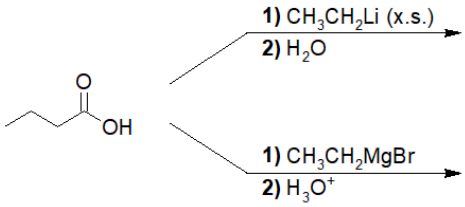


19-6 Give the final product of the following chain of reactions.

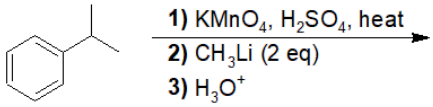


Synthesis of Ketones from Carboxylic Acids

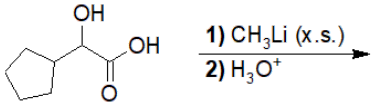
19-7 Provide the structures of the products of the following reactions.



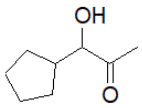
19-8 Provide the structure and IUPAC nomenclature of the product of the following reaction.



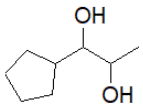
19-9 Choose the correct answer.



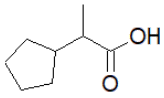
a)



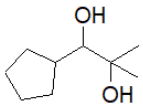
b)



c)



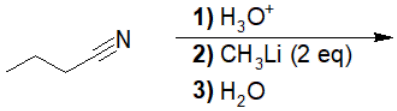
d)



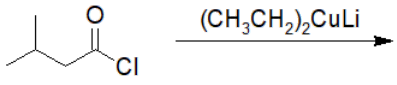
Synthesis of Ketones and Aldehydes from Acid Chlorides, Esters, and Nitriles

19-10 Provide the structures of the products of the following reactions.

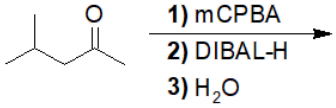
a)



b)

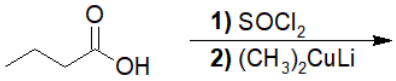


19-11 Choose the correct product of the following reaction.



a) b) c) d)

19-12 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) butanal

b) 2-methylhexan-3-one

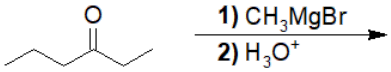
c) pentan-2-one

d) 2-methylpentan-2-ol

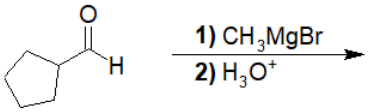
Reactions of Ketones and Aldehydes

19-13 Provide the products of the following reactions.

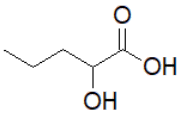
a)



b)

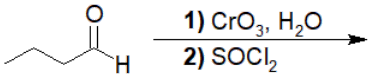


19-14 Suggest a way to make the following compound from butanol. Use any necessary reagents.



2-hydroxypentanoic acid

19-15 Choose the correct product of the following reaction.



a) 2-chloropentane

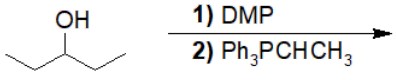
b) 1-chlorobutan-1-ol

c) 2-chlorobutanoic acid

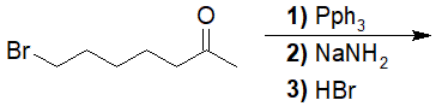
d) butanoyl chloride

The Wittig Reaction

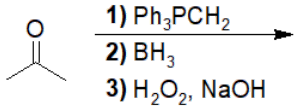
19-16 Predict the structure of the product of the following reaction.



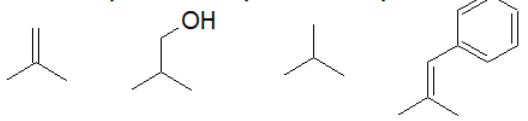
19-17 Provide the product of the following reaction.



19-18 Choose the correct product of the following reaction.

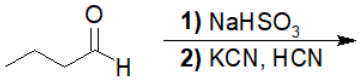


a) **b)** **c)** **d)**

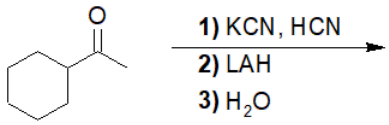


Formation of Cyanohydrins

19-19 Predict the structure of the product of the following reaction.



19-20 Provide the structure of the product of the following reaction.



19-21 Choose the correct IUPAC nomenclature of the product of the following reaction.

a) 3-ethylhex-1-yn-3-ol

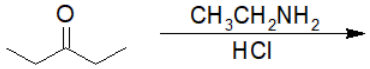
b) 2-ethyl-2-hydroxypentanenitrile

c) 3-(aminomethyl)hexan-3-ol

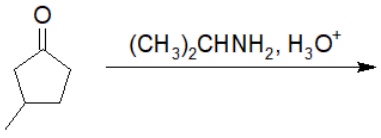
d) butanoyl cyanide

Formation of Imines

19-22 Predict the product of the following reaction.

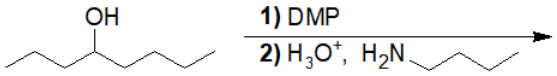


19-23 Provide the structure of the product of the following reaction.



19-24 Choose the correct IUPAC nomenclature of the product of the following reaction.

https://chem.libretexts.org/@go/page/183105



a) (4Z)-N-butyloctan-4-imine

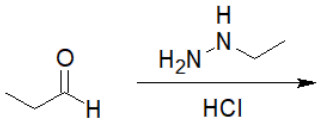
b) (4Z)-N-propyloctan-4-imine

c) (4Z)-5-propylnon-4-en-1-amine

d) 4-(butylamino)octan-4-ol

Condensations with Hydroxylamine and Hydrazines

19-25 Choose the correct IUPAC nomenclature of the product of the following reaction.



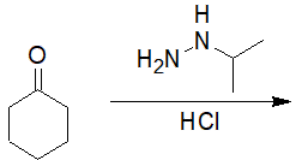
a) 1-ethyl-2-propylhydrazine

b) N-propoxyethanamine

c) (1E)-N-ethylbut-1-en-1-amine

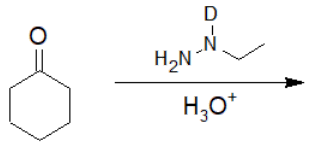
d) (2E)-1-ethyl-2-propylidenehydrazine

19-26 Provide the structure of the product of the following reaction.

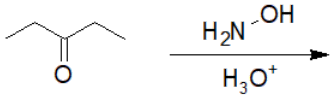


19-27 Provide the structure of the products of the following reactions.

a)

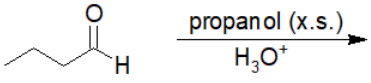


b)

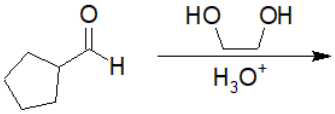


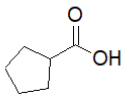
Formation and Use of Acetals

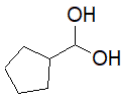
19-28 Provide the structure of the resulting acetal.

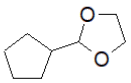


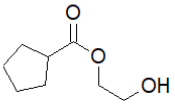
19-29 Choose the correct structure of the product of the following reaction.



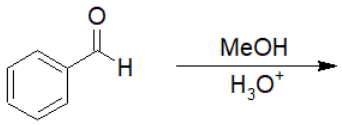
a) 

b) 

c) 

d) 

19-30 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) (dimethoxymethyl)benzene

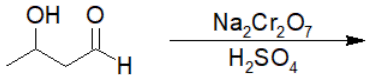
b) benzoic acid

c) phenylmethanediol

d) (methoxymethyl)benzene

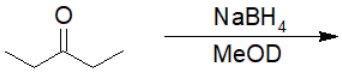
Oxidation of Aldehydes and Reductions of Ketones and Aldehydes

19-31 Draw the structure of the product of the following oxidation reaction.

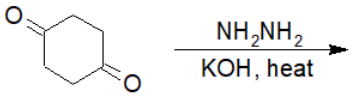


19-32 Draw the structures of the products of the following reduction reactions.

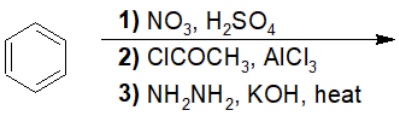
a)



b)



19-33 Predict the product of the following reaction and provide its IUPAC nomenclature.



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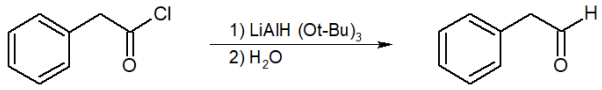
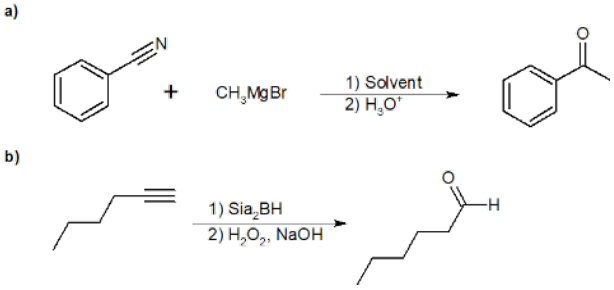
18.17: Solutions to Additional Exercises

General Review

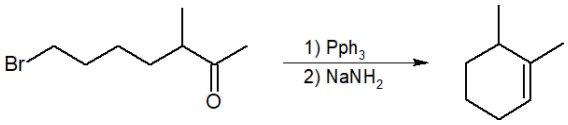
19-1



19-2



19-3

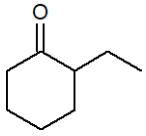


19-4

1. B
2. A

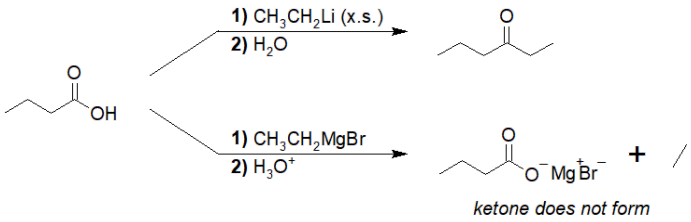
19-5 Answer: C

19-6



Synthesis of Ketones from Carboxylic Acids

19-7:



19-8:

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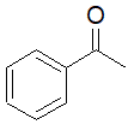


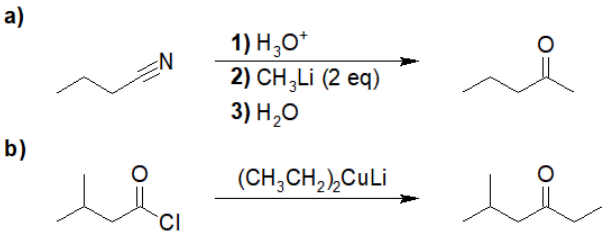
1-phenylethan-1-one

19-9:

Answer: A

Synthesis of Ketones and Aldehydes from Acid Chlorides, Esters, and Nitriles

19-10:



19-11:

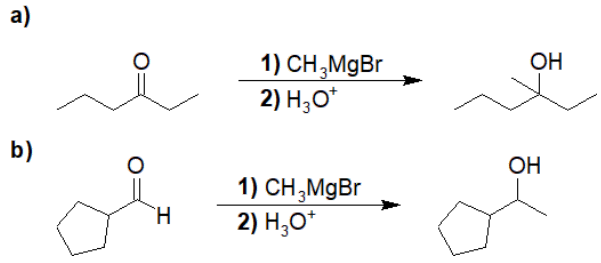
Answer: A

19-12:

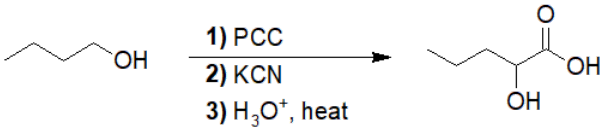
Answer: C

Reactions of Ketones and Aldehydes

19-13:



19-14:

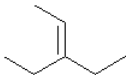


19-15:

Answer: D

The Wittig Reaction

19-16:



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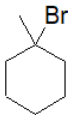
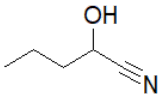


19-18:

Answer: B

Formation of Cyanohydrins

19-19:



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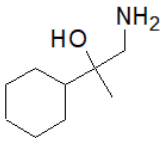
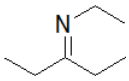


19-21:

Answer: B

Formation of Imines

19-22:



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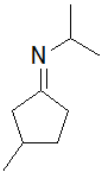


19-24:

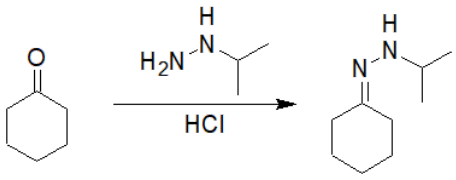
Answer: A

Condensations with Hydroxylamine and Hydrazines

19-25:

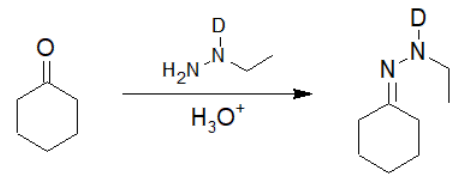
Answer: D

18-26:

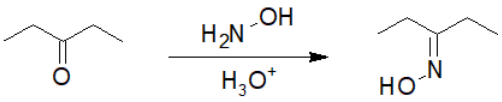


19-27:

a)

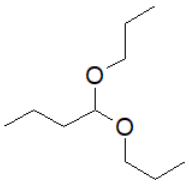


b)



Formation and Use of Acetals

19-28:



19-29:

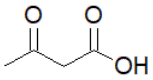
Answer: C

19-30:

Answer: A

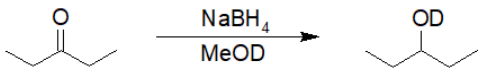
Oxidation of Aldehydes and Reductions of Ketones and Aldehydes

19-31:



19-32:

a)



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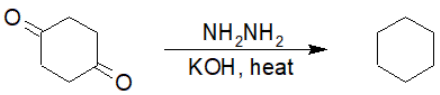

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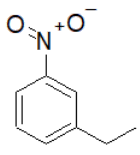

1-ethyl-3-nitrobenzene

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CHAPTER OVERVIEW

19: Carboxylic Acids
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of carboxylic acids and carboxylate salts (section 21.1)
- explain and predict the relative acidity of carboxylic acids using resonance, hybridization, and substituent effects (section 21.2)
- determine the structure of carboxylic acids from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 21.3)
- predict the products and specify the reagents to synthesize carboxylic acids (section 21.4)
- recognize and classify the major reactions of carboxylic acids (section 21.5)
- show the general mechanism for Nucleophilic Acyl Substitution Reactions (section 21.5)
- predict the products and specify the reagents for reactions of carboxylic acids with
  - sulfonyl chlorides (section 21.5)
  - alcohols (section 21.6)
  - diazomethane (section 21.7)
  - amines (section 21.8)
  - reducing agents (section 21.9)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis

Please note: IUPAC nomenclature and important common names of carboxylic acids were explained in Chapter 3.

It can useful is often required to memorize the structures for the following common names: formic acid, acetic acid, acetyl chloride, acetic anhydride, acetic formic anhydride, ethyl acetate, sodium and potassium salts of formate, acetate, and benzoate, acetamide, benzamide, acetonitrile, benzonitrile, carbonic acid, oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, and phthalic acid

19.1: Structure and Properties of Carboxylic Acids and their Salts
19.2: Acidity of Carboxylic Acids
19.3: Spectroscopy of Carboxylic Acids
19.4: Synthesis of Carboxylic Acids
19.5: Reactions of Carboxylic Acids Overview
19.6: Condensation of Acids with Alcohols: The Fischer Esterification
19.7: Methyl Ester Synthesis Using Diazomethane
19.8: Condensation of Acids with Amines
19.9: Reduction of Carboxylic Acids
19.10: Biochemically Interesting Carboxylic Acids
19.11: Additional Exercises
19.12: Solutions to Additional Exercises

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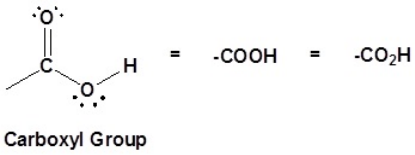
19.1: Structure and Properties of Carboxylic Acids and their Salts

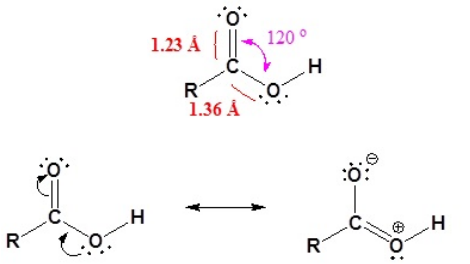
Structure of the carboxyl acid group

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 give a carbonyl group a basic trigonal shape. The hydroxyl oxygen is also sp^2 hybridized which allows one of its lone pair electrons to conjugate with the pi system of the carbonyl group. This make the carboxyl group planar an can represented with the following resonance structure.



Major Contributor Minor Contributor

Carboxylic acids are named such because they can donate a hydrogen to produce a carboxylate ion. The factors which affect the acidity of carboxylic acids are discussed in the next section of this chapter.

Carboxylic acid Carboxylate ion

Physical Properties of Some 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

Saturated			Unsaturated		
Formula	Common Name	Melting Point	Formula	Common Name	Melting Point
$CH_3(CH_2)_{10}CO_2H$	lauric acid	45 ºC	$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_{12}CO_2H$	myristic acid	55 ºC	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_{14}CO_2H$	palmitic acid	63 ºC	$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3(CH_2)_{16}CO_2H$	stearic acid	69 ºC	$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_{18}CO_2H$	arachidic acid	76 ºC	$CH_3(CH_2)_4(CH{=}CHCH_2)_4(CH_2)_2CO_2H$	arachidonic acid	-49 ºC

The table at the beginning of this page gave the melting and boiling points for a homologous group of carboxylic acids having from one to ten carbon atoms. The boiling points increased with size in a regular manner, but the melting points did not. Unbranched acids made up of an even number of carbon atoms have melting points higher than the odd numbered homologs having one more or one less carbon. This reflects differences in intermolecular attractive forces in the crystalline state. In the table of fatty acids we see that the presence of a cis-double bond significantly lowers the melting point of a compound. Thus, palmitoleic acid melts over 60º lower than palmitic acid, and similar decreases occur for the C_{18} and C_{20} compounds. Again, changes in crystal packing and intermolecular forces are responsible.

The factors that influence the relative boiling points and water solubilities of various types of compounds were discussed earlier. In general, dipolar attractive forces between molecules act to increase the boiling point of a given compound, with hydrogen bonds being an extreme example. Hydrogen bonding is also a major factor in the water solubility of covalent compounds To refresh your understanding of these principles Click Here. The following table lists a few examples of these properties for some similar sized polar compounds (the non-polar hydrocarbon hexane is provided for comparison).

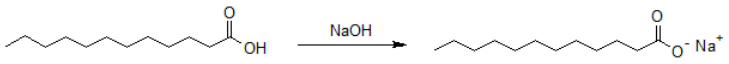
The first five entries all have oxygen functional groups, and the relatively high boiling points of the first two is clearly due to hydrogen bonding. Carboxylic acids have exceptionally high boiling points, due in large part to dimeric associations involving two hydrogen bonds. A structural formula for the dimer of acetic acid is shown here. When the mouse pointer passes over the drawing, an electron cloud diagram will appear. The high boiling points of the amides and nitriles are due in large part to strong dipole attractions, supplemented in some cases by hydrogen bonding.

Physical Properties of Some Organic Compounds

Formula	IUPAC Name	Molecular Weight	Boiling Point	Water Solubility
$CH_3(CH_2)_2CO_2H$	butanoic acid	88	164 ºC	very soluble
$CH_3(CH_2)_4OH$	1-pentanol	88	138 ºC	slightly soluble
$CH_3(CH_2)_3CHO$	pentanal	86	103 ºC	slightly soluble
$CH_3CO_2C_2H_5$	ethyl ethanoate	88	77 ºC	moderately soluble
$CH_3CH_2CO_2CH_3$	methyl propanoate	88	80 ºC	slightly soluble
$CH_3(CH_2)_2CONH_2$	butanamide	87	216 ºC	soluble
$CH_3CON(CH_3)_2$	N,N-dimethylethanamide	87	165 ºC	very soluble
$CH_3(CH_2)_4NH_2$	1-aminobutane	87	103 ºC	very soluble
$CH_3(CH_2)_3CN$	pentanenitrile	83	140 ºC	slightly soluble
$CH_3(CH_2)_4CH_3$	hexane	86	69 ºC	insoluble

Carboxylate Salts

The water solubility of carboxylic acids is determined by the ratio of carboxyl groups to the the number of carbon atoms in the molecule following the "4 to 6 Rule". As seen with amines, water solubility of carboxylic acids can be increased when they are ionized. Typically a strong base is used to deprotonate the carboxylic acid and drive the reaction to completion as shown below.



NOT H_2O Soluble H_2O Soluble

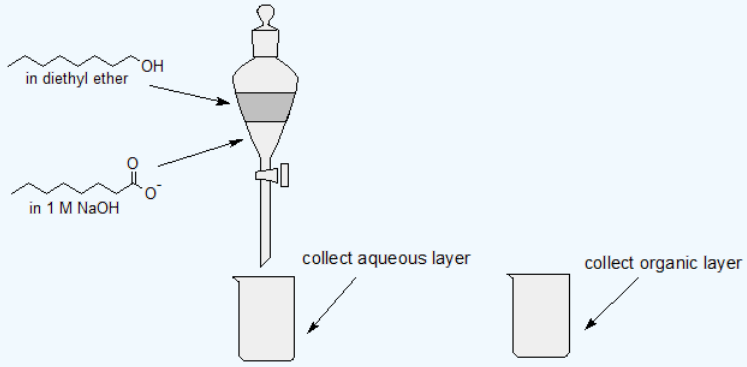
Exercise

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

1.

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.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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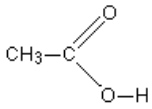
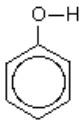
19.2: Acidity of Carboxylic Acids

Comparing the strengths of weak acids

The strengths of weak acids are measured on the pK_a scale. The smaller the number on this scale, the stronger the acid is. Three of the compounds we shall be looking at, together with their pK_a values are:

		pK_a
ethanoic acid		4.76
phenol		10.00
ethanol	$CH_3—CH_2—O—H$	about 16

Remember - the smaller the pKa, the stronger the acid. Comparing the other two to ethanoic acid, we see that phenol is very much weaker with a pK_a of 10.00, and ethanol is so weak with a pK_a of about 16 that it hardly counts as acidic at all! The pKa of ethanol is about 17, while the pKa of acetic acid is about 5: this is a 10^{12}-fold difference in the two acidity constants. In both compounds, the acidic proton is bonded to an oxygen atom. How can they be so different in terms of acidity? We begin by considering the conjugate bases.

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 localized on the second oxygen of the group. The two resonance forms for the conjugate base are equal in energy. 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 – it has nowhere else to go.

Recall the fundamental idea that electrostatic charges, whether positive or negative, are more stable when they are ‘spread out’ than when they are confined to one atom. Here, a charge is being ‘spread out’ (in other words, delocalized) *by resonance*, rather than simply by the size of the atom involved.

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 12 pK_a units between ethanol and acetic acid. The acetate ion is that much more stable than the ethoxide ion, all due to the effects of resonance delocalization.

Resonance Effects on the Acidity of Carboxylic Acids

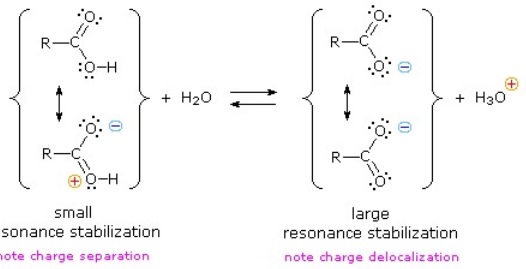
Why should the presence of a carbonyl group adjacent to a hydroxyl group have such a profound effect on the acidity of the hydroxyl proton? To answer this question we must return to the nature of acid-base equilibria and the definition of pK_a , illustrated by the general equations given below.

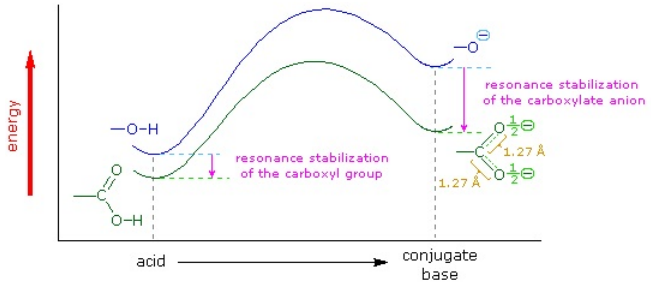
$$H\text{–}A + H_2O \rightleftharpoons H_3O^{\oplus} + A:^{\ominus} \qquad K_{eq} = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]\,[H_2O]}$$

$$K_a = \frac{[H_3O^{\oplus}]\,[A:^{\ominus}]}{[HA]} \qquad pK_a = -\log K_a = \log\left(\frac{1}{K_a}\right)$$

We know that an equilibrium favors the thermodynamically more stable side, and that the magnitude of the equilibrium constant reflects the energy difference between the components of each side. In an acid base equilibrium the equilibrium always favors the

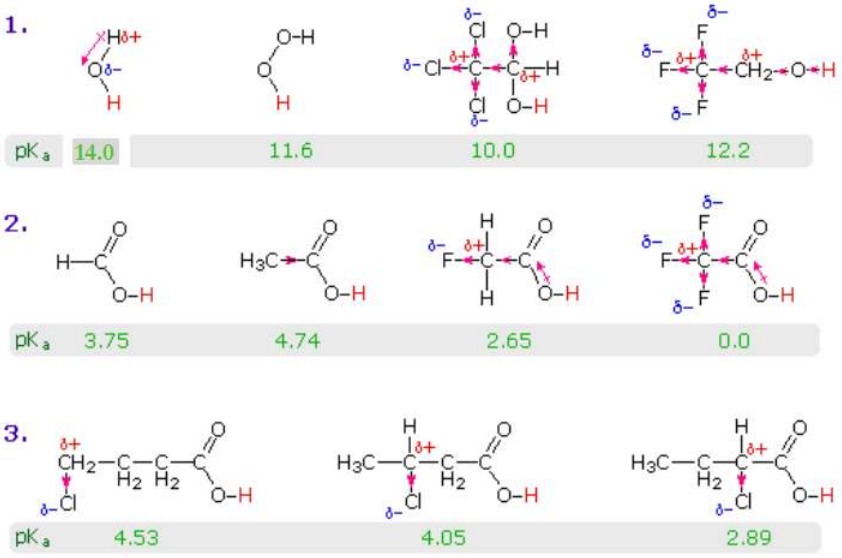
weaker acid and base (these are the more stable components). Water is the standard base used for pK_a measurements; consequently, anything that stabilizes the conjugate base ($A:^{(-)}$) of an acid will necessarily make that acid (H–A) stronger and shift the equilibrium to the right. Both the carboxyl group and the carboxylate anion are stabilized by resonance, but the stabilization of the anion is much greater than that of the neutral function, as shown in the following diagram. In the carboxylate anion the two contributing structures have equal weight in the hybrid, and the C–O bonds are of equal length (between a double and a single bond). This stabilization leads to a markedly increased acidity, as illustrated by the energy diagram displayed by clicking the "Toggle Display" button.



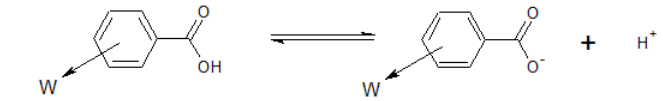


Inductive Effects on Relative Acidity

The resonance effect described here is undoubtedly the major contributor to the exceptional acidity of carboxylic acids. However, inductive effects also play a role. For example, alcohols have pK_a's of 16 or greater but their acidity is increased by electron withdrawing substituents on the alkyl group. The following diagram illustrates this factor for several simple inorganic and organic compounds (row #1), and shows how inductive electron withdrawal may also increase the acidity of carboxylic acids (rows #2 & 3). The acidic hydrogen is colored red in all examples. Water is less acidic than hydrogen peroxide because hydrogen is less electronegative than oxygen, and the covalent bond joining these atoms is polarized in the manner shown. Alcohols are slightly less acidic than water, due to the poor electronegativity of carbon, but chloral hydrate, $Cl_3CCH(OH)_2$, and 2,2,2,-trifluoroethanol are significantly more acidic than water, due to inductive electron withdrawal by the electronegative halogens (and the second oxygen in chloral hydrate). In the case of carboxylic acids, if the electrophilic character of the carbonyl carbon is decreased the acidity of the carboxylic acid will also decrease. Similarly, an increase in its electrophilicity will increase the acidity of the acid. Acetic acid is ten times weaker an acid than formic acid (first two entries in the second row), confirming the electron donating character of an alkyl group relative to hydrogen, as noted earlier in a discussion of carbocation stability. Electronegative substituents increase acidity by inductive electron withdrawal. As expected, the higher the electronegativity of the substituent the greater the increase in acidity (F > Cl > Br > I), and the closer the substituent is to the carboxyl group the greater is its effect (isomers in the 3rd row). Substituents also influence the acidity of benzoic acid derivatives, but resonance effects compete with inductive effects. The methoxy group is electron donating and the nitro group is electron withdrawing (last three entries in the table of pK_a values).



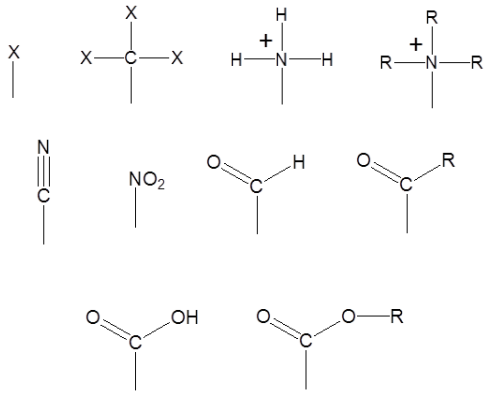
A closer look at the effects of electron-withdrawing and electron-donating groups on the stability of the conjugate bases can be seen in the pKa values of benzoic acid as shown in the table below. The conjugate base of benzoic acid is stabilized by electron-withdrawing groups. This makes the acid more acidic



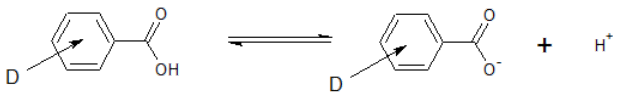
W = electron Withdrawing group

The carboxylate anion is stabilized by the electron withdrawing group increasing the acidity of the conjugate acid.

Electron-withdrawing groups deactivate the benzene ring to electrophilic reactions and make benzoic acids more acidic.



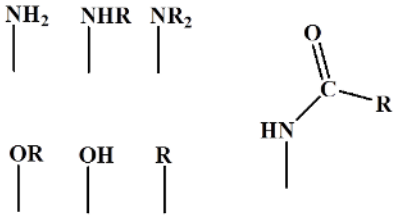
The conjugate base of benzoic acid is destabilized by electron-donating groups. This makes the acid less acidic



D = electron Donating group

The carboxylate anion is destabilized by the electron withdrawing group decreasing the acidity of the conjugate acid.

Electron-donating groups activate the benzene ring to electrophilic reactions and make benzoic acids less acidic.

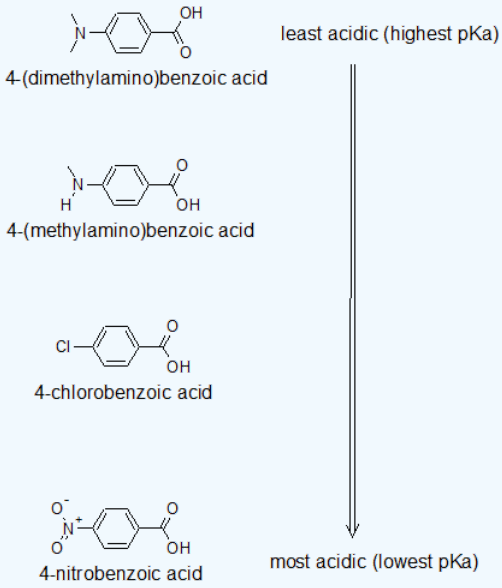


Exercise

2. Draw the bond-line structures and arrange the following compounds in order of increasing acidity: 4-nitrobenzoic acid; 4-(methylamino)benzoic acid; p-chlorobenzoic acid; 4-(dimethylamino)benzoic acid.

Answer

2.



Contributors and Attributions

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- Tom Neils (Grand Rapids Community College)

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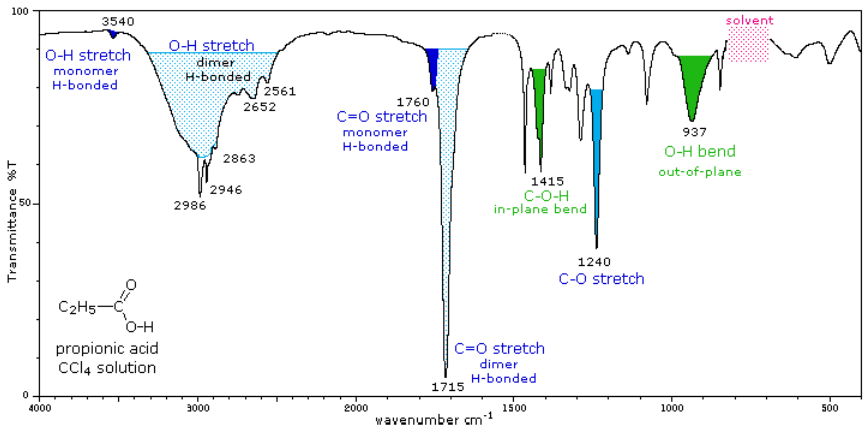
19.3: Spectroscopy of Carboxylic Acids

IR

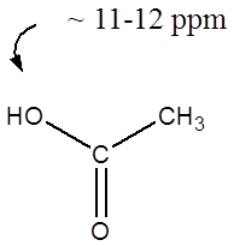
The carboxyl group is associated with two characteristic infrared stretching absorptions which change markedly with hydrogen bonding. The spectrum of a CCl_4 solution of propionic acid (propanoic acid), shown below, is illustrative. Carboxylic acids exist predominantly as hydrogen bonded dimers in condensed phases. 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 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.

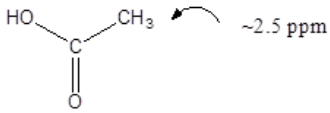


NMR

The combination of anisotropy and electronegativity causes the O-H hydrogen in a carboxylic acid to be very deshielded.



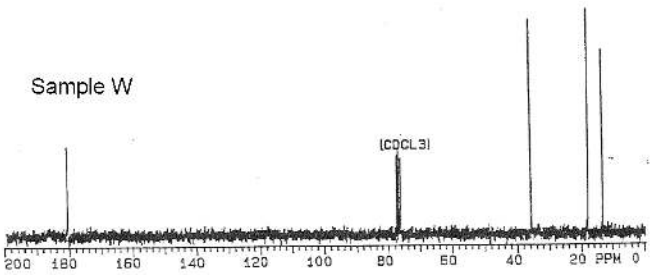
Hydrogen environments adjacent to a carboxylic acid are shifted to the region of 2.5-3.0 ppm.Deshielding occurs due to the fact that the sp2 hybridized carbon the the carboxylic acid is more electronegative than a sp3 hybridized carbon.

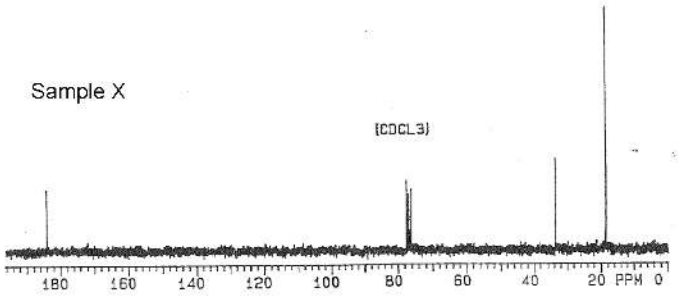


Exercise

2. 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.

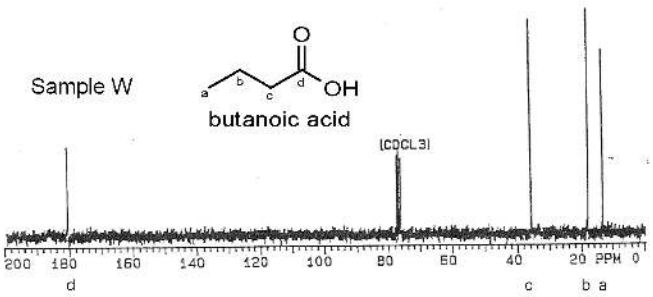
Name and draw the bond-line structures for Samples W and X and correlate the 13C NMR spectral signals to their respective compounds.

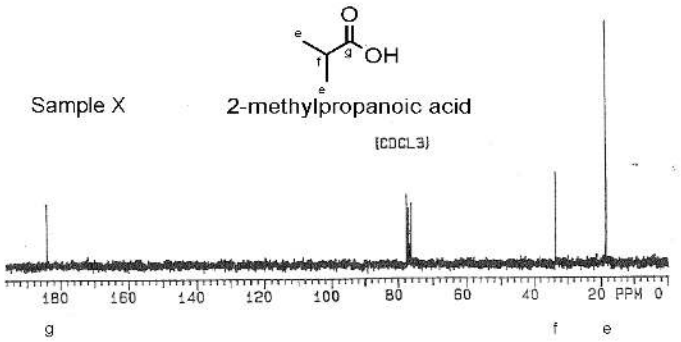




Answer

2.





Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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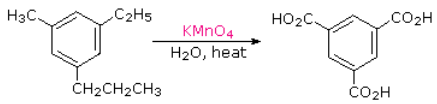
19.4: Synthesis of Carboxylic Acids

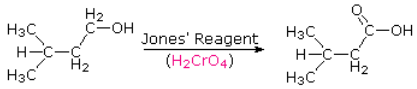
Carboxylic Acid Synthesis - Review

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, and the following diagram summarizes most of these. To review the previous discussion of any of these reaction classes simply click on the number (**1** to **4**) or descriptive heading for the group.

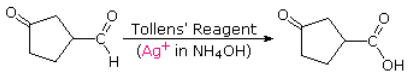
1. Oxidation of Arene Side-Chains



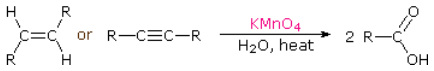
2. Oxidation of 1°-Alcohols



3. Oxidation of Aldehydes



4. Oxidative Cleavage of Alkenes and Alkynes

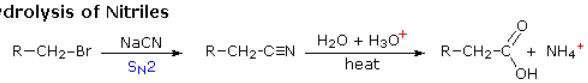


Carboxylic Acid Synthesis - New

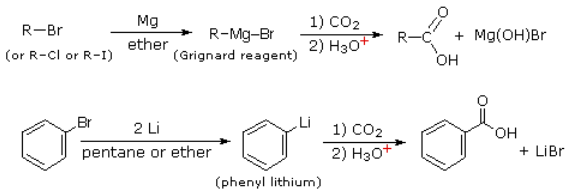
Two other useful procedures for preparing carboxylic acids involve hydrolysis of nitriles and carboxylation of organometallic intermediates. As shown in the following diagram, both methods begin with an organic halogen compound and the carboxyl group eventually replaces the halogen. Both methods require two steps, but are complementary in that the nitrile intermediate in the first procedure is generated by a S_N2 reaction, in which cyanide anion is a nucleophilic precursor of the carboxyl group. The hydrolysis may be either acid or base-catalyzed, but the latter give a carboxylate salt as the initial product.

In the second procedure the electrophilic halide is first transformed into a strongly nucleophilic metal derivative, and this adds to carbon dioxide (an electrophile). The initial product is a salt of the carboxylic acid, which must then be released by treatment with strong aqueous acid.

Hydrolysis of Nitriles



Carboxylation of Organometallic Reagents

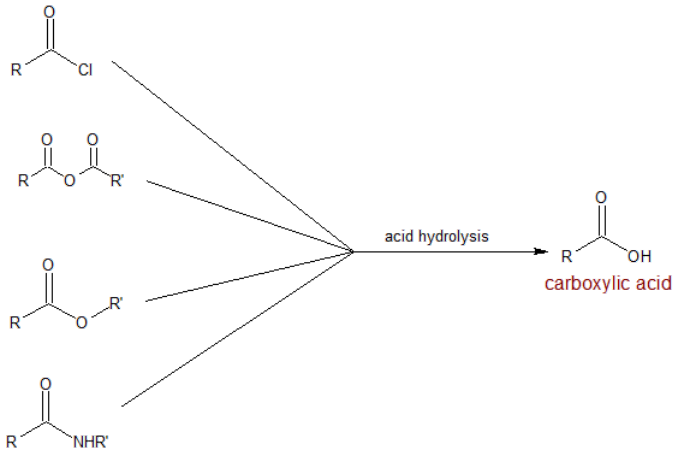


An existing carboxylic acid may be elongated by one methylene group, using a homologation procedure called the **Arndt-Eistert reaction**. To learn about this useful method Click Here.

Hydrolysis of Carboxylic Acid Derivatives and Nitriles

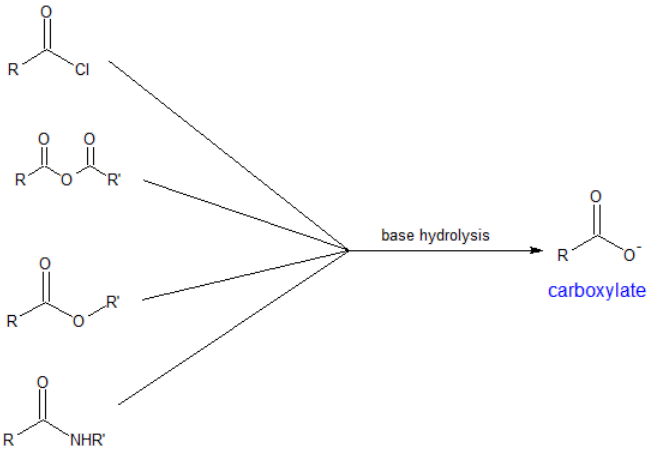
In this chapter we learn that all of the carboxylic acid derivatives can be synthesized from carboxylic acids. These reactions tend to be more useful for multiple-step syntheses to build large and complex molecules. The carboxylic acid derivatives along can be hydrolyzed to produce carboxylic acids. These hydrolysis reactions have limited use in multiple-step synthesis because the acidic proton can be problematic for many organic reactions. Biochemically, hydrolysis reactions are very important in the metabolism of food, drugs, and other nutrients. Hydrolysis can occur under acidic or basic conditions that determine the ionization of the carboxylic acid. Reactions under basic conditions will require a final neutralization step with dilute H^+ to recover the carboxylic acid. To reinforce our awareness of the pH sensitivity of carboxylic acids, both reaction maps are shown below.

- Acid Hydrolysis of the Carboxylic Acid Derivatives



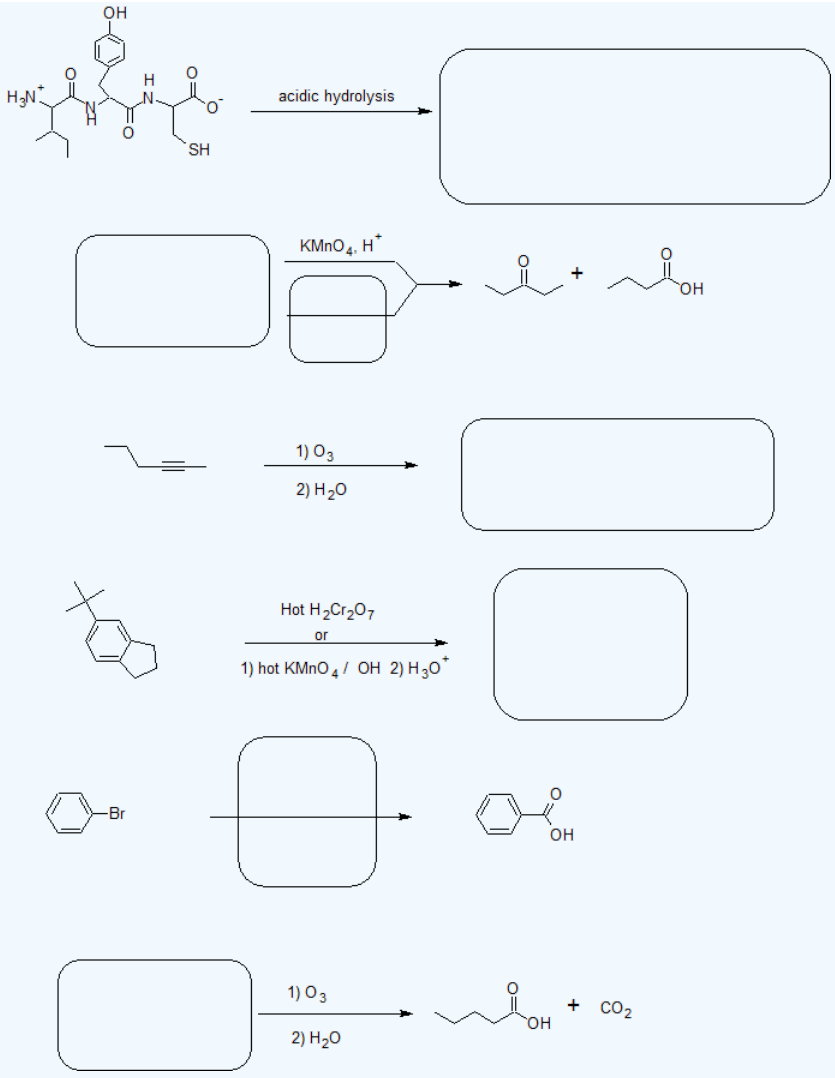
Helpful Hint: Different professors tend to use different proton sources. It is helpful to recognize reagents for their role in a reaction. For example, H_2SO_4, HCl, H_3PO_4, CH_3CO_2H, and p-TSA are all sources of H^+. It does not matter which one is used for catalysis or neutralization. Nitric acid is oxidizing, so it is typically only used in oxidation reactions. As we continue learning more reactions/reagents, it can help to group them by their reactivity: acids, bases, neutral, oxidizing, reducing, protic, aprotic, etc. For example, peroxides are oxidizing - whether is it H_2O_2 or MCPBA (m-chloroperoxybenzoic acid).

- Basic Hydrolysis of the Carboxylic Acid Derivatives



Exercise

4. Complete the reactions below.



Answer

4.

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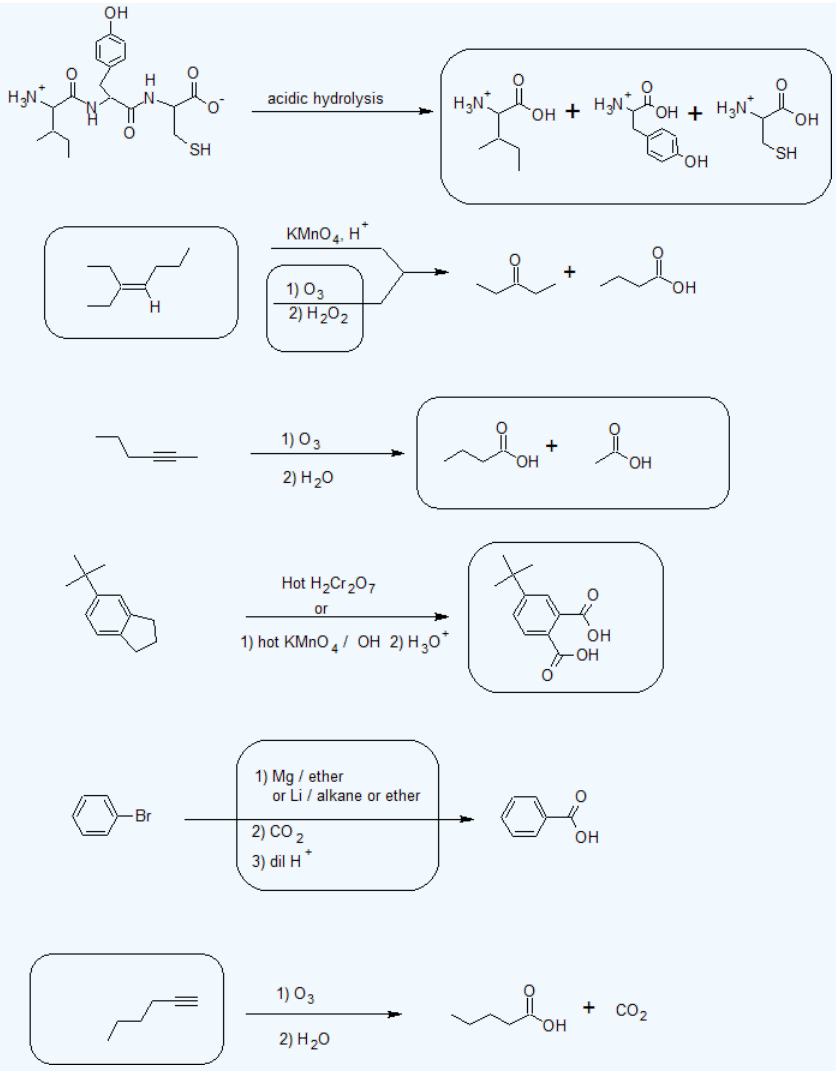

Contributors and Attributions

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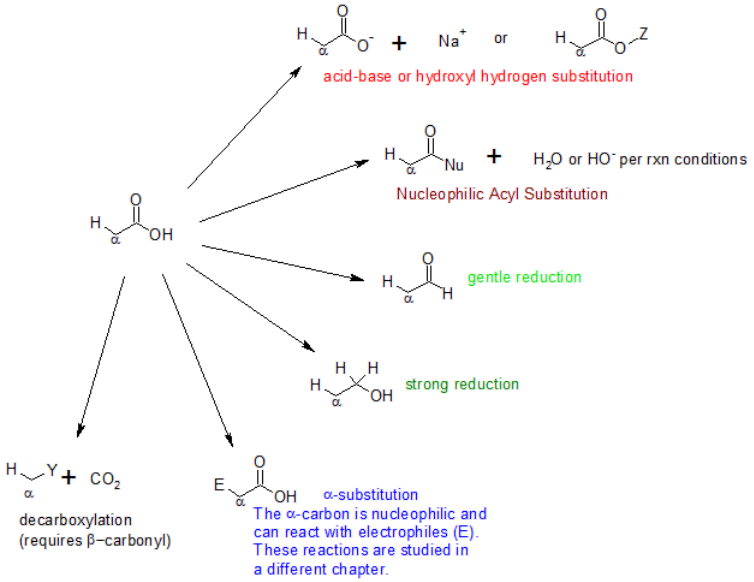
19.5: Reactions of Carboxylic Acids Overview

Carboxylic Acid Reactions Overview

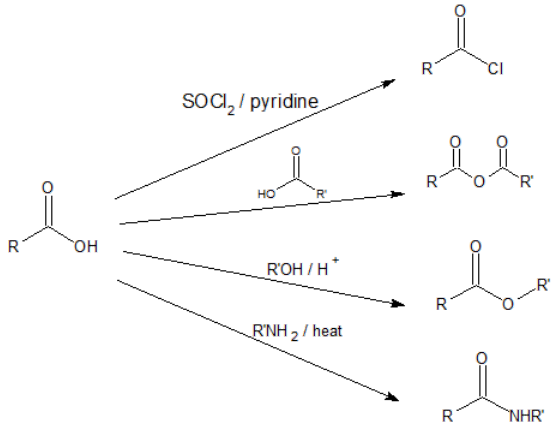
Four general reaction categories are represented here: (1) As carboxylic acid deprotonates quite readily, it is quite easy to form a carboxylate salt or to substitute the hydroxyl hydrogen. (2) The category of nucleophilic acyl substitution represents the substitution of the whole hydroxyl group, which we will see later in more detail leads to several carboxylic acid derivatives (e.g. acid halides, esters, amides, thioesters, acid anhydrides etc.). (3) Like other carbonyl compounds, carboxylic acids can be reduced by reagents like $LiAlH_4$. (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 site.

The scheme summarizes some of the general reactions that carboxylic acids undergo. The reaction details can be found in other sections of this text.

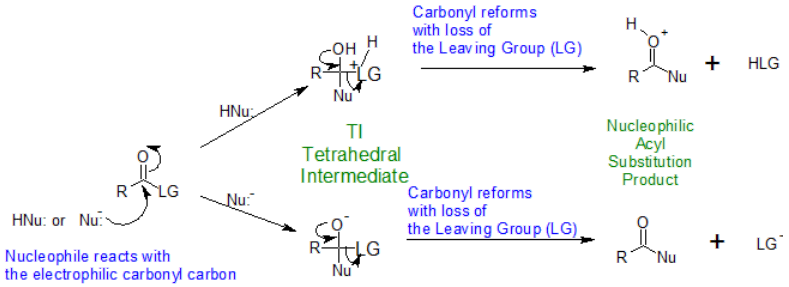


Nucleophilic Acyl Substitution Reactions and the Carboxylic Acid Derivatives

In subsequent sections, the reaction details to synthesize acyl chlorides, anhydrides, esters, and amides from carboxylic acids will be discussed. Because acyl chlorides, anhydrides, esters, and amides can all be synthesized from carboxylic acids, these functional groups are called "carboxylic acid derivatives".



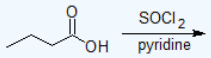
These reactions all share the same general mechanism. The nucleophile reacts with the electrophilic carbonyl carbon to produce the "Tetrahedral Intermediate or TI". The carbonyl reforms forcing the loss of the leaving group (LG) to produce the "Nucleophilic Acyl Substitution Product". The reaction mechanism depends on the pH of the reaction conditions. The reaction mechanisms for both acidic and basic conditions are shown below.

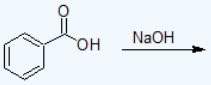


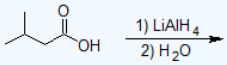
Exercise

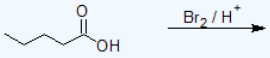
5. Draw the bond-line structures for the products and classify each reaction using the terms from the top diagram:

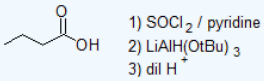
acid-base, NAS (Nucleophilic Acyl Substitutioin), gentle reduction, strong reduction, or alpha-substitution.











Answer

5.

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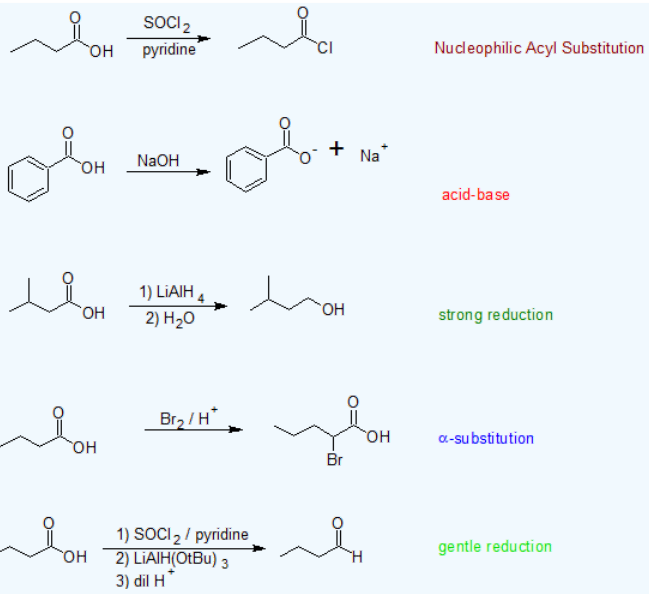

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- Prof. Steven Farmer (Sonoma State University)

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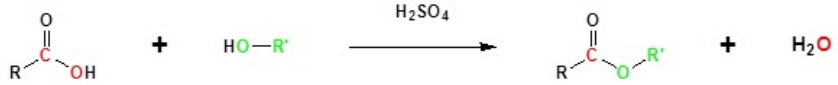
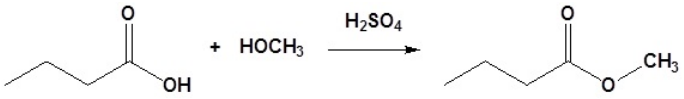
19.6: Condensation of Acids with Alcohols: The Fischer Esterification

Carboxylic acids can react with alcohols to form esters in a process called Fischer esterification. An acid catalyst is required and the alcohol is also used as the reaction solvent. The oxygen atoms are color-coded in the reaction below to help understand the reaction mechanism.

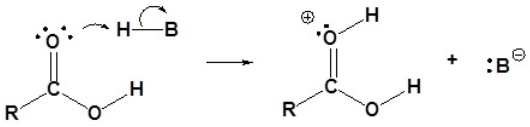


For example, butanoic acid reacts with methanol to synthsize methylbutanoate. It is important to note that any proton source can be used as the catalyst. Sulfuric acid is shown in the example below.

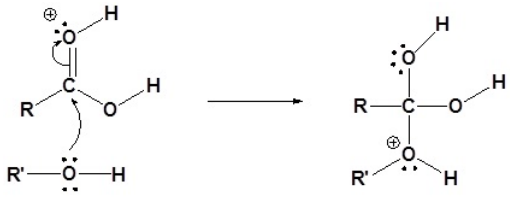


Mechanism

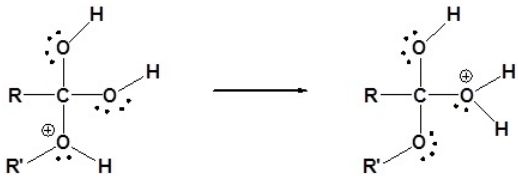
1) Protonation of the carbonyl by the acid. The carbonyl is now activated toward nucleophilic reactions.



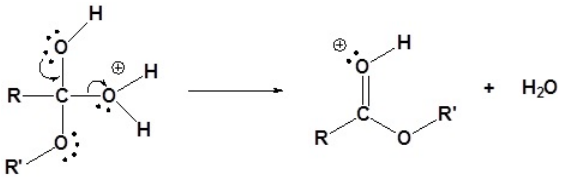
2) Nucleophilic reaction at the carbonyl



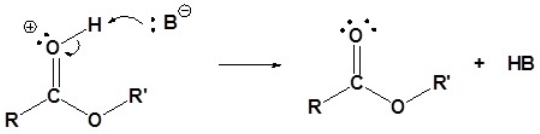
3) Proton transfer



4) Water leaves

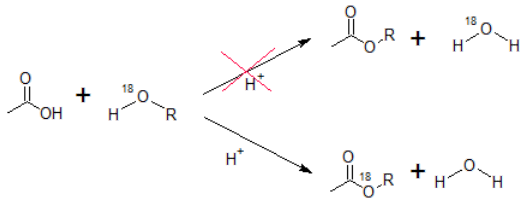


5) Deprotonation



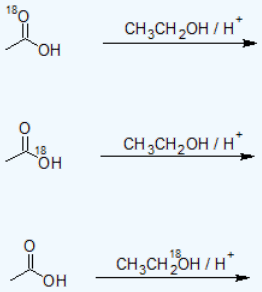
Isotopic Labeling

Evidence to support the Fischer esterfication mechanism comes from isotopic labeling experiments with oxygen-18. If the reaction is carried out with oxygen-18 labeled alcohol, the isotope is found exclusively in the ester and not the water generated.



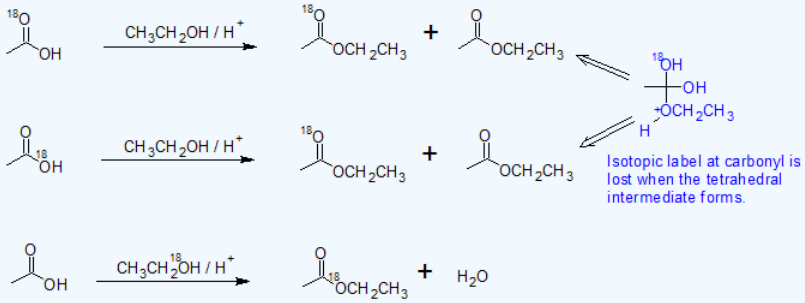
Exercise

6. Draw the bond-line structures for the products of the following reactions.



Answer

6.



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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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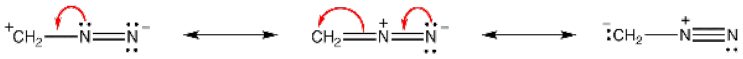
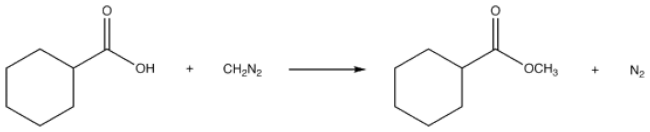
19.7: Methyl Ester Synthesis Using Diazomethane

Diazomethane, CH_2N_2, is a yellow, poisonous, potentially explosive compound, which is a gas at room temperature. The structure of diazomethane is explained using three resonance forms.

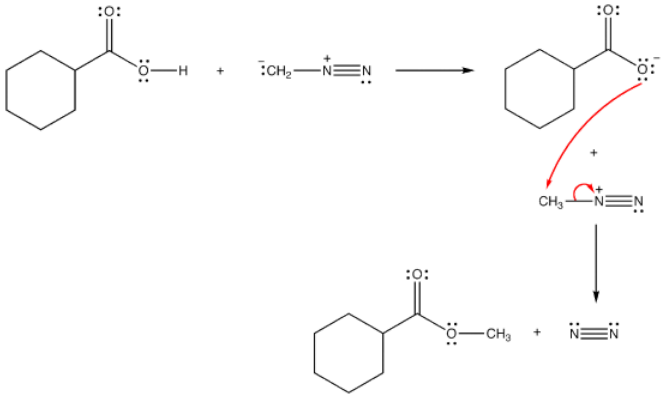


Conversion of carboxylic acids to methyl esters

Carboxylic acids react with diazomethane to produce methyl esters. Because of the high reactivity of diazomethane, it is produced in-situ and then immediately reacted with the carboxylic acid to produce the methyl ester.



The first step of the mechanism is a simple acid-base reaction to deprotonate the carboxylic acid. The carboxylate is then the nucleophile of an S_N2 reaction with protonated diazomethane to produce the methyl ester with nitrogen gas as a leaving group. It is important to keep reaction vessels vented when gases are produced to avoid explosions.



Contributors and Attributions

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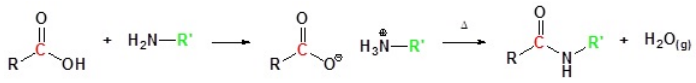
19.8: Condensation of Acids with Amines

Conversion of Carboxylic Acids to Amides

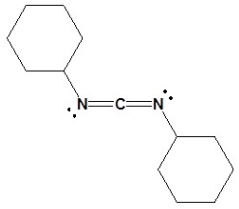
The direct reaction of a carboxylic acid with an amine would be expected to be difficult because the basic amine would deprotonate the carboxylic acid to form a highly unreactive carboxylate. However when the ammonium carboxylate salt is heated to a temperature above 100 ^{o}C water is driven off and an amide is formed.



Ammonium Carboxylate Salt

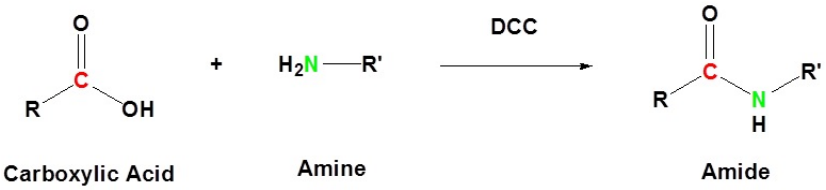
Conversion of Carboxylic acids to amide using DCC as an activating agent

The direct conversion of a carboxylic acid to an amide is difficult because amines are basic and tend to convert carboxylic acids to their highly unreactive carboxylates. In this reaction the carboxylic acid adds to the DCC molecule to form a good leaving group which can then be displaced by an amine during nucleophilic substitution.



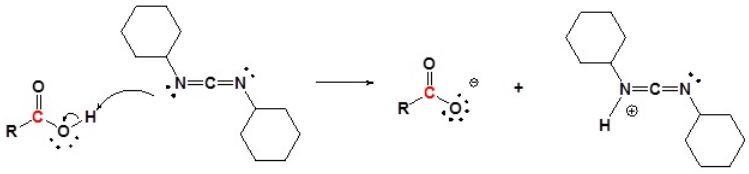
Dicyclohexylcarbodiimide (DCC)

DCC induced coupling to form an amide linkage is an important reaction in the synthesis of peptides.

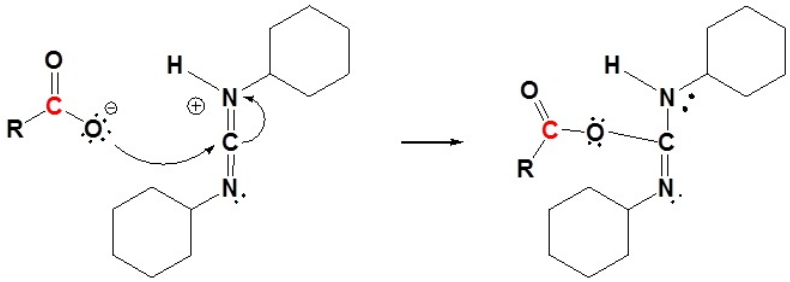


Mechanism

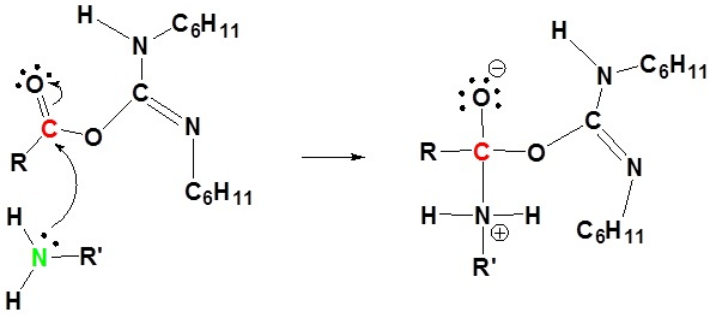
1) Deprotonation



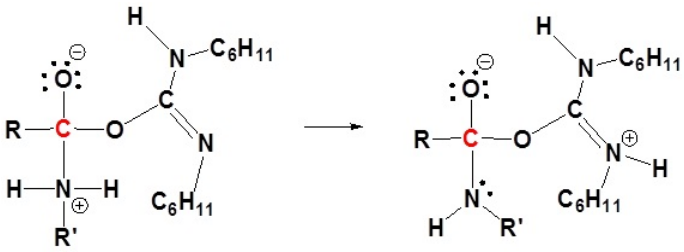
2) Nucleophilic reaction with carboxylate acting as the nucleophile



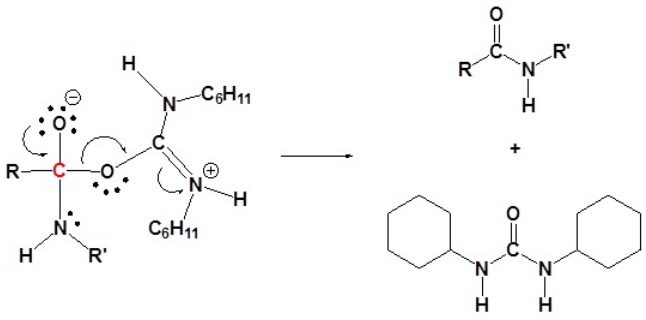
3) Nucleophilic reaction with the amine acting as the nucleophile



4) Proton transfer



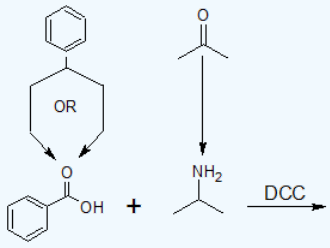
5) Leaving group removal



Dicyclohexylurea

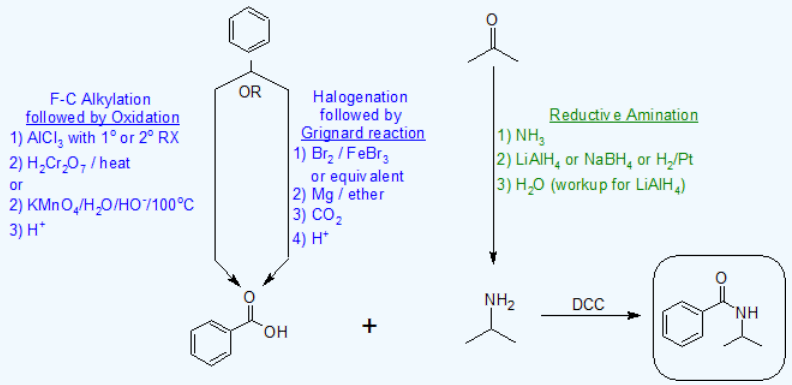
Exercise

7. Complete the reaction map below proposing two different ways to synthesize benzoic acid from benzene.



Answer

7.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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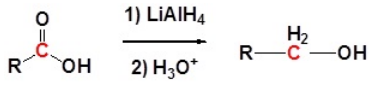
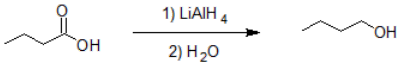
19.9: Reduction of Carboxylic Acids

Carboxylic acids can be converted to 1° alcohols using Lithium aluminum hydride ($LiAlH_4$)

Note that $NaBH_4$ is not strong enough to convert carboxylic acids or esters to alcohols. An aldehyde is produced as an intermediate during this reaction, but it cannot be isolated because it is more reactive than the original carboxylic acid.



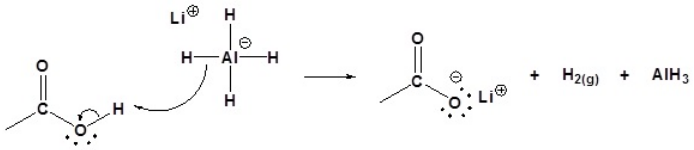
For example, butanoic acid can be reduced to butanol when reacted with lithium aluminum hydride as shown below.



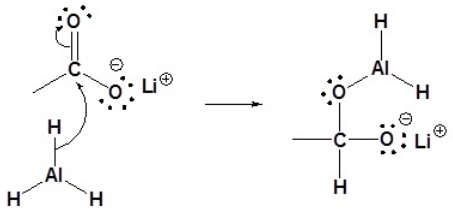
Possible Mechanism

There is not complete agreement on the mechanism for this reaction. However, the mechanism below is considered probable by many chemists.

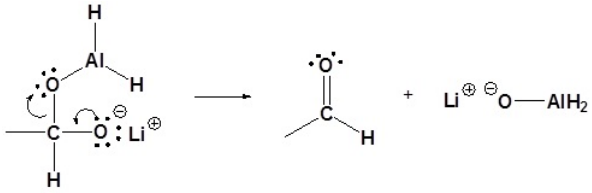
1) Deprotonation



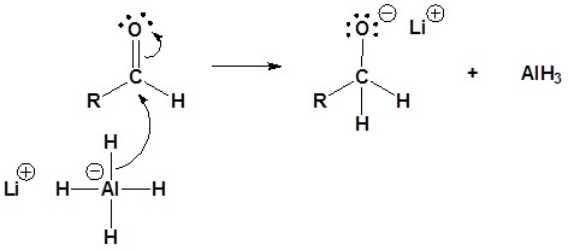
2) Nucleopilic reaction by the hydride anion



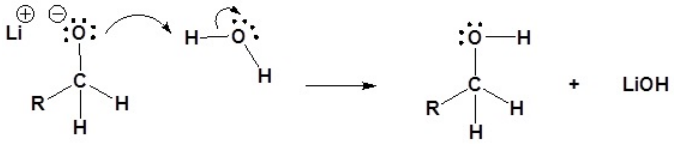
3) Leaving group removal



4) Nucleopilic reaction by the hydride anion



5) The alkoxide is protonated

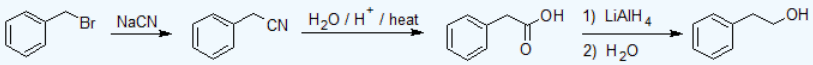


Exercise

8. Using benzyl bromide and sodium cyanide as the only source of carbons, propose a synthetic strategy to produce 2-phenyl-ethan-1-ol.

Answer

8.



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- Prof. Steven Farmer (Sonoma State University)

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19.10: Biochemically Interesting 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).

Interestingly, the molecules of most natural fatty acids have an even number of carbon atoms. Analogous compounds composed of odd numbers of carbon atoms are perfectly stable and have been made synthetically. 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. The double bonds in the unsaturated compounds listed on the right are all cis (or Z).

FATTY ACIDS

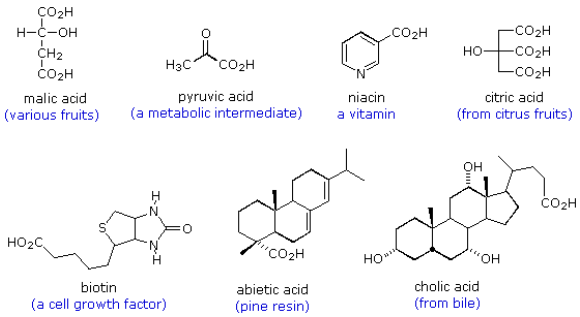
Saturated

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

Unsaturated

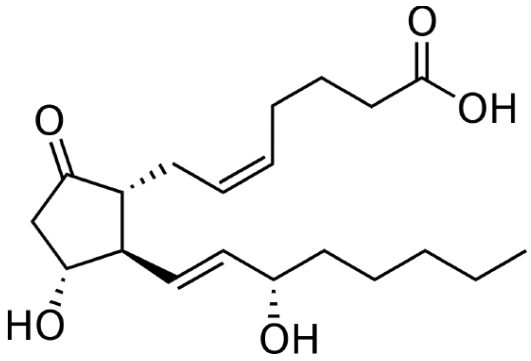
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH=CH(CH_2)_7CO_2H$	palmitoleic acid	0 ºC
$CH_3(CH_2)_7CH=CH(CH_2)_7CO_2H$	oleic acid	13 ºC
$CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linoleic acid	-5 ºC
$CH_3CH_2CH=CHCH_2CH=CHCH_2CH=CH(CH_2)_7CO_2H$	linolenic acid	-11 ºC
$CH_3(CH_2)_4(CH=CHCH_2)_4(CH_2)_2CO_2H$	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.



Aspirin, Arachidonic Acid, and 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 unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid. See the graphic on the left. 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.

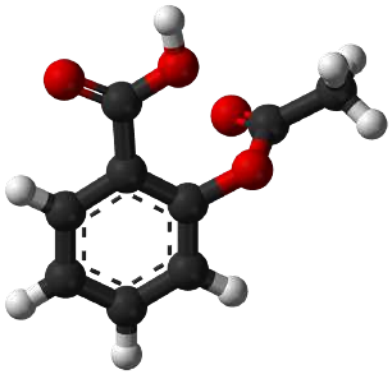


Structure of prostaglandin E2 (PGE_2)

Prostaglandins are unsaturated carboxylic acids, consisting of of a 20 carbon skeleton that also contains a five member ring and are based upon the fatty acid, arachidonic acid. There are a variety of structures one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups.

There are a variety of physiological effects associated with prostaglandins including:

1. Activation of the inflammatory response, production of pain, and fever. When tissues are damaged, white blood cells flood to the site to try to minimize tissue destruction. Prostaglandins are produced as a result.
2. Blood clots form when a blood vessel is damaged. A type of prostaglandin called thromboxane stimulates constriction and clotting of platelets. Conversely, PGI2, is produced to have the opposite effect on the walls of blood vessels where clots should not be forming.
3. Certain prostaglandins are involved with the induction of labor and other reproductive processes. PGE2 causes uterine contractions and has been used to induce labor.
4. Prostaglandins are involved in several other organs such as the gastrointestinal tract (inhibit acid synthesis and increase secretion of protective mucus), increase blood flow in kidneys, and leukotriens promote constriction of bronchi associated with asthma.



Ball-and-stick model of the aspirin molecule, as found in the solid state. Single-crystal X-ray diffraction data from Kim, Y.; Machida, K.; Taga, T.; Osaki, K. (1985). "Structure Redetermination and Packing Analysis of Aspirin Crystal". Chem. Pharm. Bull. ***33*** *(7): 2641-2647. ISSN 1347-5223.*

Effects of Aspirin and other Pain Killers on Prostaglandin Production

When you see that prostaglandins induce inflammation, pain, and fever, what comes to mind but aspirin. Aspirin blocks an enzyme called cyclooxygenase, COX-1 and COX-2, which is involved with the ring closure and addition of oxygen to arachidonic acid converting to prostaglandins. The acetyl group on aspirin is hydrolzed and then bonded to the alcohol group of serine as an ester. This has the effect of blocking the channel in the enzyme and arachidonic can not enter the active site of the enzyme. By inhibiting or blocking this enzyme, the synthesis of prostaglandins is blocked, which in turn relives some of the effects of pain and fever. Aspirin is also thought to inhibit the prostaglandin synthesis involved with unwanted blood clotting in coronary heart disease. At the same time an injury while taking aspirin may cause more extensive bleeding.

Contributors

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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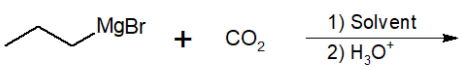
19.11: Additional Exercises

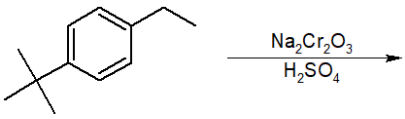
General Review

21-1 Provide the products for the following reactions.

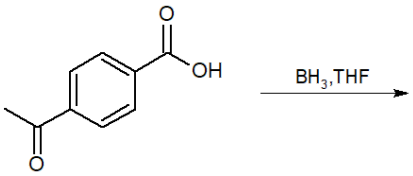
a)



b)



21-2 Provide the proper IUPAC name for the product of the following reaction.

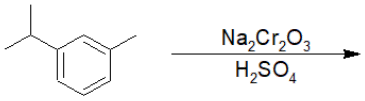


Synthesis of Carboxylic Acids

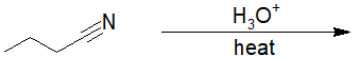
21-3 For the following reactions, predict the final product and provide their proper IUPAC nomenclature.

a)

b)



c)



21-4 Propose another method of synthesis (starting with cyclopentane) to make the product in the previous question, **21-3.a**.

21-5 Choose the correct alkene that was oxidatively cleaved by hot, concentrated potassium permanganate to form 3-methylbutanoic acid.

a) (4E/Z)-oct-4-ene

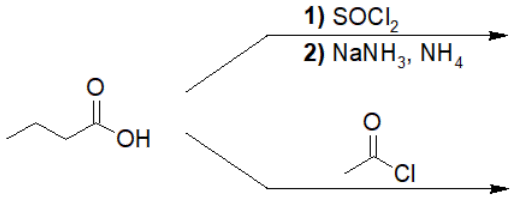
b) (4E/Z)-2-methyloct-4-ene

c) (4E/Z)-2,7-dimethyloct-4-ene

d) (3E/Z)-2,5-dimethylhex-3-ene

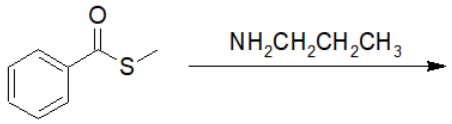
Reactions of Carboxylic Acids and Derivatives: Nucleophilic Acyl Substitution

21-6 Provide the structures of the products of the following reactions.

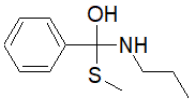


21-7 Provide the structure of the product that forms when propanoic acid reacts with thionyl chloride, then an excess of CH3CH2MgBr and finally followed by an acid workup.

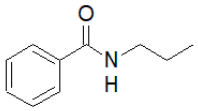
21-8 Choose the correct product of the following reaction.



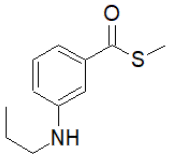
a)



b)

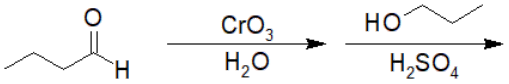


c)

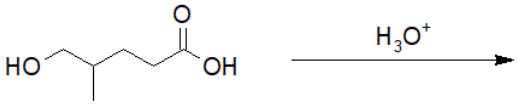


Condensation of Acids with Alcohols: the Fischer Esterification

21-9 Predict the product of the following Fischer Esterification reaction.

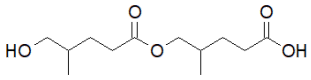


21-10 Choose the correct product of the following Fischer Esterification reaction.

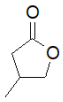


a)

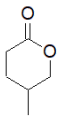
b)



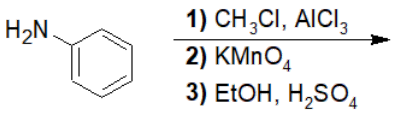
c)



d)

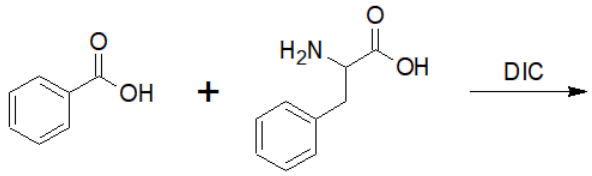


21-11 Predict the product of the following reaction (use a benzene ring with a total of two para-oriented substituents).

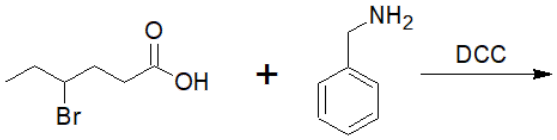


Condensation of Acids with Amines: Direct Synthesis of Amides

21-12 Give the structure of the product of the following reaction.



21-13 Choose the correct IUPAC nomenclature of the product and provide its structure.



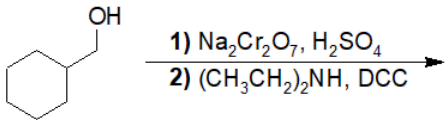
a) benzyl 4-bromohexanoate

b) (4E)-N-benzylhex-4-enamide

c) N-benzyl-4-bromohexanamide

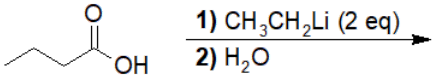
d) 4-bromo-N-phenylhexanamide

21-14 Provide the structure of the final product.



Alkylation of Carboxylic Acids to Form Ketones

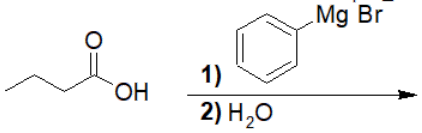
21-15 Predict the product of the following reaction.



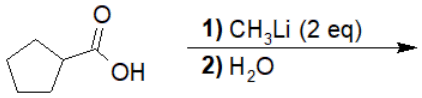
21-16 Explain why two equivalents of organolithium reagent is necessary to alkylate carboxylic acids (see problem **20-1**).

21-17 Give the products of the following reactions.

a)



b)



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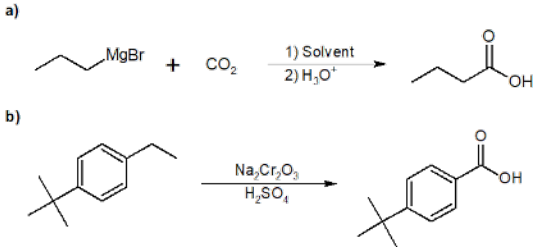
19.12: Solutions to Additional Exercises

General Review

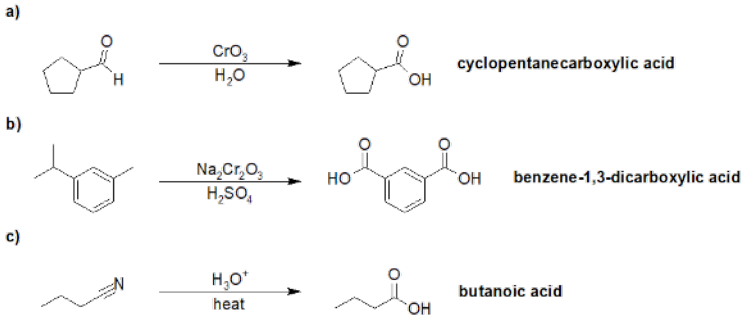
21-1



21-2 1-[4-(hydroxymethyl)phenyl]ethan-1-one

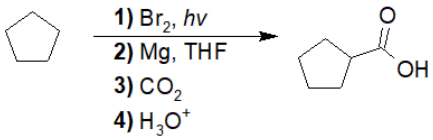
Synthesis of Carboxylic Acids

21-3:



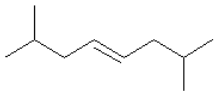
21-4:

Possible route of synthesis:



21-5:

Answer: C

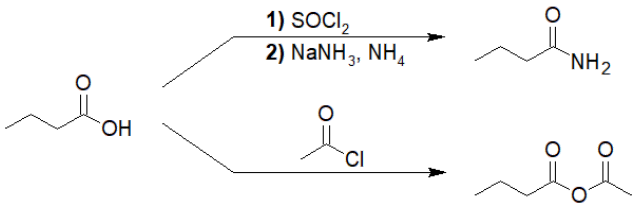


(4*E*)-2,7-dimethyloct-4-ene

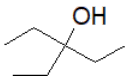
(E or Z orientation allowed)

Reactions of Carboxylic Acids and Derivatives: Nucleophilic Acyl Substitution

21-6:



21-7:

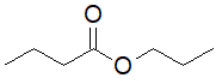


21-8:

Answer: B

Condensation of Acids with Alcohols: the Fischer Esterification

21-9:

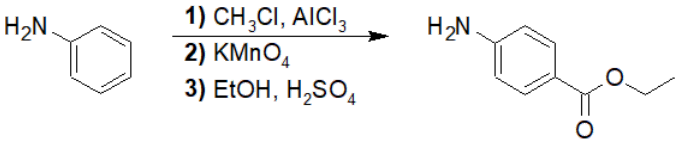


propyl butanoate

21-10:

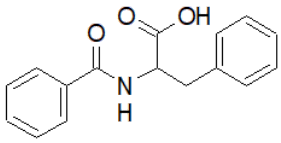
Answer: D

21-11:



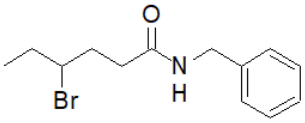
Condensation of Acids with Amines: Direct Synthesis of Amides

21-12:



21-13:

Answer: C



***N*-benzyl-4-bromohexanamide**

21-14:

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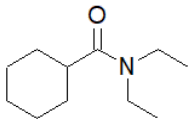
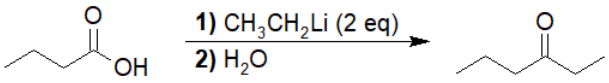


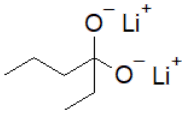
Alkylation of Carboxylic Acids to Form Ketones

21-15:



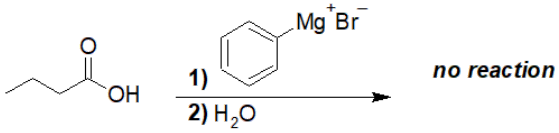
21-16:

Two equivalents of the organolithium reagent is necessary for the alkylation of carboxylic acids because one equivalent is used to form a salt with the carboxylic acid and the other equivalent is the nucleophile that adds to the carbonyl carbon.

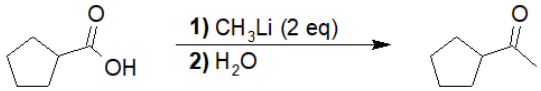

An example of the intermediate from problem **20-1**.

21-17:

a)



b)



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CHAPTER OVERVIEW

20: Carboxylic Acid Derivatives and Nitriles
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of carboxylic acid derivatives and nitriles (section 22.1)
- determine the structure of carboxylic acid derivatives and nitriles from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 22.2)
- predict the products and specify the reagents to interconvert between a carboxylic acid and its derivatives (section 22.3)
- predict the products and specify the reagents to hydrolyze carboxylic acid derivatives (22.4)
- predict the products and specify the reagents for transesterification reactions (section 22.5)
- predict the products and specify the reagents for reduction reactions of carboxylic acid derivatives (section 22.6)
- predict the products and specify the reagents for organometallic reactions with carboxylic acid derivatives (section 22.7)
- predict the products and specify the reagents for the synthesis and reactions of
  - acyl chlorides (section 22.4)
  - anhydrides (section 22.5)
  - esters (section 22.6)
  - amides (section 22.7)
  - nitriles (section 22.8)
  - thioesters (section 22.9)
  - step-growth (condensation) polymers via ester and amide bonds (section 22.10)
- discuss the chemistry of beta-lactams and biological acylation (section 22.11 and 22.12 respectively)
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis

Please note: IUPAC nomenclature and important common names of carboxylic acid derivatives and nitriles were explained in Chapter 3.

Topic hierarchy

20.1: Structure and Physical Properties of Acid Derivatives
20.2: Spectroscopy of Carboxylic Acid Derivatives
20.3: Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution
20.4: Acid Halide Chemistry
20.5: Acid Anhydride Chemistry
20.6: Ester Chemistry
20.7: Amide Chemistry
20.8: Nitrile Chemistry
20.9: Thioesters: Biological Carboxylic Acid Derivatives
20.10: Polyamides and Polyesters: Step-Growth Polymers
20.11: Beta-Lactams: An Application
20.12: Biological Acylation Reactions
20.13: Additional Exercises
20.14: Solutions to Additional Exercises

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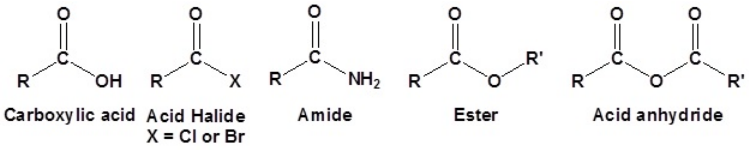
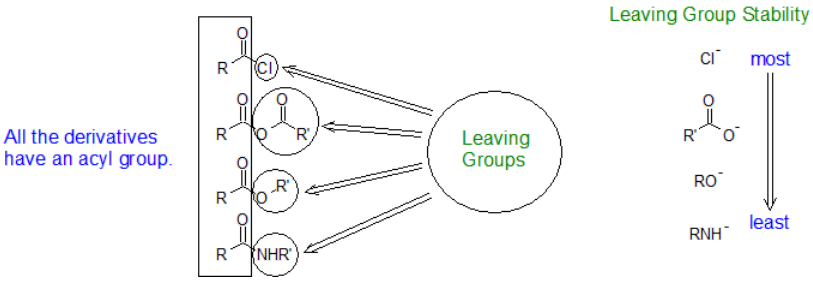
20.1: Structure and Physical Properties of Acid Derivatives

The Structure of Carboxylic Acid Derivatives

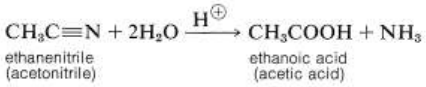
Carboxylic acid and its derivatives are functional groups with closely related chemistry.



The carboxylic acid derivatives all include an acyl group, an R-group bonded to a carbonyl carbon. The "other group" bonded to the carbonyl carbon distinguishes the derivatives from each other and has a strong influence on the relative reactivity between the derivatives. This "other group" takes the role of the "Leaving Group or LG" in Nucleophilic Acyl Substitution (NAS) reactions.



Although there are many types of carboxylic acid derivatives known, this chapter focuses on four: acid halides (acyl halides), acid anhydrides, esters, and amides. Another common feature of carboxylic acid derivatives is that they can be hydrolyzed back to the original carboxylic acid. For this reason, nitriles are sometimes grouped with the carboxylic acid derivatives and will also be discussed in this chapter. The hydrolysis reaction for acetonitrile is shown below as an example.

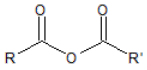
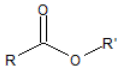
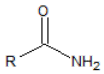


Physical Properties of Carboxylic Acid Derivatives

The intermolecular forces of the respective acyl group combine with the size and structure of the R-group to determine the physical properties of the the carboxylic acid derivatives as shown in the summary below.

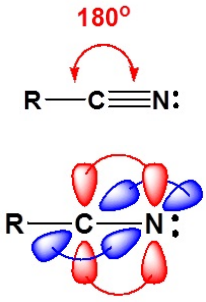
https://chem.libretexts.org/@go/page/183121

Carboxylic Acid Derivatives and their Physical Properties

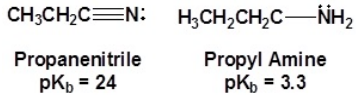
Name	Carboxylic Acid Derivative	Polarity & IMF's	Relative BP	Soluble in H_2O	General Comments
acyl chloride		polar no H's to donate	51	no	acrid piercing odors
acid anhydride		polar no H's to donate	140	no	acrid piercing odors
ester		polar no H's to donate	57	no	volatile fragrant liquids
carboxylic acid		H-bond dimers	118	yes if ≤ C4	acrid piercing odors
amide		complex H-bonds	221	yes if ≤ C3	biologically important (proteins)
nitrile		among most polar cpds w/o H-bonds	82	yes if ≤ C3	CH_3CN is useful, polar aprotic solvent

Structure and Properties of Nitriles

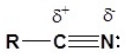
The electronic structure of nitriles is very similar to that of an alkyne with the main difference being the presence of a set of lone pair electrons on the nitrogen. Both the carbon and the nitrogen are *sp* hydridized which leaves them both with two p orbitals which overlap to form the two π bond in the triple bond. The R-C-N bond angle in and nitrile is 180° which give a nitrile functional group a linear shape.



The lone pair electrons on the nitrogen are contained in a *sp* hybrid orbital which makes them much less basic and an amine. The 50% character of an *sp* hybrid orbital close to the nucleus and therefore less basic compared to other nitrogen containing compounds such as amines.



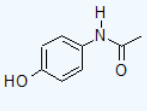
The presence of an electronegative nitrogen causes nitriles to be very polar molecules. Consequently, nitriles tend to have higher boiling points than molecules with a similar size.



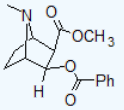
	Boiling Point
$CH_3CH_2C{\equiv}N$	96-98 °C
Propanenitrile	
$CH_3CH_2C{\equiv}C{-}H$	8.1 °C
Butyne	
$CH_3CH_2CH_2CH_3$	-1-1 °C
Butane	

Exercise

1. Design an extraction separation strategy to separate acetaminophen from cocaine using ether, 1 M HCl, and 3 M $NaHCO_3$. The structures for acetaminophen and cocaine are shown below.



acetaminophen

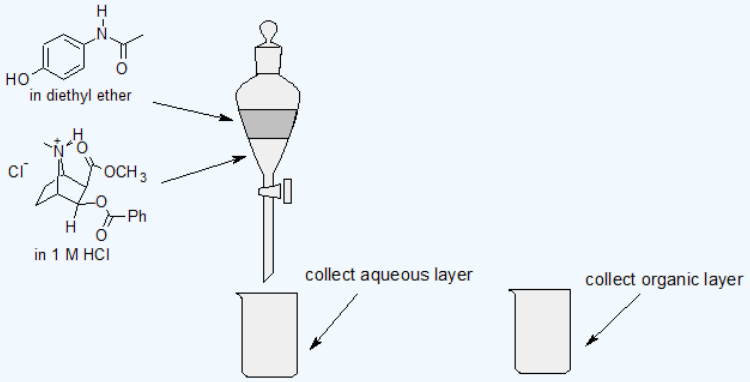


cocaine (free base form)

Answer

1.

Step 1: Dissolve both compounds in ether and add to a separatory funnel.
Step 2: Add 1 M HCl to the separatory funnel.
Step 3: Mix well to protonate the cocaine to a water soluble ammonium ion.
Step 4: Collect the aqueous and organic layers.



Step 5: Neutralize the aqueous layer using 3 M $NaHCO_3$ to deprotonate cocaine hydrochloride to the free base.
Step 6 Isolate the free base cocaine by vacuum filtration and allow the sample to dry.
Step 7: Isolate the acetaminophen by removing the ether from the organic layer with evaporation using a warm water bath & a gentle flow of nitrogen gas.

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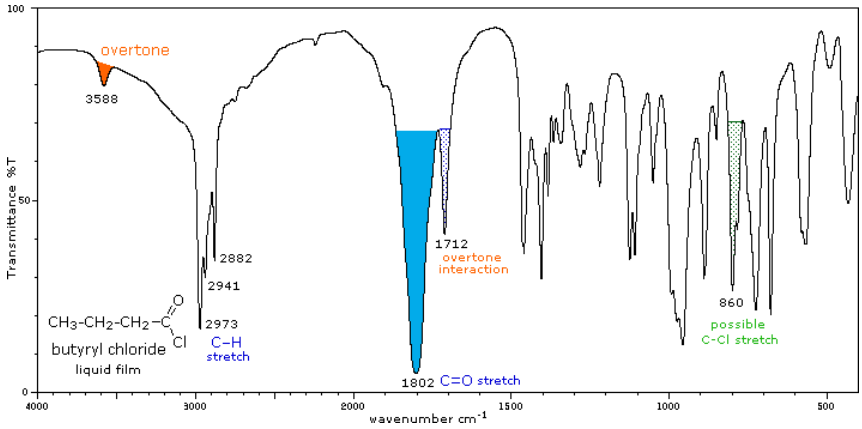
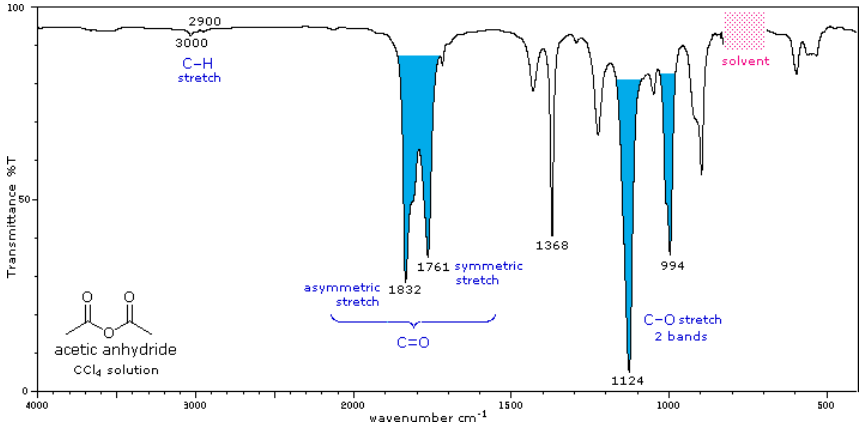
20.2: Spectroscopy of Carboxylic Acid Derivatives

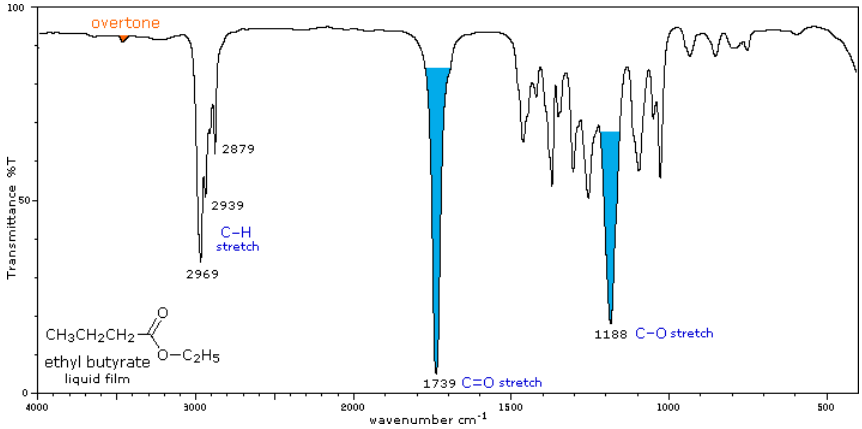
Infrared Spectroscopy (IR)

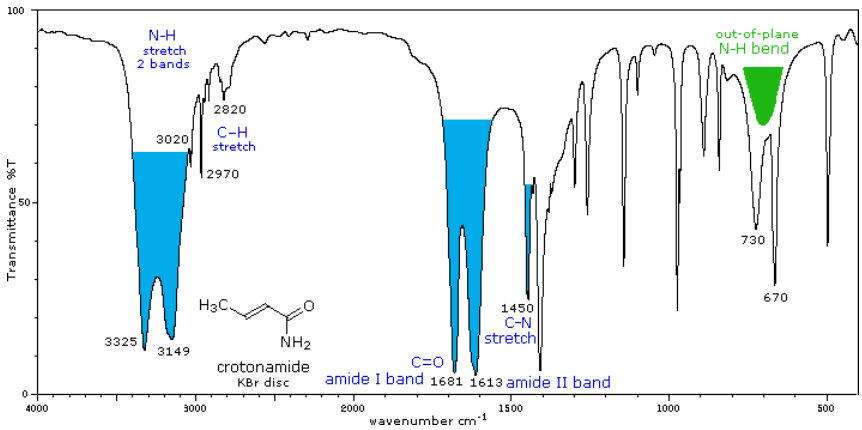
While all of the carboxylic acid derivatives include a carbonyl group, the heteroatoms that characterize the derivative can be used to distinguish between the derivatives. Additionally, there is a useful correlation between the reactivity of the carboxylic acid derivatives and their carbonyl stretching frequencies. Thus, the very reactive acyl halides and anhydrides absorb at frequencies significantly higher, while the relatively unreactive amides absorb at lower frequencies. The IR spectral characteristics that can be used to determine the identity of carboxylic acid derivatives 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.









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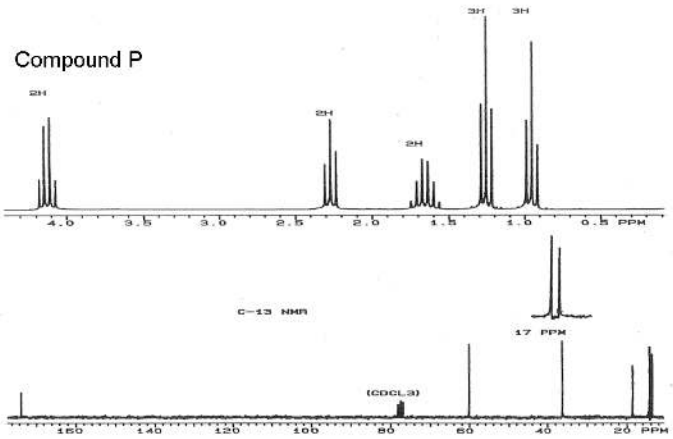
NMR Spectra

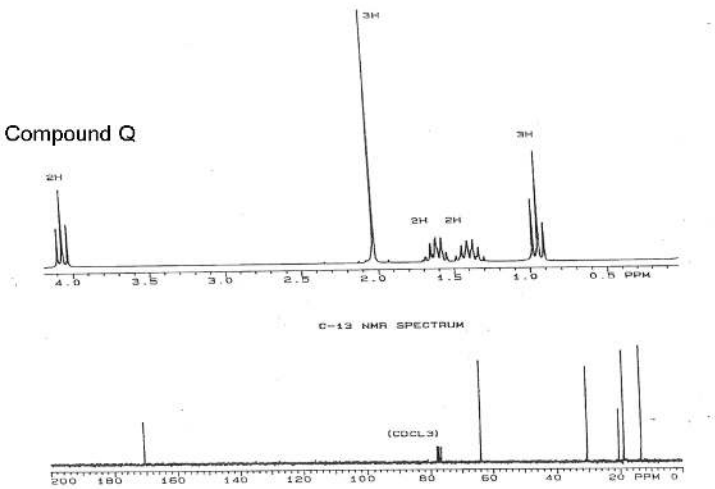
For NMR, there are a few spectral characteristics that can help identify the carboxylic acid derivative. The protons on carbons adjacent to carbonyls absorb at ~2.0-2.5 ppm. For amides, the N-H protons attached to primary and secondary amines absorb at ~7.5-8.5. For ^{13}C NMR, the carbonyl carbon in carboxylic acid derivatives shows up betweem ~ 160-180 ppm with the carbon in a nitrile appearing ~ 115-120 ppm in their ^{13}C NMR because of its *sp* hybridization.

Exercise

2. Esters are known for their sweet, fruity aromas. Compound P smells like pineapple and is used as a flavor enhancer for orange juices. Compound Q is responsible for the sweet smell of Red Delicious apples. Compounds P and Q are structural isomers with the following composition: 62.04% C, 0.41% H, and 27.55% O. The IR spectrum for each compound includes several moderate bands around 2940 cm-1, a strong band near 1740 cm-1, and a moderate band near 1200 cm-1. The 1H and 13C NMR spectrum for each compound is shown below.

Name, draw the bond-line structure, and correlate the NMR signals to their respective compound.





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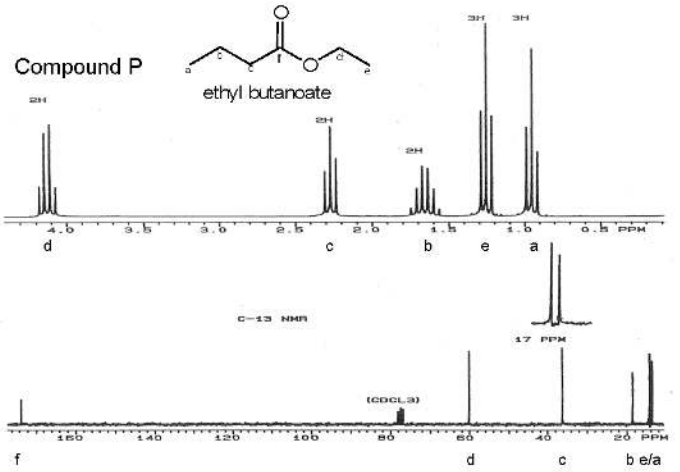
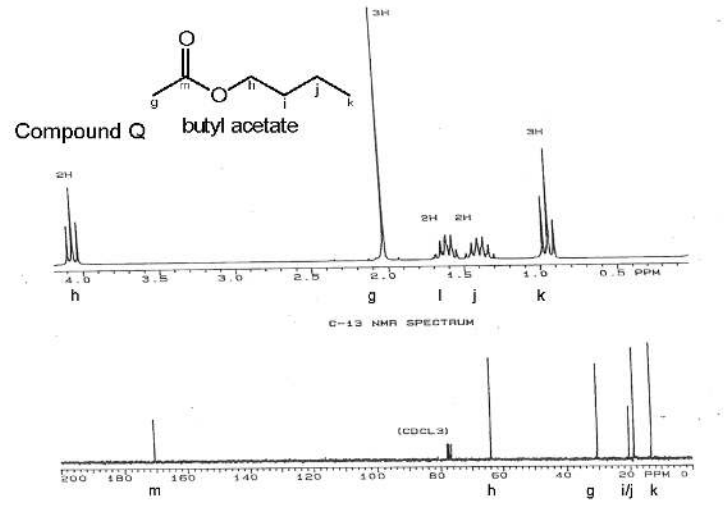
Answer

2.





Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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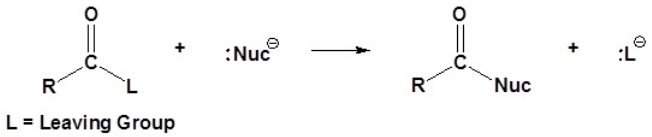
20.3: Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

General reaction

Carboxylic acid derivatives are electrophilic and can react with nucleophiles to form nucleophilic acyl substitution products. The driving force of these reactions is the stability of the leaving group shown as $:L^-$ below.

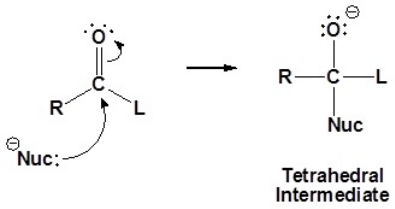


L = Leaving Group

General mechanism

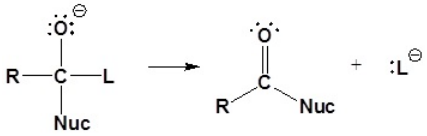
The nucleophile reacts with the electrophilic carbonyl carbon to form the tetrahedral intermediate. When the carbonyl reforms, the leaving group is lost to form the substitution product as shown in the mechanism below.

1) Nucleophilic reaction at the carbonyl



Tetrahedral Intermediate

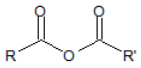
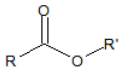
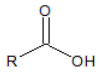
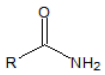
2) Carbonyl reforms and leaving group is removed



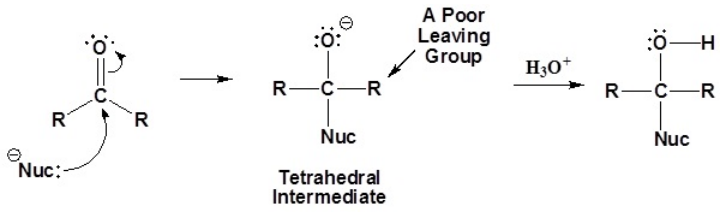
Relative Reactivity to Nucleophilic Acyl Substitution

The relative reactivity of carbonyl compounds toward nucleophile substitutions is related to the stability of the leaving group - the more stable the leaving group, the more favorable the substitution reaction. Evaluating leaving group stability is analogous to evaluating conjugate base stability as shown in the table below.

Carbonyl Compounds and their Leaving Groups

Name	Carbonyl Compound	Leaving Group	Conjugate acid of the Leaving Group	pKa
acyl chloride		Cl^-	HCl	-7
acid anhydride				3-5
ester		$^-OR_2$	ROH	15-16
carboxylic acid		HO^-	H_2O	15.7
amide		$^-NH_2$	NH_3	36
ketone		R'^-	RH	50
aldehyde		H^-	H_2	very large

Although aldehydes and ketones also contain carbonyls, their chemistry is distinctly different because they do not contain suitable leaving groups. Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls because the carbide (RC^-) and hydride (H^-) leaving groups are too unstable. Therefore, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



Integrating all of this information into the single table below summarizes the relative reactivity of carboxylic acids and their derivatives.

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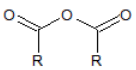
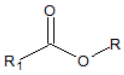
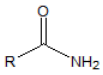
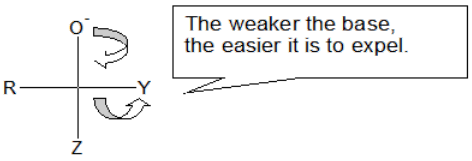
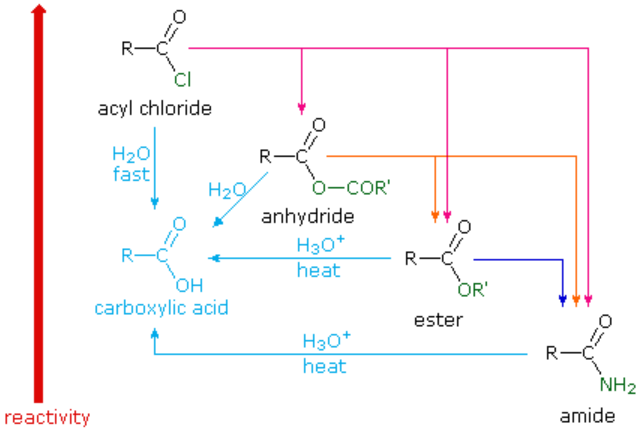
Carboxylic Acid Derivatives and their Relative Reactivity

Name	Carboxylic Acid Derivative	LG	Relative Basicity	Relative Reactivity
acyl chloride		Cl^-	weakest base	most reactive
anhydride				
ester		$^-OR_2$		
carboxylic acid		^-OH		
amide		$^-NH_2$	strongest base	least reactive



Acid Derivative Interconversion

From this understanding, multiple step synthesis strategies can be developed. The derivatives with the most stable leaving groups can be used to synthesize the derivatives with the least stable leaving groups as illustrated in the diagram below.



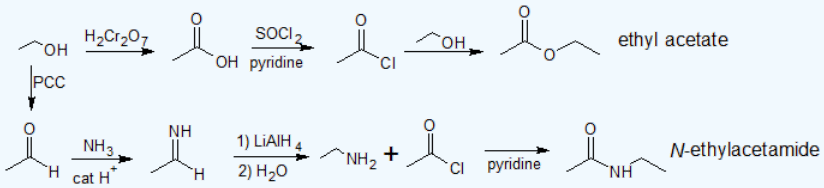
While it may appear from diagram above that the acyl chlorides are the "source" of the acid derivatives, acyl chlorides are so highly reactive that it is common to convert the carboxylic acid to the acid chloride and then immediately form the derivative. From a laboratory synthesis perspective, the reaction sequence begins with the carboxylic acid.

Exercise

3. Using ethanol as the only source of carbons in the final products, show how to synthesize ethyl acetate and N-ethylacetamide.

Answer

3.



Contributors and Attributions

- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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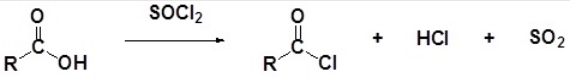
20.4: Acid Halide Chemistry

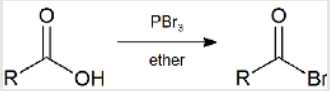
Please Note: The terms "acid halide" and "acyl halide" are synonymous and are both used in this text. In biochemistry, the term "acyl" is used more frequently.

Acid Halide Synthesis

Carboxylic acids react with thionyl chloride ($SOCl_2$) or oxalyl chloride ($C_2O_2Cl_2$) to form acid chlorides. Typically the reactions occur in the presence of a proton scavanger like pyridine to minimize unwanted side reactions. During the reaction the hydroxyl group of the carboxylic acid is converted to a chlorosulfite intermediate making it a better leaving group. The chloride anion produced during the reaction acts a nucleophile.

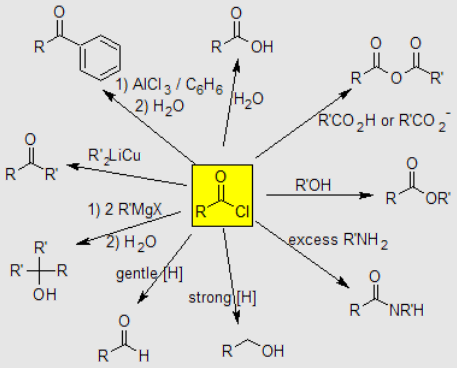


Analogous to the reactions of primary and secondary alcohols with PBr_3 to produce the corresponding alkyl bromide, acid bromides can be formed from the reaction of phosphorous tribromide with carboxylic acids.



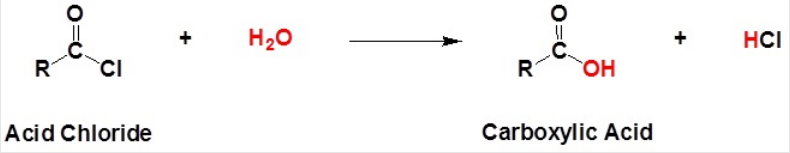
Acyl Halide Reactivity

Acyl halides can be hydrolyzed to carboxylic acids and converted to carboxylic acid derivatives. Acid halides can also undergo reduction reactions and reactions with Grignard reagents and organolithium cuprates along with Fridel-Crafts acylation of benzene. The reaction map below summarizes the reactivity of acyl halides.



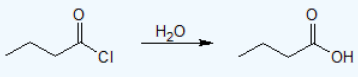
Acid Halide Hydrolysis

The hydrolysis reaction of acid chlorides is shown below.



The hydrolysis of butonyl chloride is shown below as an example.

Example: Acyl Chloride Hydrolysis

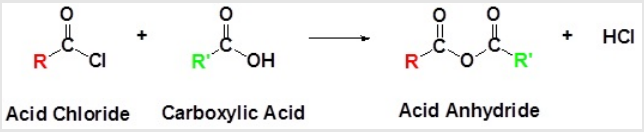


Carboxylic Acid Derivative Synthesis from Acyl Chlorides

Carboxylic acid derivatives can be synthesized from acyl chlorides via the nucleophilic acyl substitution mechanism previously discussed.

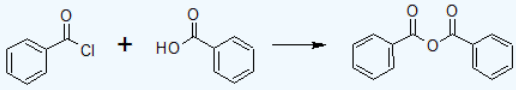
Anhydride Synthesis

Acid chlorides react with carboxylic acids to form acid anhydrides as shown in the reaction below.



The synthesis of benzoic anhydride from benzoyl chloride and benzoic acid is shown as an example.

Example: Anhydride Synthesis from Acyl Chlorides

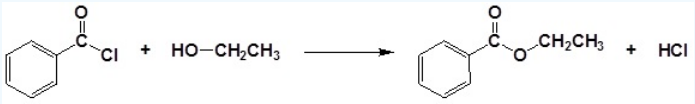


Ester Synthesis

Acid chlorides react with alcohols for form esters are shown in the reaction below.

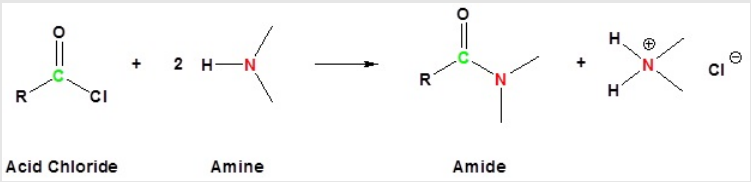
The synthesis of ethyl benzoate from benzoyl chloride and ethanol is shown as an example.

Example: Ester Synthesis from Acyl Chlorides



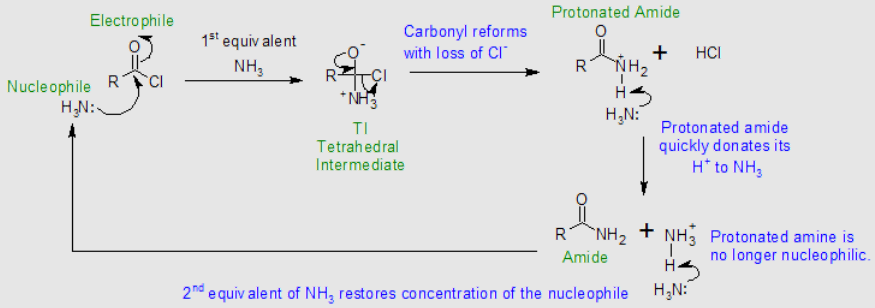
Amide Synthesis

Acid chlorides react with "ammonia, 1° amines and 2° amines" to form amides as shown in the reaction below.



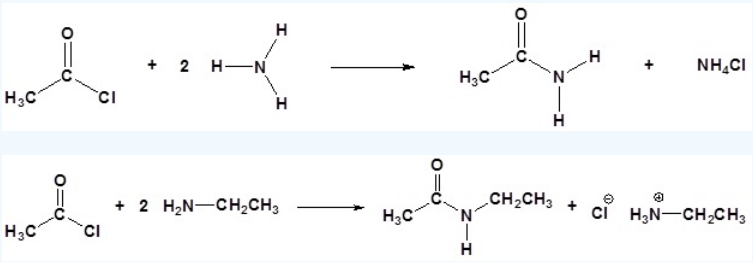
The reaction requires 1 equivalent of the "ammonia/1° or 2° amine" with a proton scavenger (aka base) like pyridine OR two equivalents of "ammonia/1° or 2° amine". The additional equivalent the nucleophile or base is needed to maintain the nucleophilic character of "ammonia/1° or 2° amine". As shown in the mechanism below, the amide is briefly protonated after the carbonyl reforms from the tetrahedral complex. Since amides are considered neutral with no significant basicity, the "ammonia/1° or 2° amine" quickly accepts their proton and is no longer a nucleophile. The second equivalent of "ammonia/1° or 2° amine" restores the concentration of the nucleophile. For clarity, the mechanism below is shown with ammonia as the nucleophile.

Mechanism



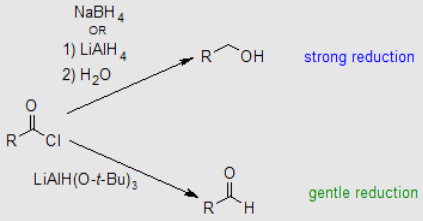
The syntheses of acetamide and N-ethylacetamide from acetyl chloride are shown as examples.

Example: Amide Synthesis from Acyl Chlorides



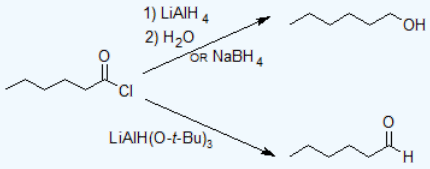
Acid Chloride Reduction

Acid chlorides can be fully reduced to primary alcohols using either sodium borohydride or lithium aluminum hydride. Acid chlorides can be partially reduced to aldehydes using the lithium tri-tert-butoxyaluminum hydride ($LiAlH(O\text{-}t\text{-}Bu)_3$). These reactions are summarized in the reaction map below.



The syntheses of 1-hexanol and hexanal from hexanoyl chloride are shown as examples.

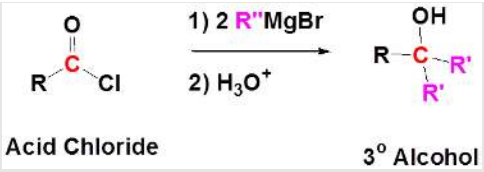
Example: Reduction Acyl Chlorides



Acid Chloride Reactions with Organometallic Compounds

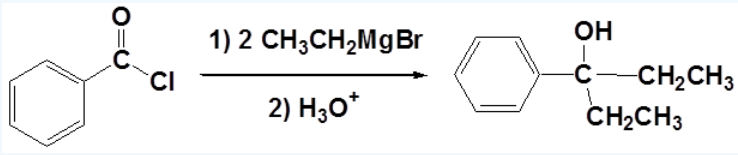
Grignard reagents

Acid chlorides react with Grignard reagents to produce tertiary alcohols. Two equivalents of the Grignard reagent are needed because the first equivalent reacts to form a ketone which then reacts with the second equivalent. Because of the high reactivity of the Grigard reagent, the reaction can NOT be stopped at the ketone.



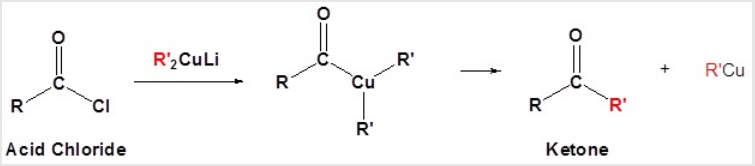
The syntheses of 3-phenylpentan-3-ol from benzoyl chloride is shown as an example.

Example: Acyl Chloride Reactions with Grignard Reagents



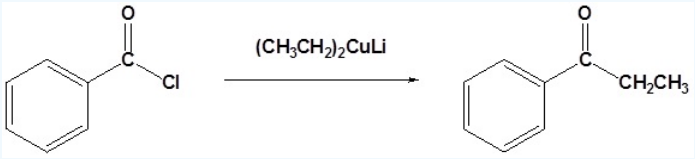
Organolithium Cuprates

Organolithium cuprate reagents are less reactive than Grignard reagents and can convert acid chlorides to ketones as shown below.



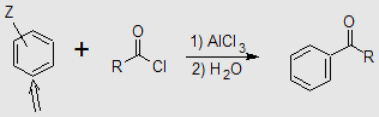
The synthesis of 1-phenylpropan-1-one from benzoyl chloride is shown as an example.

Example: Acyl Chloride Reactions with Organolithium Cuprates



Friedel-Crafts Acylation of Benzene

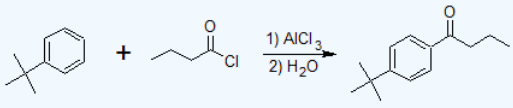
Benzene rings can be acylated via the Friedel-Crafts acylation reaction with acid chlorides in the presence of aluminum chloride followed by an aqueous work-up as shown below.



For F-C Acylation, the benzene ring can have electron donating groups or a halogen, but cannot contain electron withdrawing groups, such as the nitro (-NO_2) or sulfono (-SO_3H) groups.

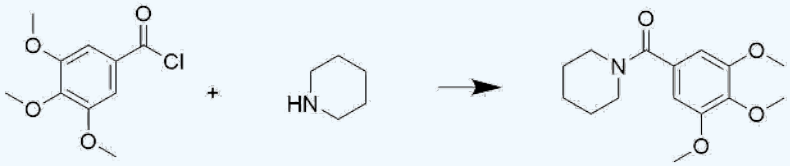
The synthesis of 1-(4-tert-butylphenyl)butan-1-one from t-butylbenzene and butonyl chloride is shown as an example.

Example: Friedel-Crafts Acylation



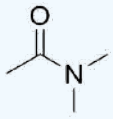
Exercise

4. Draw the mechanism for the following reaction

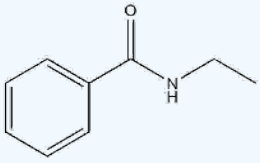


5. Propose a synthesis of the following molecules from an acid chloride and an amide.

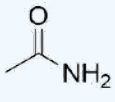
(a)



(b)

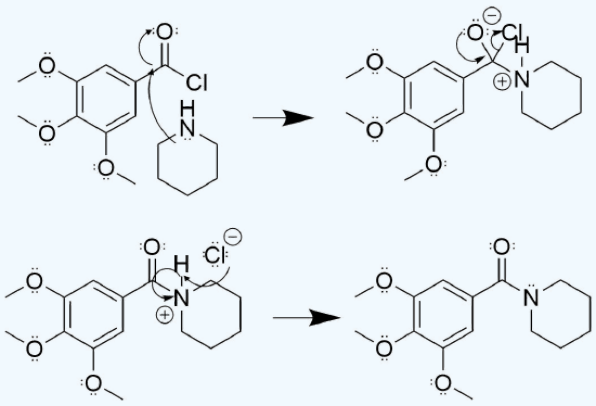


(c)



Answer

4.



5.

a) Acetyl chloride and dimethylamine

b) Benzoyl chloride and ethylamine

c) Acetyl chloride and ammonia

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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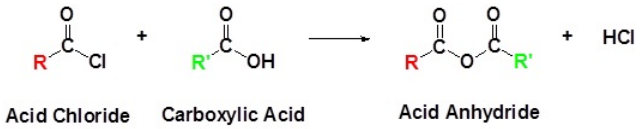
20.5: Acid Anhydride Chemistry

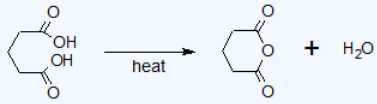
Synthesis of Acid Anhydrides

Acid chlorides react with carboxylic acids to form anhydrides as shown in the reaction below.



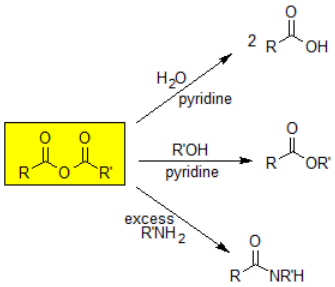
Some cyclic anhydrides can be synthesized from the corresponding dicarboxylic acid with gentle heating. The example below shows the reaction of glutaric acid to form a cyclic anhydride.

Example: Acid Anhydride Synthesis



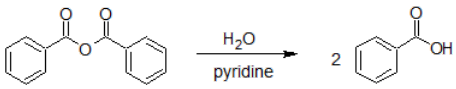
Acid Anhydride Reactivity

Acid anhydrides undergo hydrolysis and nucleophilic acyl substitution reactions.



Acid Anhydride Hydrolysis

Acid anhydrides readily hydrolyze to carboxylic acids. In many cases, this reaction is an unwanted side reaction and steps will be taken in the lab to keep the system "dry" (aka water free). The presence of pyridine facilitates proton transfers during the reaction. The hydrolysis reaction for benzoic anhydride is shown below.



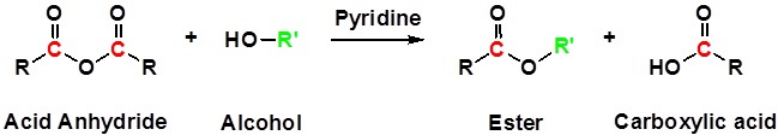
The mechanism is analogous to the mechanism for ester synthesis from acid anhydrides and is shown below is detail.

Nuclephilic Acyl Substitution Reactions from Acid Anhydrides

Carboxylic acid derivatives can be synthesized from acid anhydrides via the nucleophilic acyl substitution mechanism previously discussed.

Ester Synthesis

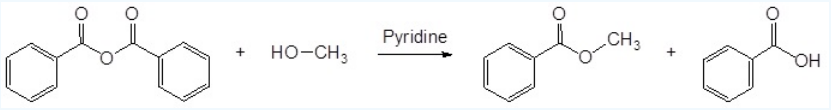
Acid anhydrides react with alcohols to produce esters as shown in the reaction below. The reactions of anhydrides frequently use pyridine as a solvent.



A carboxylic acid is also produced, but is not considered a synthetic product. The ester is considered the "product of interest".

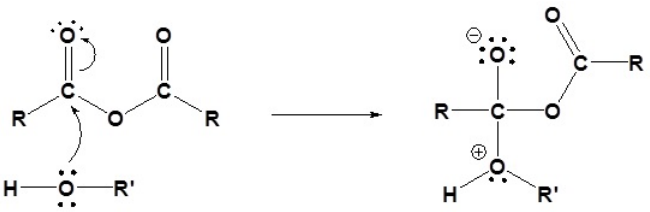
The synthesis of methyl benzoate from benzoic anhydride and methanol is shown in the example.

Example: Ester Sythesis

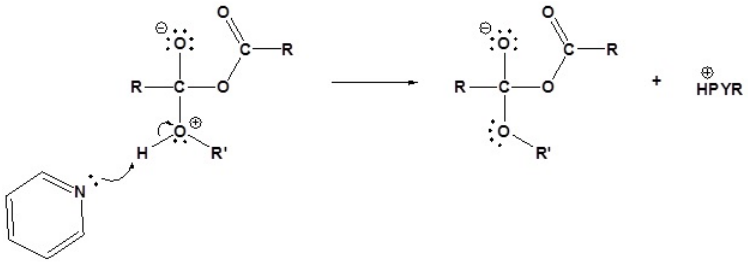


The mechanism follows the nucleophililc acyl substitution mechanism as previously discussed and reviewed below.

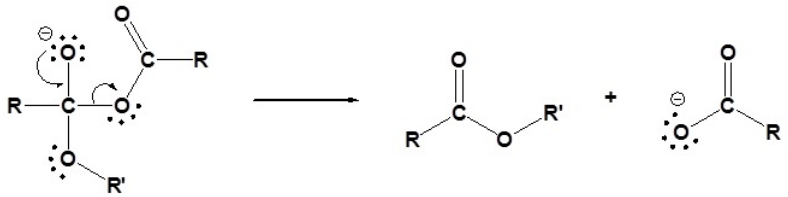
1) Nucleophilic Alcohol reacts with Electrophilic Carbonyl



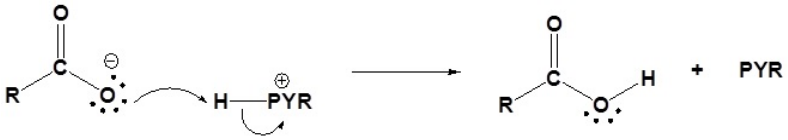
2) Deprotonation by pyridine



3) Leaving group removal

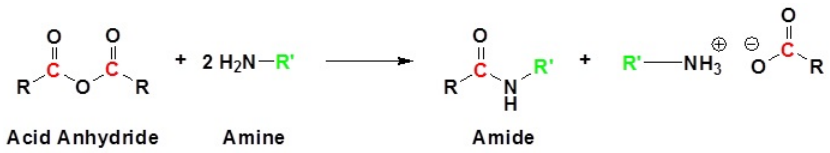


4) Protonation of the carboxylate

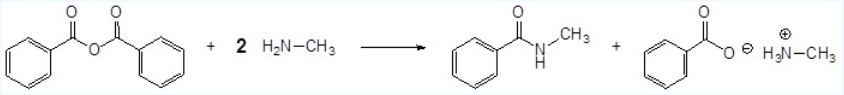


Amide Synthesis

Acid Anhydrides react with amines to form amides. As seen with acid halide reactions, a second equivalent of the amine must be present for the reaction to proceed.

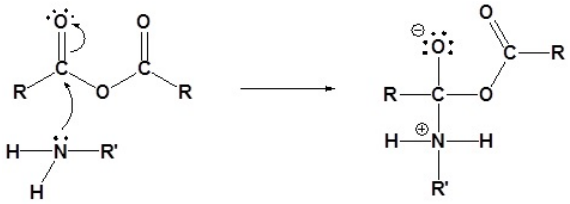


Example: Amide Synthesis

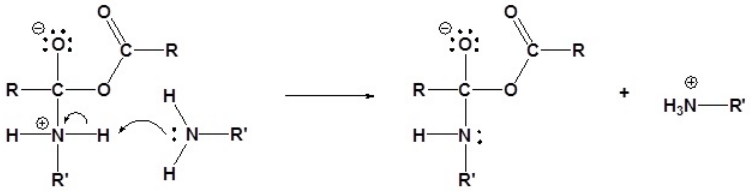


The mechanism for amide synthesis is analogous to the mechanism for ester formation. The only minor difference is that a second equivalent of the amine or ammonia is used instead of the pyridine.

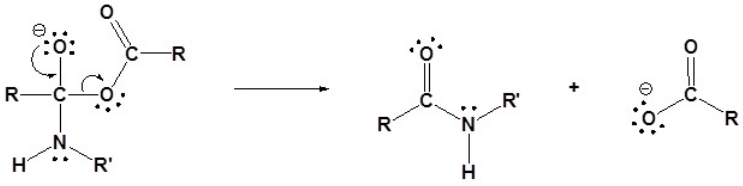
1) Nucleophilic Amine reacts with Electrophilic Carbonyl



2) Deprotonation by the amine

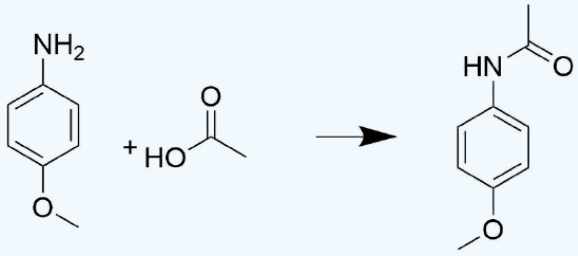


3) Leaving group removal



Exercise

6. Draw out the mechanism for the following reaction.



7. Draw the product of the reaction between these two molecules.

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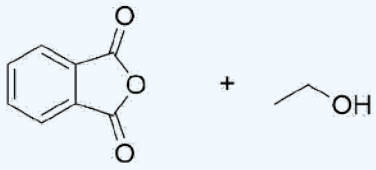
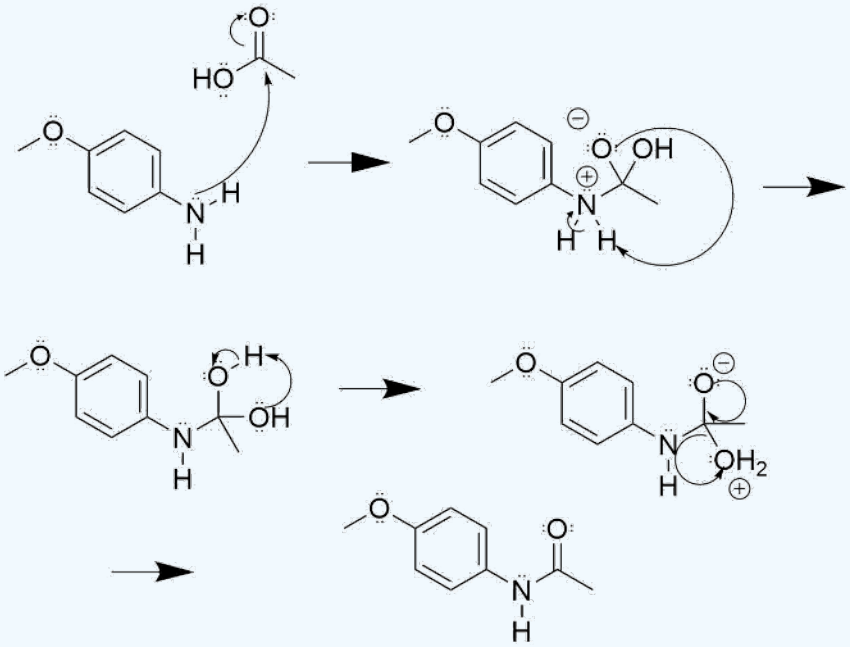
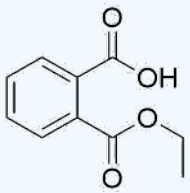


Answer

6.



7.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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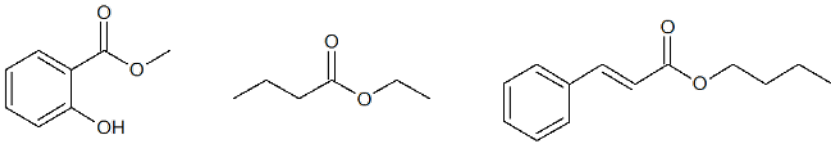
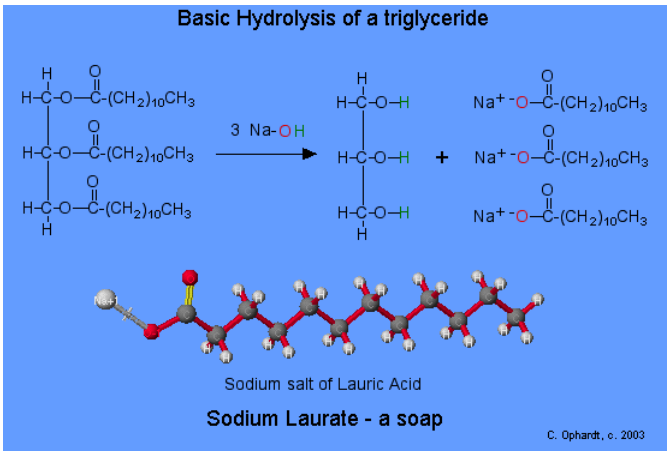
20.6: Ester Chemistry

Introduction

Esters are readily synthesized and naturally abundant. Esters are frequently the source of flavors and aromas in many fruits and flowers.

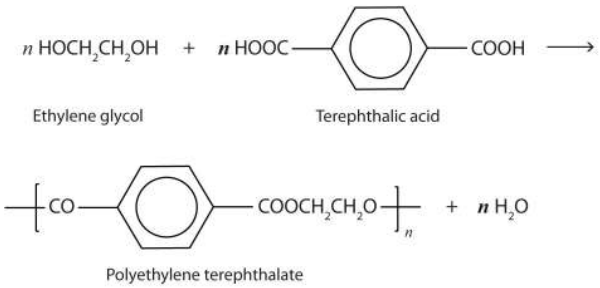


Esters also make up the bulk of animal fats and vegetable oils—glycerides (fatty acid esters of glycerol). Soap is produced by a saponification (basic hydrolysis) reaction of a fat or oil.



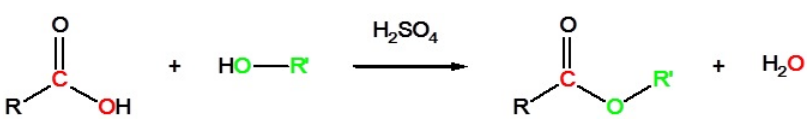
Esters are also present in a number of important biological molecules and have several commercial and synthetic application. For example, polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:

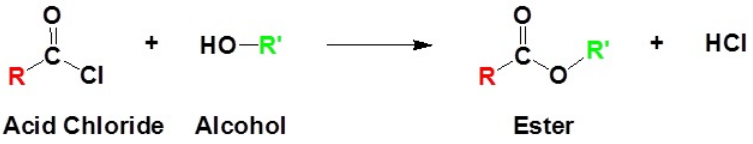


Synthesis of Esters

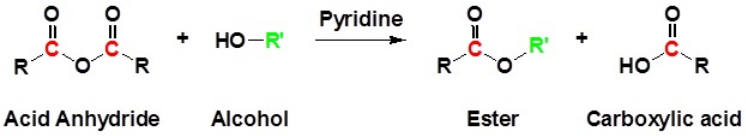
Carboxylic acids can react with alcohols to form esters in the presence of an acid catalyst as shown in the reaction below.



Acid chlorides react with alcohols to form esters as shown in the reaction below.

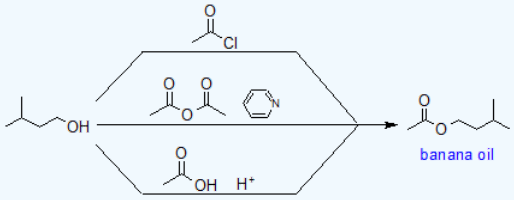


Acid anhydrides also react with alcohols to form esters as shown in the reaction below.



As an example, the synthesis of banana oil (isoamyl acetate) is an example of these two reactions.

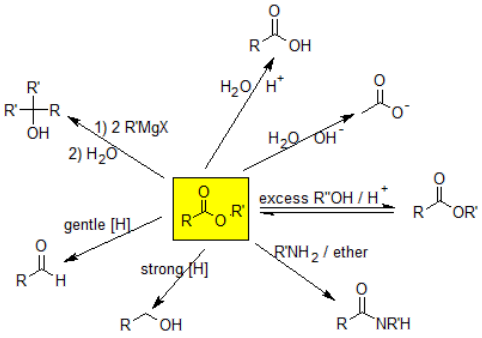
Example: Ester Synthesis



Esters can be also be synthesized from trans-esterification reactions. Trans-esterification is discussed in the next section on Reactivity of Esters

Reactivity of Esters

Esters can be hydrolyzed to carboxylic acids under acidic or basic conditions. Basic hydrolysis can be used to convert fats and oils into soap and is called a saponification reaction. Esters can be converted to amides via an aminolysis reaction. Esters can undergo trans-esterification reactions to form different esters by applying LeChatlier's principle to this equilibrium reaction. Esters can be reduced to form alcohols or aldehydes depending on the reducing agent. Esters also react with organometallic compounds to form tertiary alcohols. The reaction map for esters is shown below.

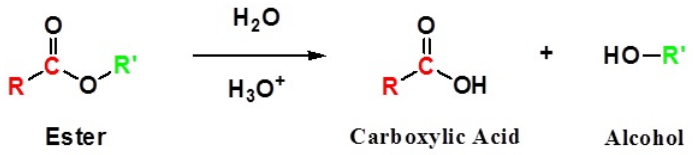


Ester Hydrolysis

Ester hydrolysis requires an acid catalyst or base promotion to occur. Esters are less reactive than acyl halides and acid anhydrides because the alkoxide group is a poor leaving group with its negative charge fully localized on a single oxygen atom.

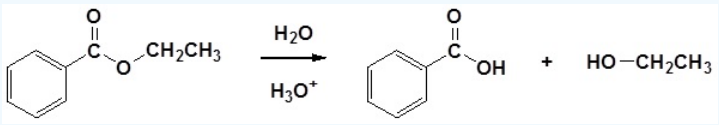
Ester Hydrolysis - Acid Catalyzed

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a catalytic amount of acid as shown in the reaction below.



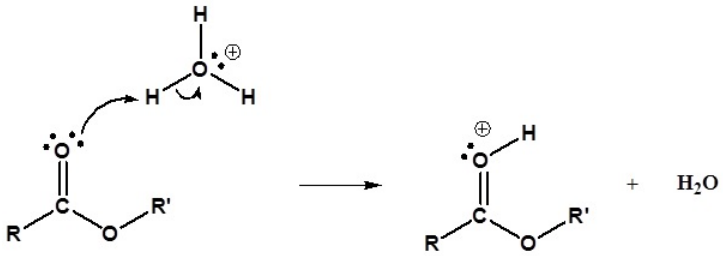
The acid catalyzed hydrolysis of ethyl benzoate is shown below as an example.

Example: Acid Catalyzed Ester Hydrolysis

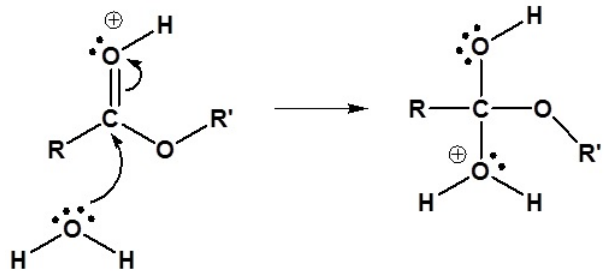


The mechanism for the acid catalyzed hydrolysis reaction begins with protonation of the carbonyl oxygen to increase the reactivity of the ester. The nucleophilic water reacts with the electrophilic carbonyl carbon atom to form the tetrahedral intermediate. Proton transfer reactions occur to create a good leaving group when the carbonyl reforms. The complete mechanism is shown below.

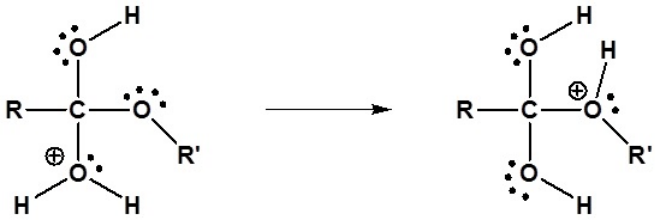
1) Protonation of the Carbonyl



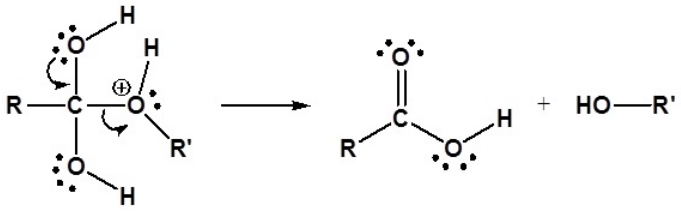
2) Nucleophilic reaction by water



3) Proton transfer

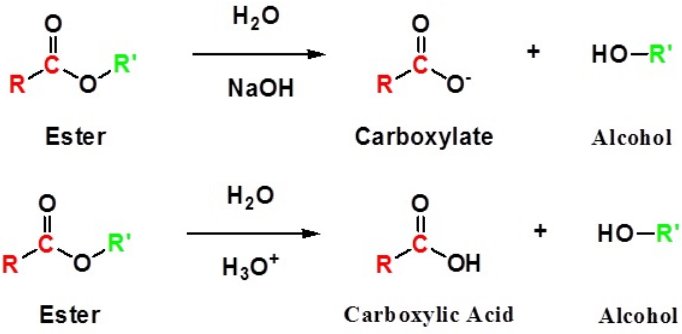


4) Leaving group removal



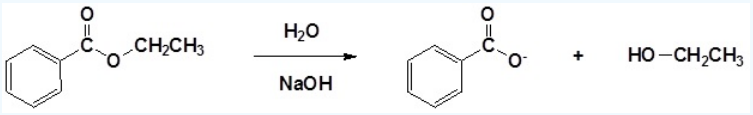
Ester Hydrolysis - Base promoted

Esters can be cleaved back into a carboxylic acid and an alcohol by reaction with water and a base. The reaction is called a saponification from the Latin *sapo* which means soap. The name comes from the fact that soap used to me made by the ester hydrolysis of fats. Due to the basic conditions, a carboxylate ion is made rather than a carboxylic acid. The hydroxide ions are consumed in the reaction so it is described as "base promoted".



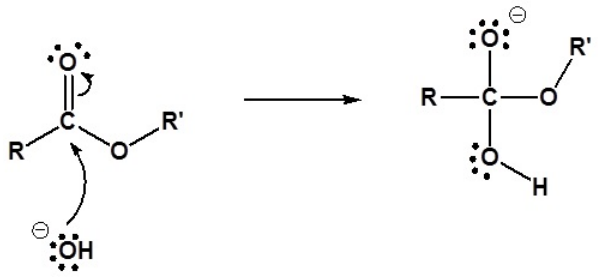
The base promoted hydrolysis of ethyl benzoate is shown below as an example.

Example: Base Promoted Hydrolysis of Esters

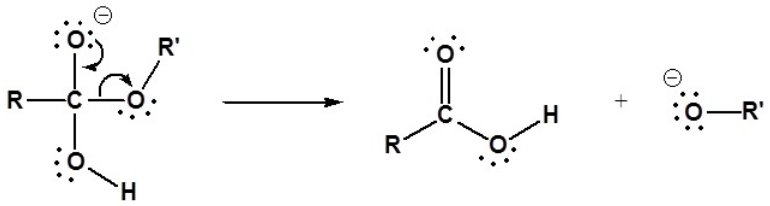


The mechanism for the base promoted hydrolysis reaction begins with the nucleophilic hydroxide reacting with the electrophilic carbonyl carbon atom to form the tetrahedral intermediate. The carbonyl reforms with the loss of the alkoxide leaving group. The alkoxide then deprotonates the resulting carboxylic acid. The complete mechanism is shown below.

1) Nucleophilic reaction by hydroxide



2) Leaving group removal



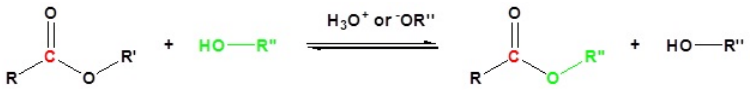
3) Deprotonation

Nuclephilic Acyl Substitution Reactions from Esters

Carboxylic acid derivatives can be synthesized from esters via the nucleophilic acyl substitution mechanism previously discussed.

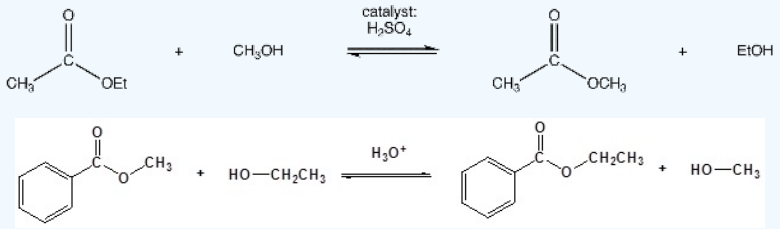
Ester Synthesis: Trans-Esterification

Trans-esterification is the conversion of a carboxylic acid ester into a different carboxylic acid ester. When an ester is placed in a large excess of an alcohol along with presence of either an acid or a base there can be an exchange of alkoxy groups. The large excess of alcohol is used to drive the reaction forward. The most common method of trans-esterification is the reaction of the ester with an alcohol in the presence of an acid catalyst as shown below.

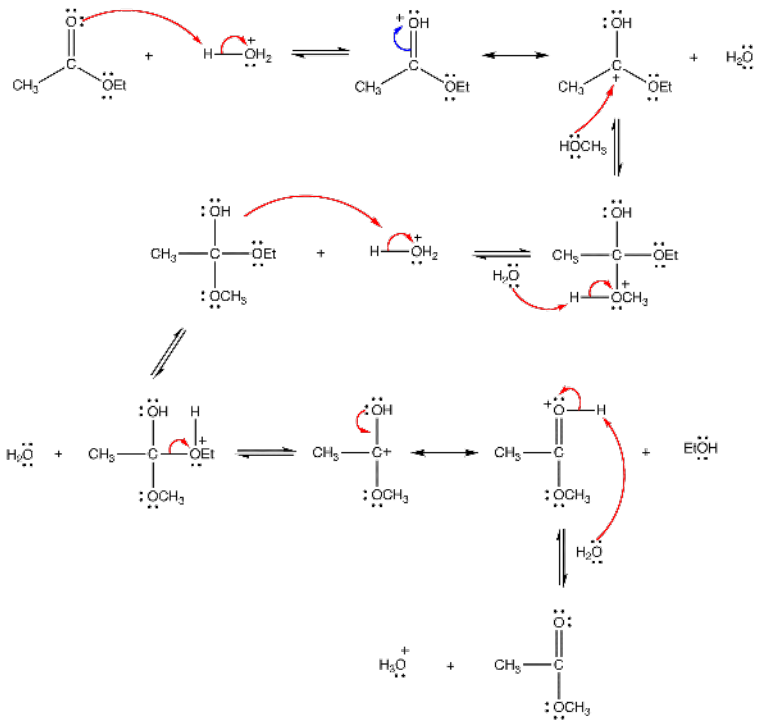


The trans-esterification of ethyl acetate to methyl acetate and methyl benzoate to ethyl benzoate are shown below as examples.

Example: Trans-esterification Reactions



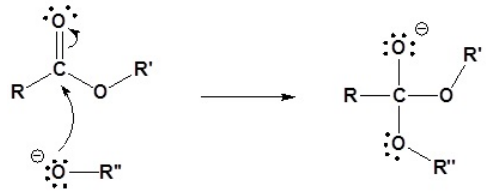
Under acidic conditions, the reaction mechanism begins with protonation of the carbonyl oxygen which increases the reactivity of the ester. An alcohol then reactions with protonated ester to form the tetrahedral intermediate. After several proton transfers, the carbonyl reforms to produce a new ester. The complete mechanism is shown below for the trans-esterification of ethyl actetae to methyl acetate.



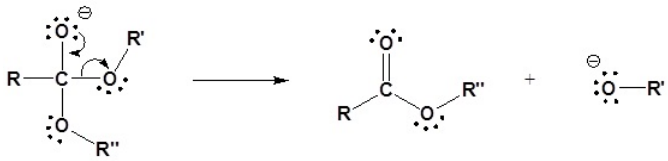
Since both the reactants and the products are an ester and an alcohol, the reaction is reversible and the equilibrium constant is close to one. Consequently, the Le Chatelier's principle has to be exploited to drive the reaction to completion. The simplest way to do so is to use the alcohol as the solvent as well.

Under basic conditions, the mechanism begins with the nucleophilic reaction of the alkoxide with the carbonyl carbon to produce the tetrahedral intermediate. The carbonyl reforms with the loss of the leaving group to produce a new ester.

1) Nucleophilic reaction by an alkoxide

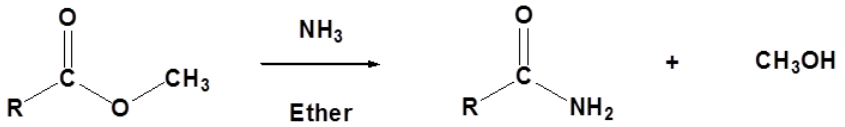


2) Leaving group removal



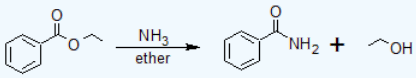
Aminolysis: Conversion of Esters into Amides

Esters react with ammonia and 1º or 2º alkyl amines to yield amides in a reaction called aminolysis.



The aminolysis of ethyl benzoate is shown below as an example. The mechanism for this reaction is analogous to the base promoted hydrolysis reaction of esters shown above.

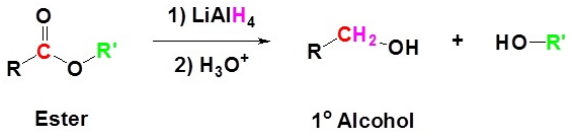
Example: Aminolysis of Esters



Ester Reduction Reactions

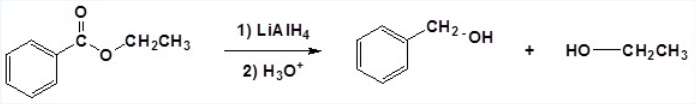
Ester Reduction to a 1° Alcohol

Esters can be converted to 1° alcohols using $LiAlH_4$, while sodium borohydride ($NaBH_4$) is not a strong enough reducing agent to perform this reaction.



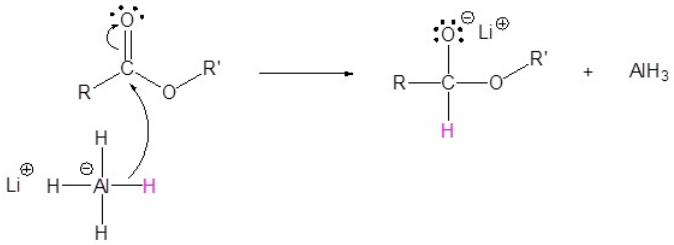
The reduction of ethyl benzoate to benzyl alcohol and ethanol is shown as an example.

Example: Ester Reduction to a 1° Alcohol

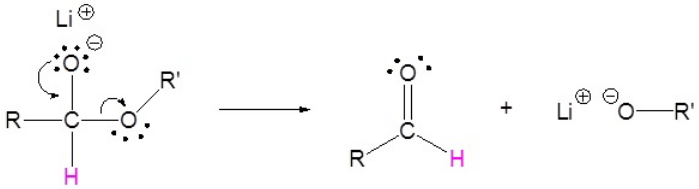


The mechanism begins with a hydride nucleophile reacting with the ester carbonyl carbon to form the tetrahedral intermediate. The carbonyl reforms to produce an aldehyde with the loss of the alkoxide ion. The resulting aldehyde undergoes a subsequent reaction with a hydride nucleophile to form another tetrahedral intermediate. The carbonyl is not able to reform, because there are no stable leaving groups. Therefore, the alkoxide (tetrahedral intermediate) is protonated to produce a primary alcohol. The complete mechanism is shown below.

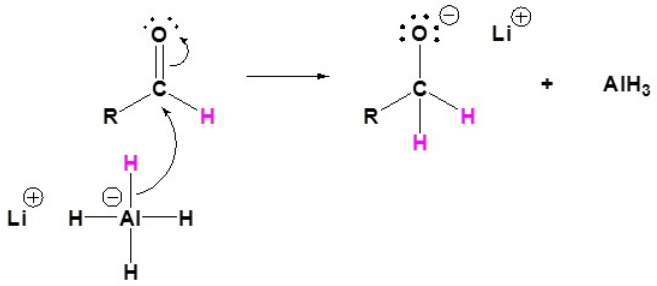
1) Nucleophilic reaction by the hydride



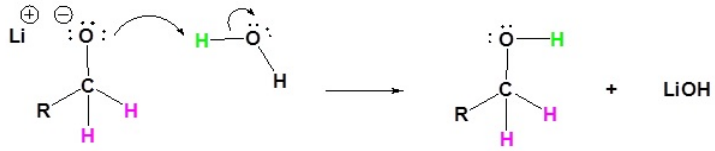
2) Leaving group removal



3) Nucleopilic reaction by the hydride anion

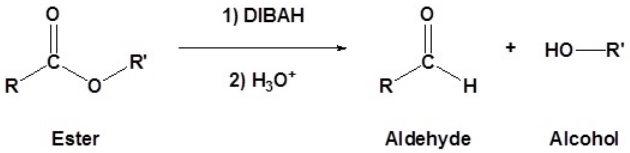


4) The alkoxide is protonated



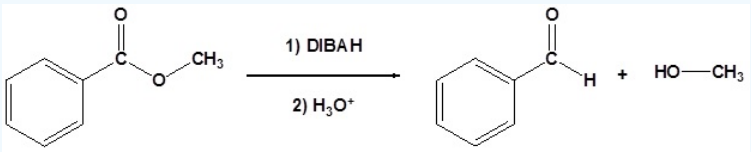
Ester Reduction to an Aldehyde

Esters can be converted to aldehydes using diisobutylaluminum hydride (DIBAH). The reaction is usually carried out at -78 ^{o}C to prevent reaction with the aldehyde product.



The reduction of methyl benzoate to form benzaldehyde is shown as an example. The mechanism is analogous to the $LiAlH_4$ mechanism shown above with the important difference that the reaction stops after the aldehyde is produced because the DIBAH reducing agent is not strong enough to reduce the aldehyde at low temperatures.

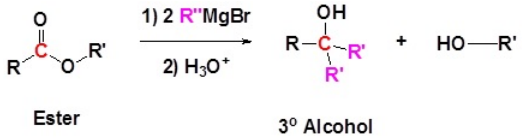
Example: Ester Reduction to an Aldehyde



Ester Reactions with Organometallic Compounds

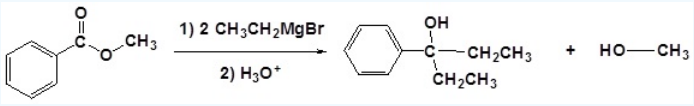
Grignard reagents

Esters react with Grignard reagents to form tertiary alcohols. This reaction is analogous to the reaction discussed for acid chlorides with Grignard reagents. The first equivalent of the Grignard reagent produces a ketone which reacts with the second equivalent of the Grignard reagent to produce a tertiary alcohol. In effect, the Grignard reagent adds twice as shown in the reaction below.



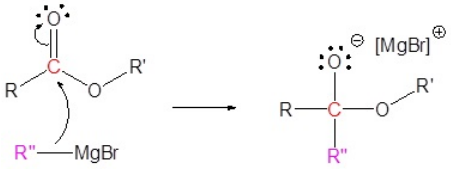
The reaction of methyl benzoate with a Grignard reagent to produce 3-phenyl-3-pentanol.

Example: Ester Reaction with a Grignard Reagent

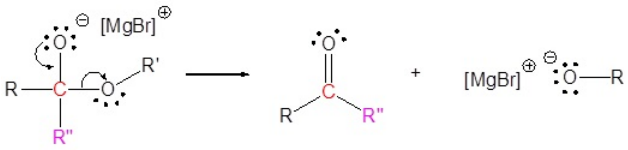


The mechanism begins with a carbide nucleophile from the Grignard reagent reacting with the ester carbonyl carbon to form the tetrahedral intermediate. The carbonyl reforms to produce a ketone with the loss of the alkoxide ion. The resulting ketone undergoes a subsequent reaction with a carbide nucleophile from the Grignard reagent to form another tetrahedral intermediate. The carbonyl is not able to reform, because there are no stable leaving groups. Therefore, the alkoxide (tetrahedral intermediate) is protonated to produce a tertiary alcohol. The complete mechanism is shown below.

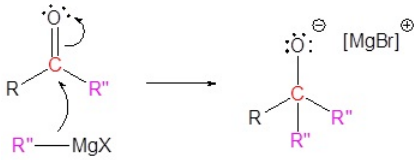
1) Nucleophilic reaction



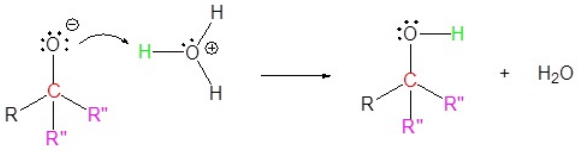
2) Leaving group removal



3) Nucleophilic reaction



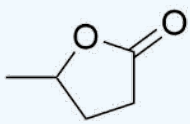
4) Protonation



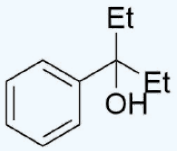
Exercise

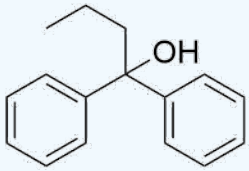
8. Why is the alkaline hydrolysis of an ester not a reversible process? Why doesn't the reaction with a hydroxide ion and a carboxylic acid produce an ester?

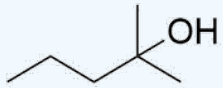
9. Draw the product of the reaction between the following molecule and $LiAlH_4$, and the product of the reaction between the following molecule and DIBAL.



10. Prepare the following molecules from esters and Grignards?

(a) 

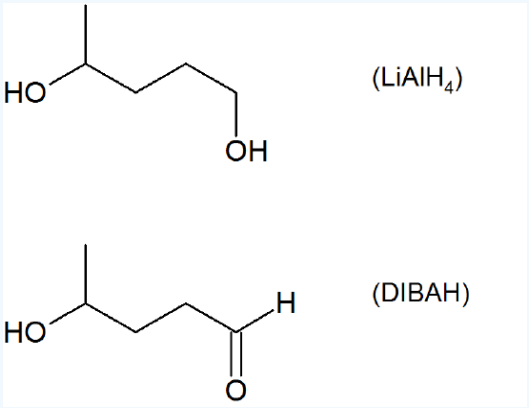
(b) 

(c) 

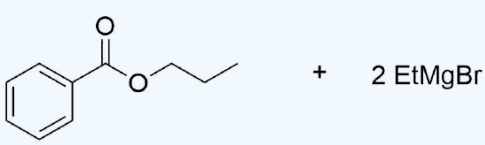
Answer

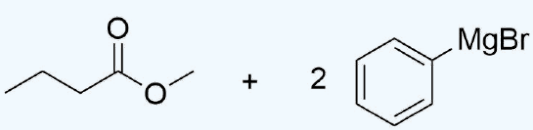
8. The reaction between a carboxylic acid and a hydroxide ion is an acid base reaction, which produces water and a carboxylate anion.

9.



10.

(a) 

(b) 

(c)

Contributors and Attributions

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Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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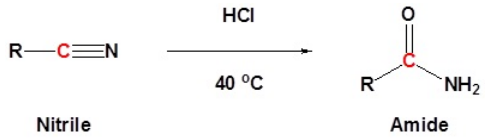
20.7: Amide Chemistry

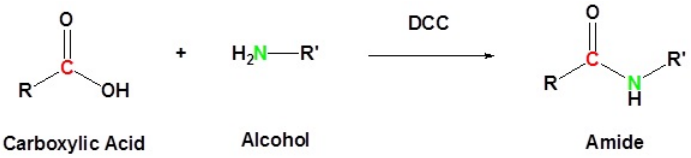
Synthesis of Amides

There are five synthetic routes to produce amides: nitrile conversion and the acyl nucleophilic substitution reactions of acid halides, acid anhydrides, and carboxylic acids.

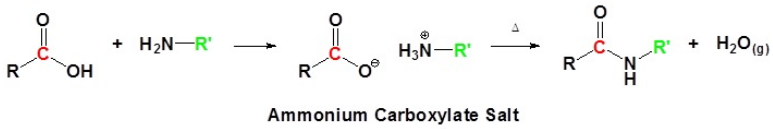
Nitriles can be converted to amides. This reaction can be acid or base catalyzed



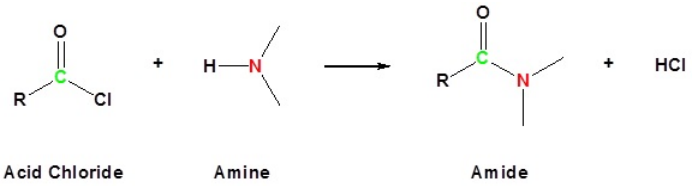
Carboxylic acid can be converted to amides by using DCC as an activating agent



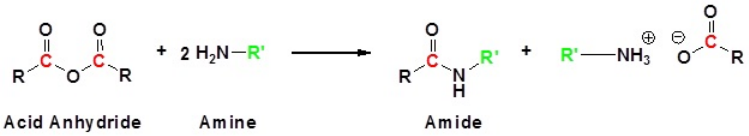
Direct conversion of a carboxylic acid to an amide by reaction with an amine.



Acid chlorides react with ammonia, 1° amines and 2° amines to form amides



Acid Anhydrides react with ammonia, 1° amines and 2° amines to form amides



Hydrolysis of Amides

Hydrolysis under acidic conditions

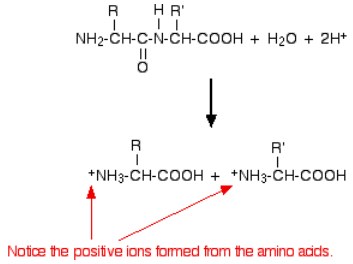
Taking acetamide (ethanamide) as a typical amide. If acetamide is heated with a dilute acid (such as dilute hydrochloric acid), acetic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and acetic acid.

Hydrolysis under alkaline conditions

Also, if acetamide is heated with sodium hydroxide solution, ammonia gas is given off and you are left with a solution containing sodium acetate.

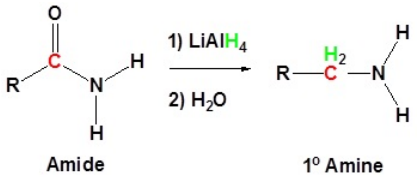
Peptide hydrolysis

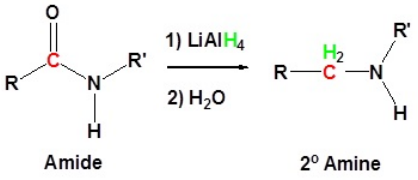
Peptide hydrolysis of proteins is amide hydrolysis. What biologists and biochemists call a peptide link (in proteins, for example) is what chemists call an amide link. Apply either hydrolysis reaction above to the dipeptide below to produce two amino acids. The amines in the products are shown in their protonated form because this hydrolysis reaction was performed under acidic conditions.

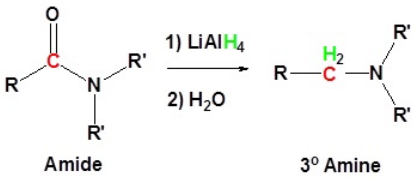


Reduction of Amides into Amines

Amides can be converted to 1°, 2° or 3° amines using $LiAlH_4$ followed by an aqueous work-up. Alkyl groups attached to the amide nitrogen do not affect the reaction. The amine classification correlates with the amide as shown in the reaction summary below.

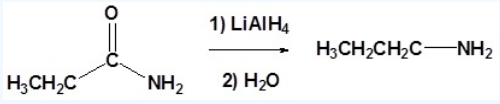


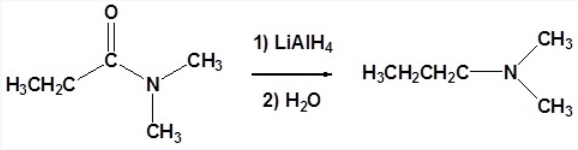




The reductions of propanamide and N,N-dimethylpropanamide are shown as examples.

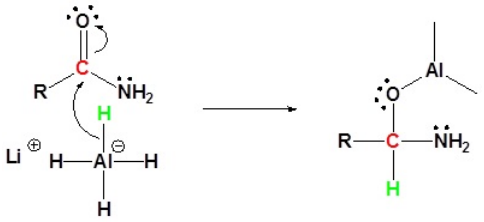
Example: Amide Reductions



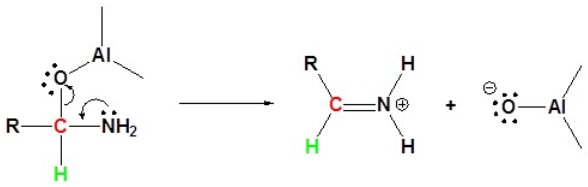


The mechanism begins with nucleophilic hydride reacting with the carbonyl carbon to produce the tetrahedral intermediate. An imine forms in concert with the loss on the leaving group. A second hydride nucleophile reacts with the imine carbon to produce the final product.

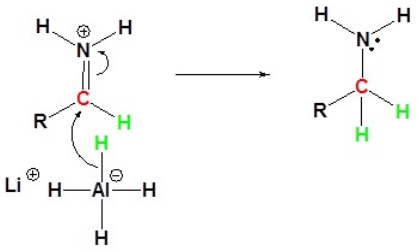
1) Nucleophilic reaction by the hydride



2) Imine formation with loss of leaving group



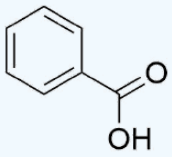
3) Nucleophilic reaction by the hydride



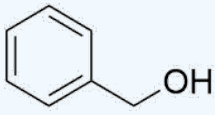
Exercise

11. How would you prepare the following compounds from N-Propypl benzamide?

(a)



(b)



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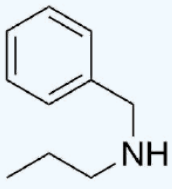
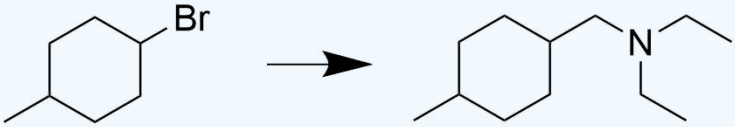


12.

Propose a synthesis for the following.



Answer

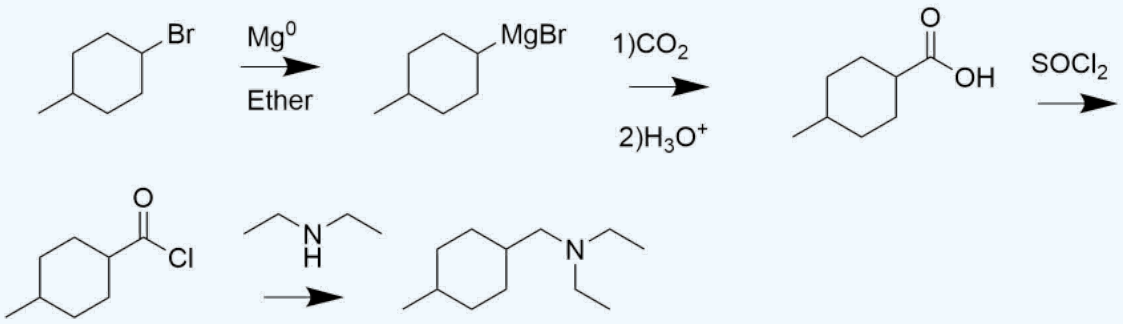
11.

a) NaOH, H_2O

b) NaOH, H_2O, then $LiAlH_4$

c) $LiAlH_4$

12.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)

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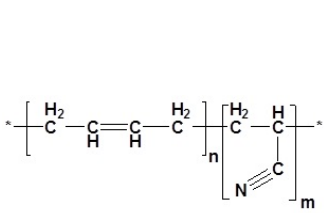
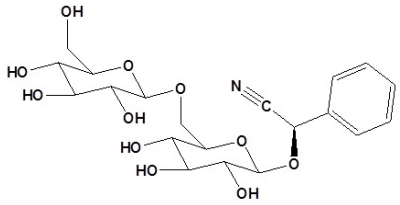
20.8: Nitrile Chemistry

Interesting Nitriles

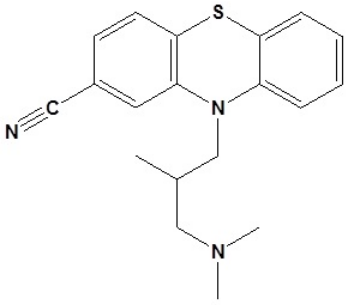
One of the most common occurrences of nitriles is nitrile rubber. Nitrile rubber is a synthetic copolymer of acrylonitrile and butadiene. This form of rubber is highly resistant to chemicals and is used to make protective gloves, hoses and seals.



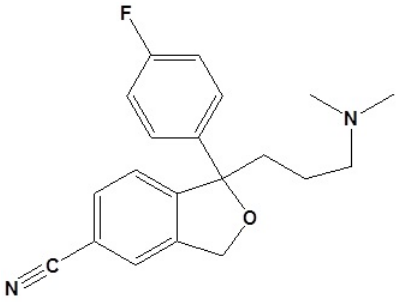
Nitrile Rubber



Amygdalin: Found in Bitter Almonds



Cyamemazine: an antipsychotic

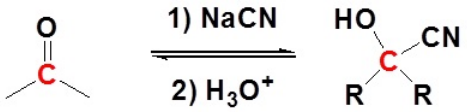


Citalopram: an antidepressant

Synthesis of Nitriles

Nitriles can be synthesized from the reaction of nucleophilic cyanide with electrophilic groups, such as the carbonyls (aldehydes and ketones) and alkyl halides that are suitable for S_N2 reactions. Amides can react with thionyl chloride to produce nitriles.

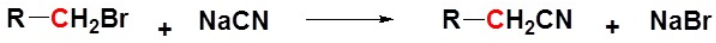
Addition of cyanide ($^-$:C≡N) to an aldehyde or ketone forms a cyanohydrin.



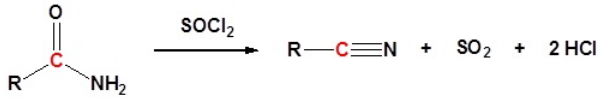
Aldehyde or Ketone

Cyanohydrin

Nitriles are formed by an S_N2 reaction between an alkyl bromide and sodium cyanide



Primary (1°) amides can be converted to nitriles by dehydration with thionyl chloride (or other dehydrating agents like P_2O_5, or $POCl_3$).



1° Amide

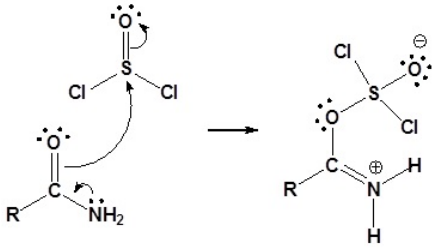
Nitrile

For the reaction of primary amides with thionyl chloride, the mechanism begins with the lone pair of the nitrogen atom formimg a protonated imine and pushing the pi electrons of the carbonyl to form a sigma bond with the sulfur of thionyl chloride. The sulfonyl

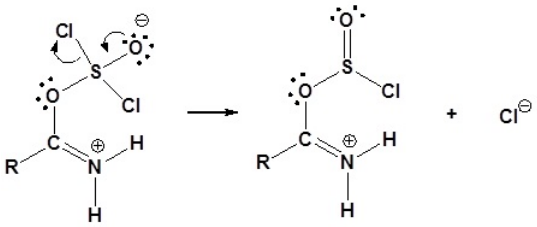
bond reforms in concert with the loss of the leaving group (Cl^-). The protonated imine is neutralized by any base. The nitrile is produced by one last deprotonation reaction with a loss of sulfur dioxide and chloride as the leaving groups.

The complete mechanism is shown below.

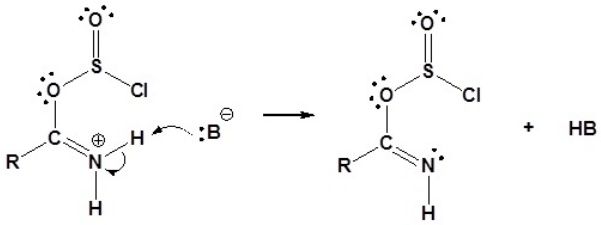
1) Protonated imine formation with Nucleophilic reaction of carbonyl pi bond



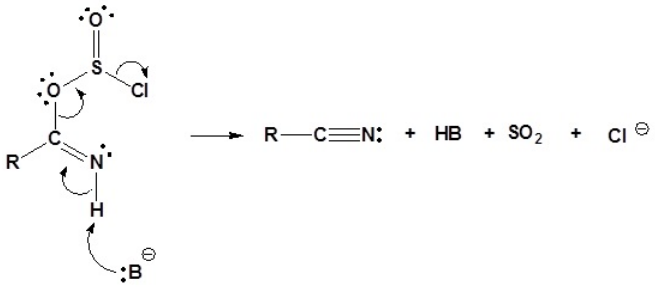
2) Leaving group removal



3) Deprotonation

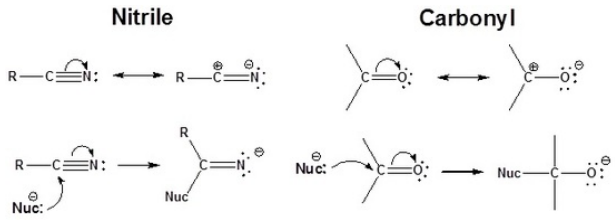


4) Deprotonation & Leaving group removal

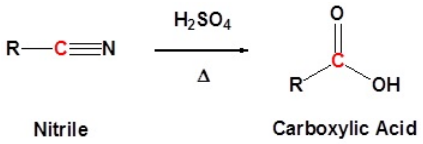


Reactivity of Nitriles

The carbon in a nitrile is electrophilic because a resonance structure can be drawn which places a positive charge on it. Because of this the triple bond of a nitrile accepts a nucleophile in a manner similar to a carbonyl.

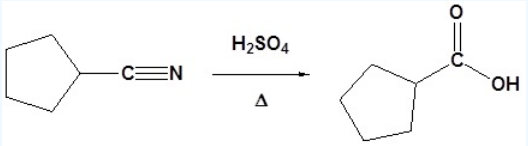


Nitriles can be converted to carboxylic acid with heating in sulfuric acid. During the reaction an amide intermediate is formed.



The hydrolysis of cyclopentanecarbonitrile is shown below as an example.

Example: Nitrile Hydrolysis

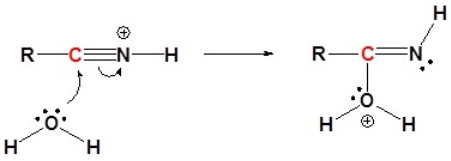


Note that the presence of water is understood.

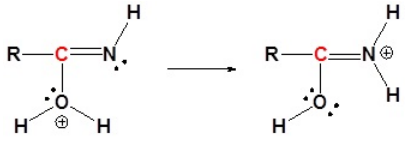
The mechanism begins with the protonation of the nitrile to make it more electrophilic to nucleophilic water. Once the water has reacted with the nitrile carbon, proton transfers occur to produce a resonance stabilized intermediate. Water acts as a weak base to deprotonate the carbonyl to form the amide which is hydrolyzed to the carboxylic acid.

1) Protonation

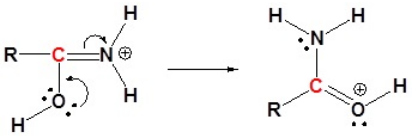
2) Nucleophilic reaction by water



3) Proton Transfer

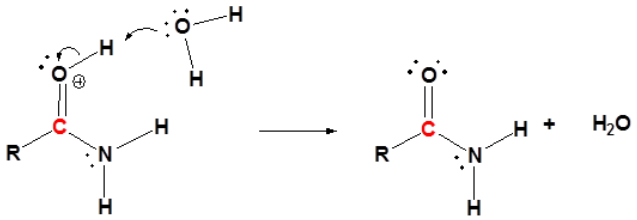


4) Resonance

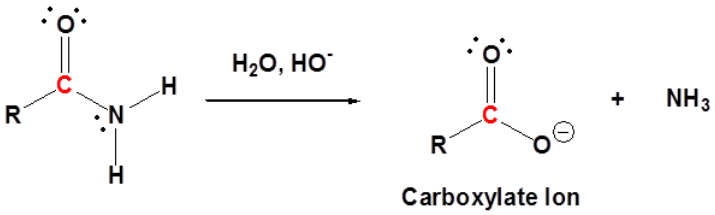


5) Deprotonation

https://chem.libretexts.org/@go/page/183128

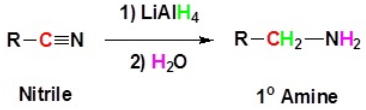


6) Further hydrolysis of the amide shown in amide section of this chapter.



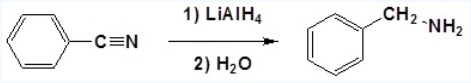
Nitrile Reduction

Nitriles can be reduced to primary amines with lithium aluminum hydride followed by an aqueous work-up. During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation, the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water to neutralize the reaction environment. The general reaction is shown below.



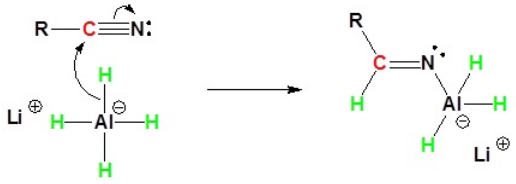
The reduction of cyclopentanecarbonitrile is shown below as an example.

Example: Nitrile Reduction

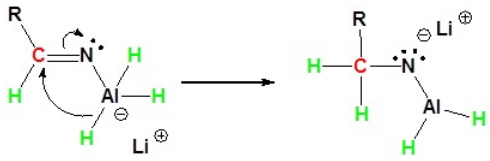


The mechanism begins with the nucleophilic hydride reacting with the electrophilc carbon of the nitrile to form an anionic aluminum complex. A second hydride nucleophile reacts with the same electrophilic carbon to form a tetrahedral complex. Protonation by addition of water produces the primary amine in its neutral form.

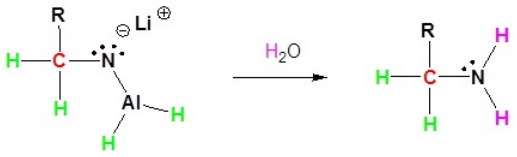
1) Nucleophilic reaction by the Hydride



2) Second nucleophilic reaction by the hydride.

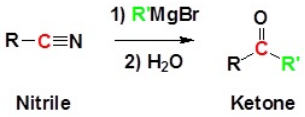


3) Protonation by addition of water to give an amine



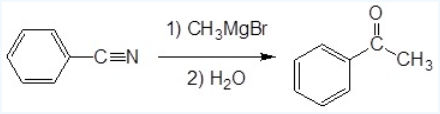
Organometallic Reaction with Nitriles

Grignard reagents can react with nitriles to form an imine salt that can be hydrolyzed to form a ketone as shown in the reaction below.



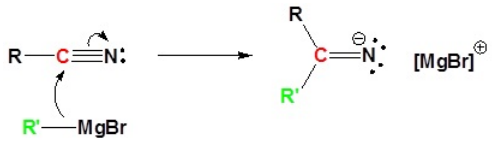
The reaction of benzonitrile with the methyl-Grignard reagent to form acetophenone is shown below as an example.

Example: Nitrile reaction with a Grignard Reagent

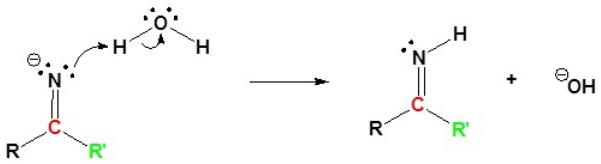


The mechanism begins with the nucleophilic Grignard Reagent reacting with the electrophilic carbon of the nitrile to form an imine salt. The imine salt is hydrolyzed to produce a ketone through a series of nucleophilic and proton transfer reactions. The complete mechanism is shown below for those who are curious.

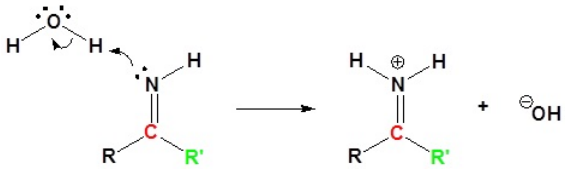
1) Nucleophilic reaction by the Grignard Reagent



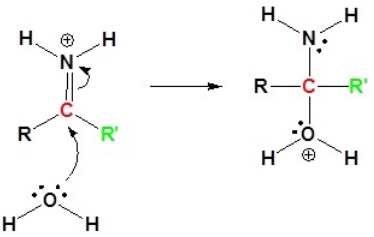
2) Protonation



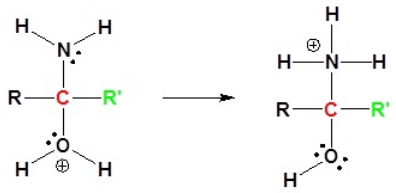
3) Protonation



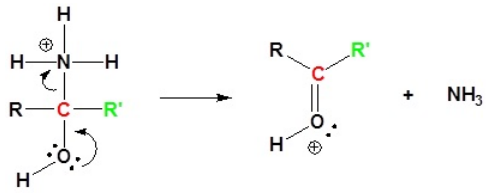
4) Nucleophilic reaction by water



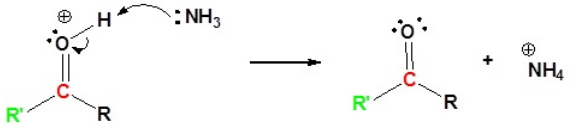
5) Proton Transfer



6) Leaving group removal



7) Deprotonation

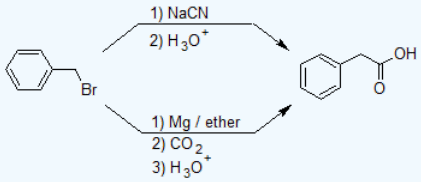


Exercise

13. Propose two different synthetic routes to convert benzyl bromide into 2-phenyl acetic acid.

Answer

13.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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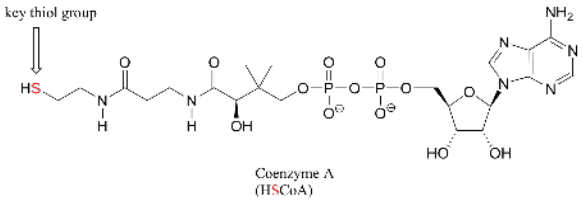
20.9: Thioesters: Biological Carboxylic Acid Derivatives

Introduction to thioesters and Coenzyme A

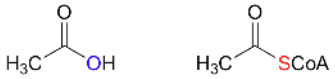
In the metabolism of lipids (fats and oils), thioesters are the principal form of activated carboxylate groups. They are employed as acyl carriers, assisting with the transfer of acyl groups such as fatty acids from one acyl X substrate to another.

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
(HSCoA)

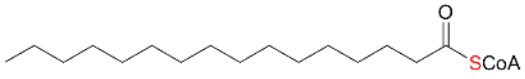
Coenzyme A is often abbreviated HSCoA, in order to emphasize that it is the thiol sulfur that provides the critical thioester linkage to acyl groups. When fuel (carbohydrate and fat) is broken down in your body, it is eventually converted to a simple two-carbon unit called acetyl CoA, which is essentially a thioester derivative of acetic acid:



acetic acid acetyl-SCoA

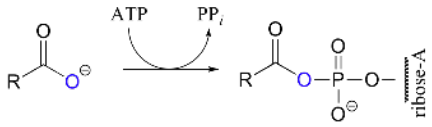
Activation of fatty acids by coenzyme A: a thioesterification reaction

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:



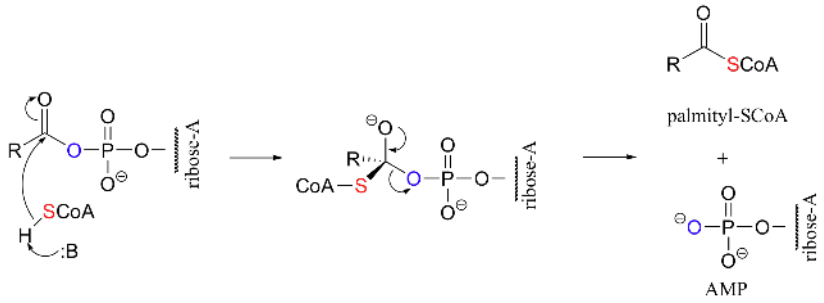
palmityl-SCoA

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.



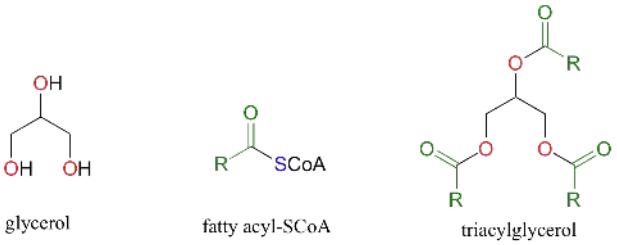
palmitate palmityl-AMP

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.

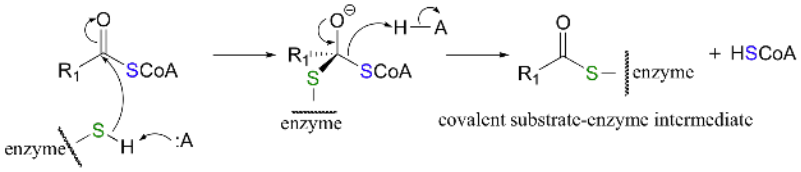


Transfer of fatty acyl groups to glycerol: a thioester to ester substitution

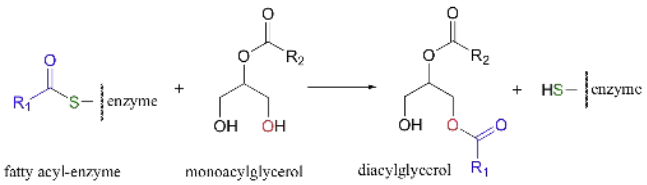
The -SCoA thioester form of the fatty acid is a good substrate for a number of metabolic transformations. This is the form of fatty acid, for example, that is oxidized and broken down for energy in the mitochondria of your cells. Fatty acyl CoA also serves as substrate for the construction of triacylglycerol, which is the fat molecule that your body uses to store energy in fat cells. Recall 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.



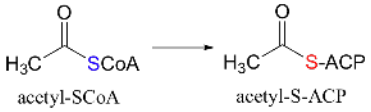
The fatty acyl group is now ready to be transferred to glycerol, trading its thioester linkage to the cysteine for a new ester linkage to one of the alcohol groups on glycerol. The attacking nucelophile in this reaction is of course the alcohol oxygen of monoacylglycerol.

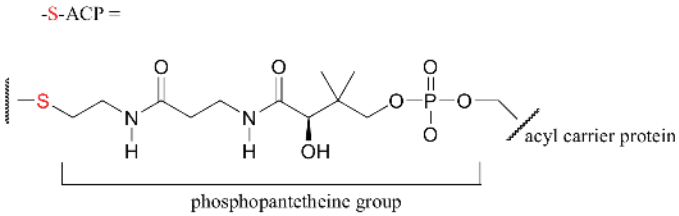


Because esters are more stable than thioesters, this is an energetically downhill reaction.

Transthioesterification reactions

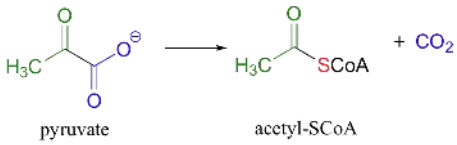
In the previous section we saw one example of a transthioesterification. Another important transthioesterification reaction involves acetyl CoA, the activated form of acetic acid and the basic two-carbon building block for fats and oils. Before it can be incorporated into a growing fatty acid molecule, 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.



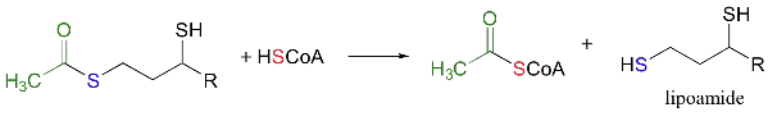


Notice that the structure of this carrier group (called phosphopantetheine) is identical to the region of coenzyme A (structure shown earlier in this section) near the thiol group. Once attached to the ACP, the two-carbon acetyl group condenses with another acyl group (which is also attached to its own ACP), and the fatty acid chain begins to grow.

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.



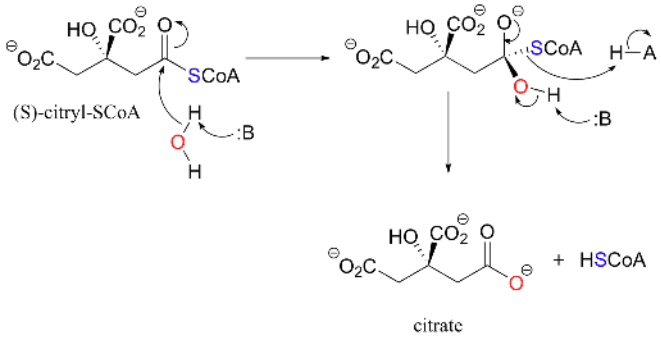
The overall reaction looks simple, but is actually quite complex and involves several intermediate species. The final step in the process is a transthioesterification, involving a dithiol molecule called lipoamide:



We will look more closely at the complete biochemical transformation catalyzed by the pyruvate dehydrogenase complex in section 16.12B.

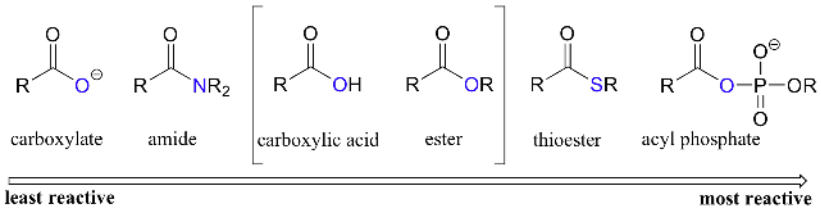
Hydrolysis of thioesters

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)-cityl CoA to citrate in the citric acid cycle (also known as the Krebs cycle).



Reactivity of thioesters and acyl phosphates

Thioesters are reactive among the biologically relevant acyl groups. However, thioesters are not as reactive as an acid chlorides or acid anhydrides.



Relative reactivity of biologically relevant acyl groups

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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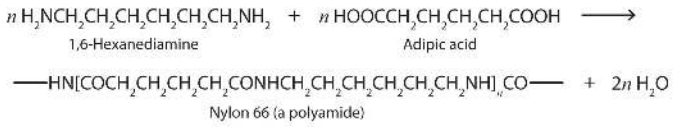
20.10: Polyamides and Polyesters: Step-Growth Polymers

Polyamides

Just as the reaction of a diol and a diacid forms a polyester, the reaction of a diacid and a diamine yields a polyamide. The two difunctional monomers often employed are adipic acid and 1,6-hexanediamine. The monomers condense by splitting out water to form a new product, which is still difunctional and thus can react further to yield a polyamide polymer.

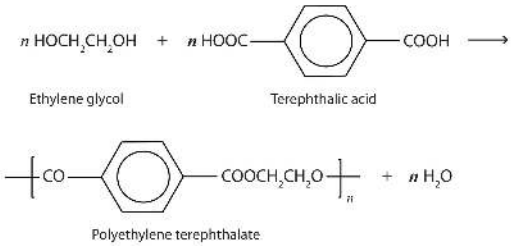


Some polyamides are known as *nylons*. Nylons are among the most widely used synthetic fibers—for example, they are used in ropes, sails, carpets, clothing, tires, brushes, and parachutes. They also can be molded into blocks for use in electrical equipment, gears, bearings, and valves.

Polyesters

A commercially important esterification reaction is condensation polymerization, in which a reaction occurs between a dicarboxylic acid and a dihydric alcohol (diol), with the elimination of water. Such a reaction yields an ester that contains a free (unreacted) carboxyl group at one end and a free alcohol group at the other end. Further condensation reactions then occur, producing polyester polymers.

The most important polyester, polyethylene terephthalate (PET), is made from terephthalic acid and ethylene glycol monomers:

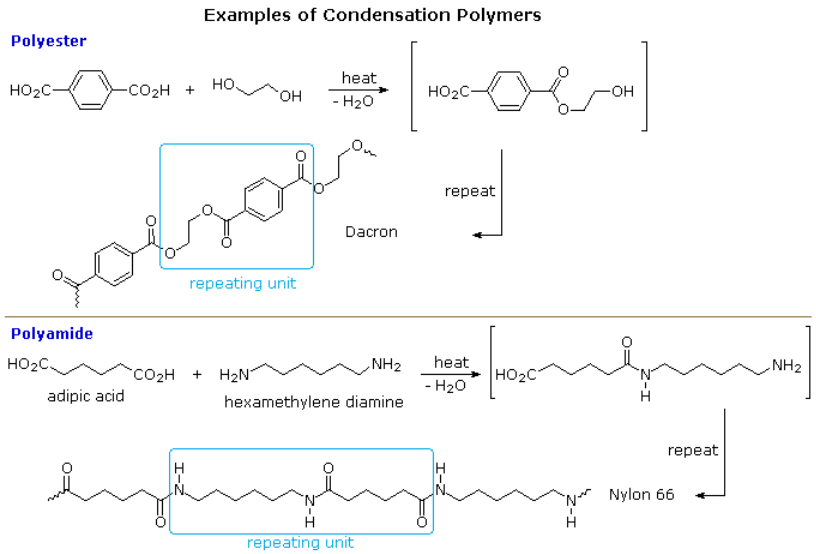


Polyester molecules make excellent fibers and are used in many fabrics. A knitted polyester tube, which is biologically inert, can be used in surgery to repair or replace diseased sections of blood vessels. PET is used to make bottles for soda pop and other beverages. It is also formed into films called Mylar. When magnetically coated, Mylar tape is used in audio- and videocassettes. Synthetic arteries can be made from PET, polytetrafluoroethylene, and other polymers.

Condensation Polymers

A large number of important and useful polymeric materials are not formed by chain-growth processes involving reactive species such as radicals, but proceed instead by conventional functional group transformations of polyfunctional reactants. These polymerizations often (but not always) occur with loss of a small byproduct, such as water, and generally (but not always) combine two different components in an alternating structure. The polyester Dacron and the polyamide Nylon 66, shown here, are two examples of synthetic condensation polymers, also known as step-growth polymers. In contrast to chain-growth polymers, most of which grow by carbon-carbon bond formation, step-growth polymers generally grow by carbon-heteroatom bond formation (C-O & C-N in Dacron & Nylon respectively). Although polymers of this kind might be considered to be alternating copolymers, the repeating monomeric unit is usually defined as a combined moiety.

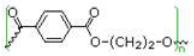
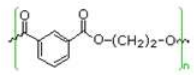
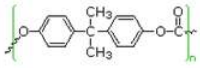
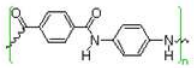
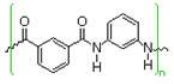
Examples of naturally occurring condensation polymers are cellulose, the polypeptide chains of proteins, and poly(β-hydroxybutyric acid), a polyester synthesized in large quantity by certain soil and water bacteria. Formulas for these will be displayed below by clicking on the diagram.



Characteristics of Condensation Polymers

Condensation polymers form more slowly than addition polymers, often requiring heat, and they are generally lower in molecular weight. The terminal functional groups on a chain remain active, so that groups of shorter chains combine into longer chains in the late stages of polymerization. The presence of polar functional groups on the chains often enhances chain-chain attractions, particularly if these involve hydrogen bonding, and thereby crystallinity and tensile strength. The following examples of condensation polymers are illustrative.

Note that for commercial synthesis the carboxylic acid components may actually be employed in the form of derivatives such as simple esters. Also, the polymerization reactions for Nylon 6 and Spandex do not proceed by elimination of water or other small molecules. Nevertheless, the polymer clearly forms by a step-growth process. Some Condensation 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

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

John D. Robert and Marjorie C. Caserio (1977) *Basic Principles of Organic Chemistry, second edition.* W. A. Benjamin, Inc. , Menlo Park, CA. ISBN 0-8053-8329-8. This content is copyrighted under the following conditions, "You are granted permission for individual, educational, research and non-commercial reproduction, distribution, display and performance of this work in any format."

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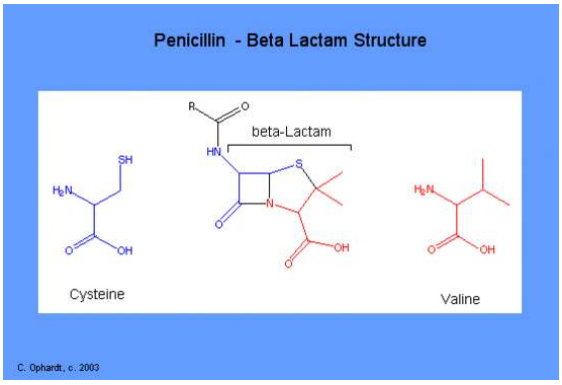
20.11: Beta-Lactams: An Application

The Mechanism of Action of β-Lactam Antibiotics

Antibiotics are specific chemical substances derived from or produced by living organisms that are capable of inhibiting the life processes of other organisms. The first antibiotics were isolated from microorganisms but some are now obtained from higher plants and animals. Over 3,000 antibiotics have been identified but only a few dozen are used in medicine. Antibiotics are the most widely prescribed class of drugs comprising 12% of the prescriptions in the United States. The penicillins were the first antibiotics discovered as natural products from the mold Penicillium.

Introduction

In 1928, Sir Alexander Fleming, professor of bacteriology at St. Mary's Hospital in London, was culturing Staphylococcus aureus. He noticed zones of inhibition where mold spores were growing. He named the mold Penicillium rubrum. It was determined that a secretion of the mold was effective against Gram-positive bacteria.



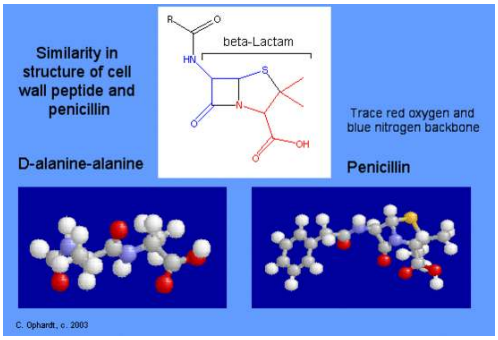
Penicillins as well as cephalosporins are called beta-lactam antibiotics and are characterized by three fundamental structural requirements: the fused beta-lactam structure (shown in the blue and red rings, a free carboxyl acid group (shown in red bottom right), and one or more substituted amino acid side chains (shown in black). The lactam structure can also be viewed as the covalent bonding of pieces of two amino acids - cysteine (blue) and valine (red).

Penicillin-G where R = an ethyl pheny group, is the most potent of all penicillin derivatives. It has several shortcomings and is effective only against gram-positive bacteria. It may be broken down in the stomach by gastric acids and is poorly and irregularly absorbed into the blood stream. In addition many disease producing staphylococci are able to produce an enzyme capable of inactivating penicillin-G. Various semisynthetic derivatives have been produced which overcome these shortcomings.

Powerful electron-attracting groups attached to the amino acid side chain such as in phenethicillin prevent acid attack. A bulky group attached to the amino acid side chain provides steric hindrance which interferes with the enzyme attachment which would deactivate the pencillins i.e. methicillin. Refer to Table 2 for the structures. Finally if the polar character is increased as in ampicillin or carbenicillin, there is a greater activity against Gram-negative bacteria.

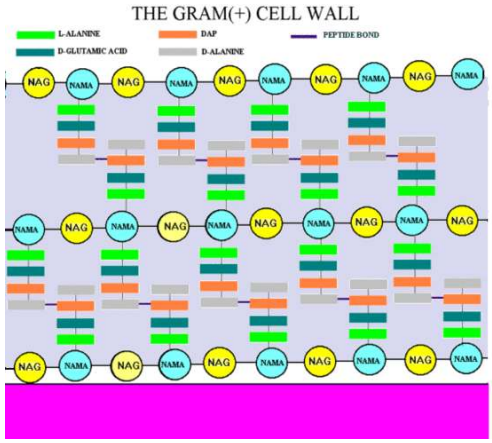
Penicillin Mode of Action

All penicillin derivatives produce their bacteriocidal effects by inhibition of bacterial cell wall synthesis. Specifically, the cross linking of peptides on the mucosaccharide chains is prevented. If cell walls are improperly made cell walls allow water to flow into the cell causing it to burst. Resemblances between a segment of penicillin structure and the backbone of a peptide chain have been used to explain the mechanism of action of beta-lactam antibiotics. The structures of a beta-lactam antibiotic and a peptide are shown on the left for comparison. Follow the trace of the red oxygens and blue nitrogen atoms.



Gram-positive bacteria possess a thick cell wall composed of a cellulose-like structural sugar polymer covalently bound to short peptide units in layers.The polysaccharide portion of the peptidoglycan structure is made of repeating units of N-acetylglucosamine linked b-1,4 to N-acetylmuramic acid (NAG-NAM). The peptide varies, but begins with L-Ala and ends with D-Ala. In the middle is a dibasic amino acid, diaminopimelate (DAP). DAP (orange) provides a linkage to the D-Ala (gray) residue on an adjacent peptide.

The bacterial cell wall synthesis is completed when a cross link between two peptide chains attached to polysaccharide backbones is formed. The cross linking is catalyzed by the enzyme transpeptidase. First the terminal alanine from each peptide is hydrolyzed and secondly one alanine is joined to lysine through an amide bond.



Penicillin binds at the active site of the transpeptidase enzyme that cross-links the peptidoglycan strands. It does this by mimicking the D-alanyl-D-alanine residues that would normally bind to this site. Penicillin irreversibly inhibits the enzyme transpeptidase by reacting with a serine residue in the transpeptidase. This reaction is irreversible and so the growth of the bacterial cell wall is inhibited. Since mammal cells do not have the same type of cell walls, penicillin specifically inhibits only bacterial cell wall synthesis.

Bacterial Resistance

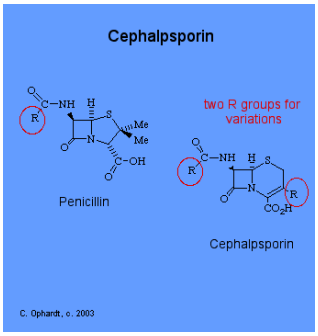
As early as the 1940s, bacteria began to combat the effectiveness of penicillin. Penicillinases (or beta-lactamases) are enzymes produced by structurally susceptable bacteria which renders penicillin useless by hydrolysing the peptide bond in the beta-lactam ring of the nucleus. Penicillinase is a response of bacterial adaptation to its adverse environment, namely the presence of a substance which inhibits its growth. Many other antibiotics are also rendered ineffective because of this same type of resistance.

Severe Allergic Shock

It is estimated that between 300-500 people die each year from penicillin-induced anaphylaxis, a severe allergic shock reaction to penicillin. In afflicted individuals, the beta-lactam ring binds to serum proteins, initiating an IgE-mediated inflammatory response. Penicillin and ala-ala peptide - Chime in new window

Cephalosporins

Cephalosporins are the second major group of beta-lactam antibiotics. They differ from penicillins by having the beta-lactam ring as a 6 member ring. The other difference, which is more significant from a medicinal chemistry stand point, is the existence of a functional group (R) at position 3 of the fused ring system. This now allows for molecular variations to effect changes in properties by diversifying the groups at position 3.



The first member of the newer series of beta-lactams was isolated in 1956 from extracts of Cephalosporium acremonium, a sewer fungus. Like penicillin, cephalosporins are valuable because of their low toxicity and their broad spectrum of action against various diseases. In this way, cephalosporin is very similar to penicillin. Cephalosporins are one of the most widely used antibiotics, and economically speaking, has about 29% of the antibiotic market. The cephalosporins are possibly the single most important group of antibiotics today and are equal in importance to penicillin.

The structure and mode of action of the cephalosporins are similar to that of penicillin. They affect bacterial growth by inhibiting cell wall synthesis, in Gram-positive and negative bacteria. Some brand names include: cefachlor, cefadroxil, cefoxitin, ceftriaxone. Cephalexin - Chime in new window

Contributors and Attributions

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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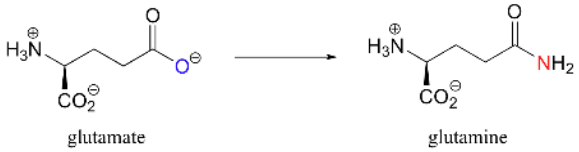
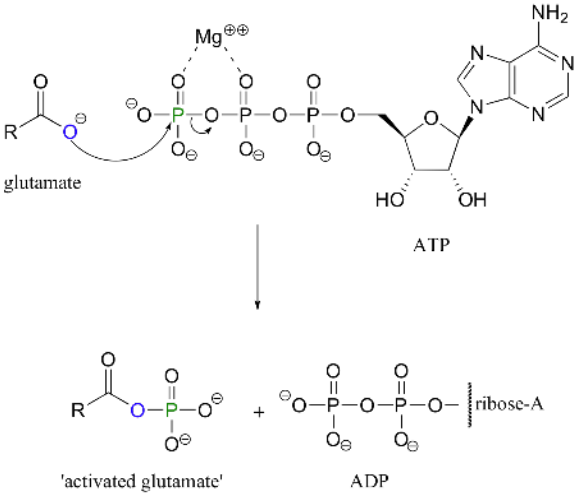
20.12: Biological Acylation Reactions

Glutamine synthetase

The carboxylate functional group is a very unreactive substrate for an enzyme-catalyzed acyl substitution reactions. How, then, does a living system accomplish an 'uphill' reaction such as the one shown below, where glutamate (a carboxylate) is converted to glutamine (an amide)?

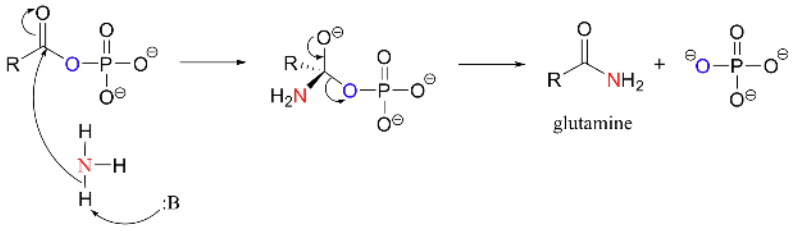


It turns out that this conversion is not carried out directly. Rather, the first conversion is from a carboxylate (the *least* reactive acyl transfer substrate) to an acyl phosphate (the *most* reactive acyl transfer substrate). This transformation requires a reaction that we are familiar with from chapter 10: phosphorylation of a carboxylate oxygen with ATP as the phosphate donor.

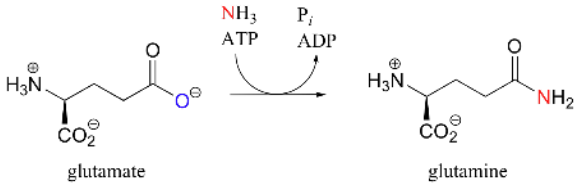


Note that this is just one of the many ways that ATP is used as a energy storage unit: in order to make a high energy acyl phosphate molecule from a low energy carboxylate, the cell must 'spend' the energy of one ATP molecule.

The acyl phosphate version of glutamate is now ready to be converted directly to an amide (glutamine) *via* a nucleophilic acyl substitution reaction, as an ammonia molecule attacks the carbonyl and the phosphate is expelled.

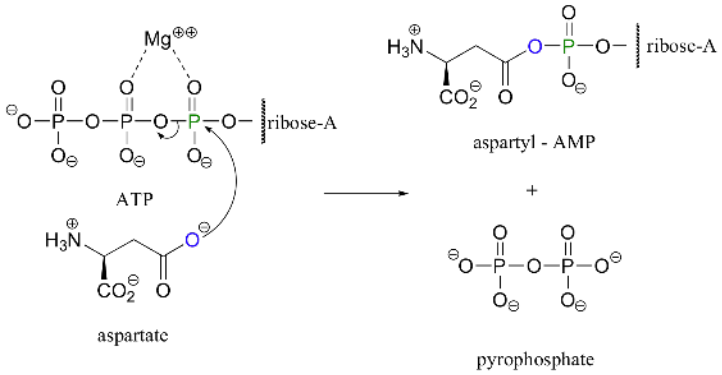


Overall, this reaction can be written as:



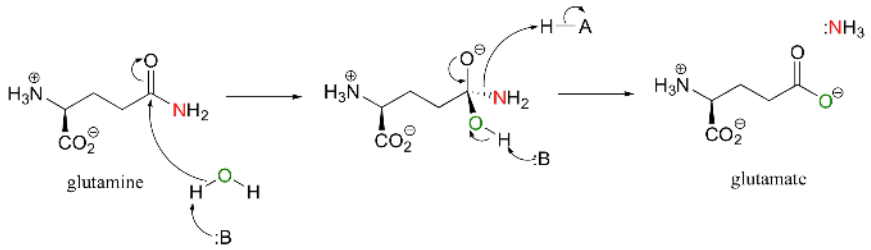
Asparagine synthetase

Another common form of activated carboxylate group is an acyl adenosine phosphate. Consider another amino acid reaction, the conversion of aspartate to asparagine. In the first step, the carboxylate group of aspartate must be activated:

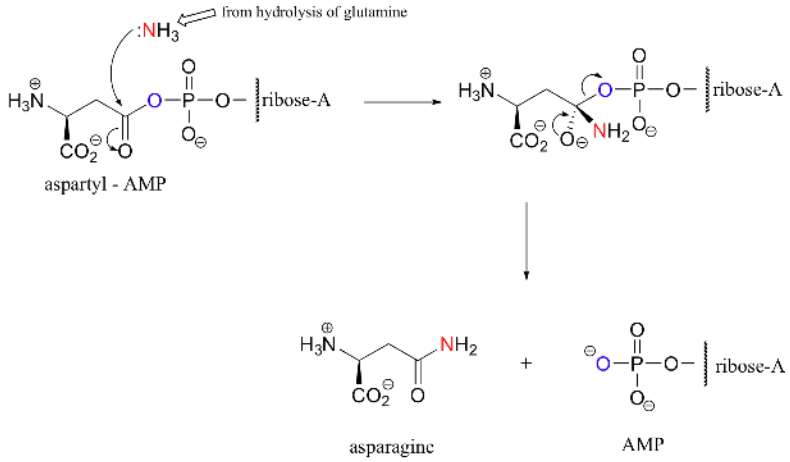


Once again, ATP provides the energy for driving the uphill reaction. This time, however, the activated carboxylate takes the form of an acyl adenosine (mono)phosphate. All that has happened is that the carboxylate oxygen has attacked the a-phosphate of ATP rather than the g-phosphate.

The reactive acyl-AMP version of aspartate is now ready to be converted to an amide (asparagine) via nucleophilic attack by ammonia. In the case of glutamine synthase, the source of ammonia was free ammonium ion in solution. In the case of asparagine synthase, the NH_3 is derived from the hydrolysis of glutamine (this is simply another acyl substitution reaction):

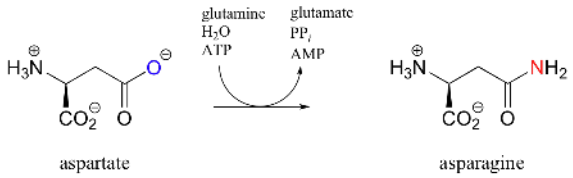


The hydrolysis reaction is happening in the same enzyme active site – as the NH_3 is expelled in the hydrolysis of glutamine, it immediately turns around and acts as the nucleophile in the conversion of aspartyl-AMP to asparagine:



Keep in mind that the same enzyme is also binding ATP and using it to activate aspartate – this is a busy construction zone!

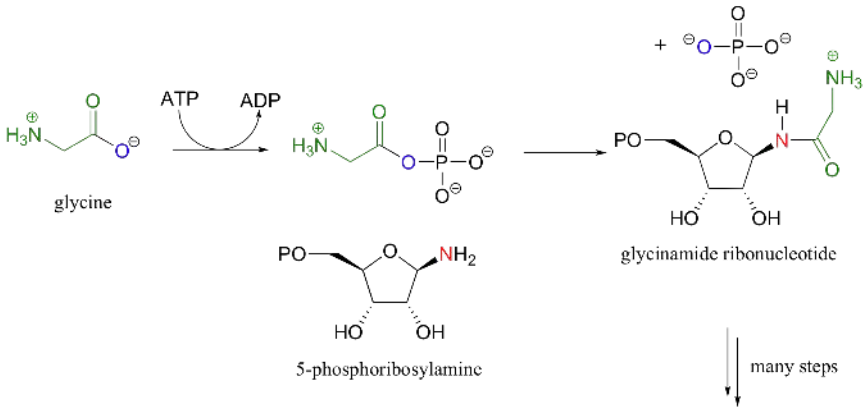
Overall, this reaction can be written in condensed form as:

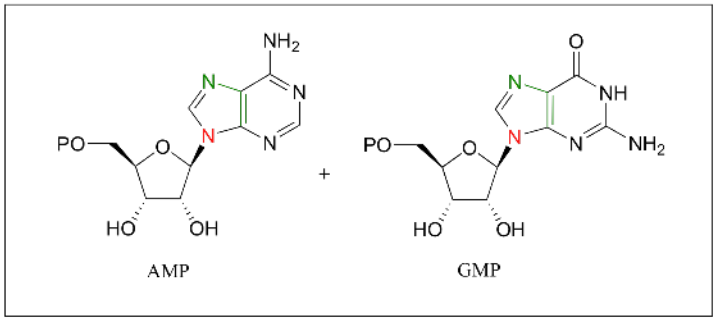


The use of glutamine as a 'carrier' for ammonia is a fairly common strategy in metabolic pathways. This strategy makes sense, as it allows cells to maintain a constant source of NH_3 for reactions that require it, without the need for high solution concentrations of free ammonia.

Glycinamide ribonucleotide synthetase

One of the early steps in the construction of purine bases (the adenine and guanine bases in DNA and RNA) involves an acyl substitution reaction with an acyl phosphate intermediate. In this case, the attacking nucleophile is not ammonia but a primary amine. The strategy, however, is similar to that of glutamine synthase. The carboxylate group on glycine is converted to an acyl phosphate, at the cost of one ATP molecule. The acyl group is then transferred to 5-phosphoribosylamine, resulting in an amide product.





Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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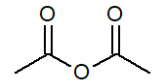
20.13: Additional Exercises

General Review

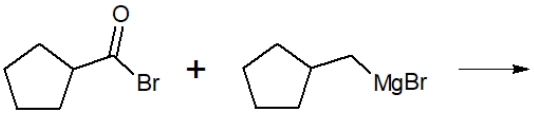
22-1 Suggest a carboxylic acid and an acid derivative that could be reacted together to form the following molecule.



acetic anhydride

22-2 For the following reaction, predict the product if:

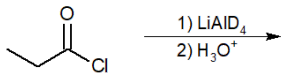
- only one equivalent of the Grignard reagent was used (and the product could be isolated)
- if two equivalents were used (followed by an acid workup)



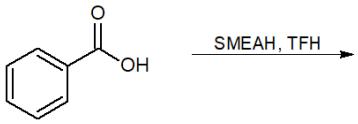
(Grignard Reagent)

22-3 Provide the final products of the following reactions.

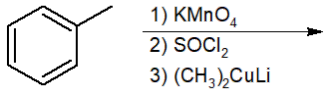
a)



b)



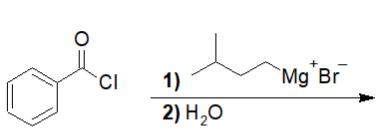
22-4 Predict the final product of the following reaction.



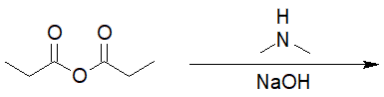
Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

22-5 Predict the interconverted acid derivatives of the following reactions.

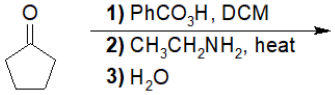
a)



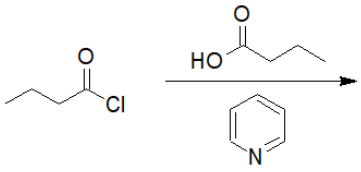
b)



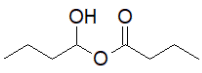
22-6 Predict the structure of the product and give its IUPAC nomenclature.



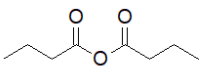
22-7 Choose the correct answer for the product of the following reaction.



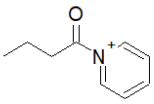
a)



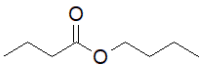
b)



c)

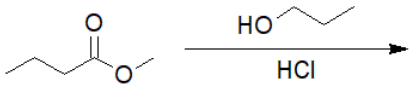


d)



Transesterification

22-8 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) ethyl butanoate

b) propan-2-yl butanoate

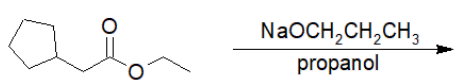
c) dipropyl carbonate

d) propyl butanoate

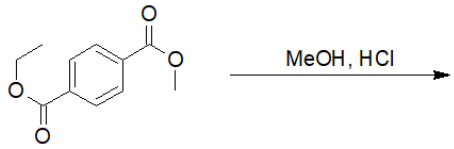
22-9 Explain why transesterification can be done under acidic or basic conditions.

22-10 Give the products of the following transesterification reactions.

a)

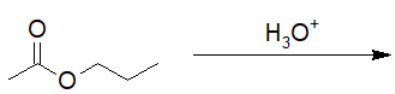


b)

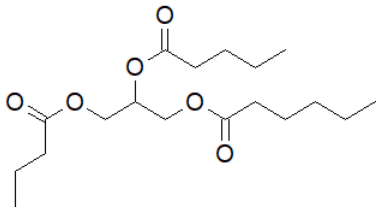


Hydrolysis of Carboxylic Acid Derivatives

22-11 Provide the correct structure of the product of the following hydrolysis reaction.

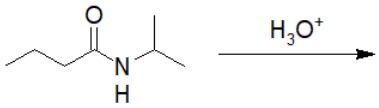


22-12 Provide the structure of all the products resulting from the hydrolysis of the following triglyceride.

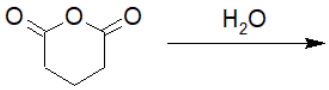


22-13 Provide the structures and IUPAC nomenclature of the products.

a)

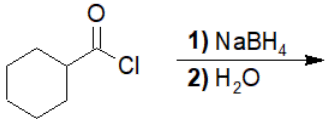


b)

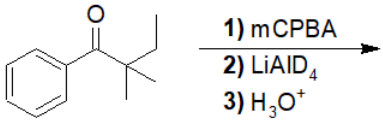


Reduction of Acid Derivatives

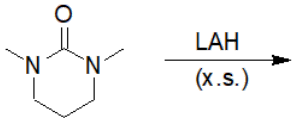
22-14 Give the structure of the product of the following reaction.



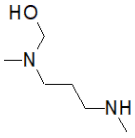
22-15 Provide the structure of all the products (including leaving groups) formed in the following reaction.



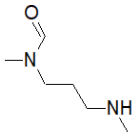
22-16 Choose the correct answer that gives the products of a fully reduced 1,3-dimethyl-1,3-diazinan-2-one.



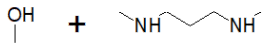
a)



b)

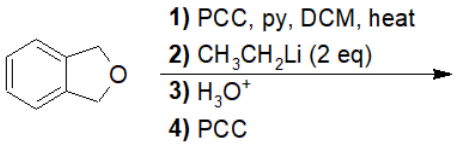


c)

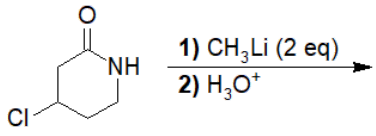


Reactions of Acid Derivatives with Organometallic Reagents

22-17 Predict the product of the following reaction.



22-18 Choose the correct IUPAC nomenclature of the product of the following reaction.



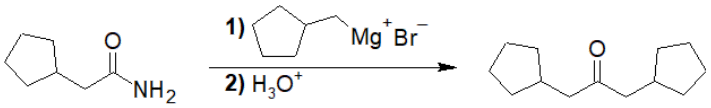
a) 6-amino-5-chlorohexan-2-one

b) 6-amino-5-chloro-2-methylhexan-2-ol

c) 6-amino-4-chloro-2-methylhexan-2-ol

d) 4-chloro-2-methylpiperidin-2-ol

22-19 Decide whether or not the following reaction is the best way to obtain the final product. If not, suggest a better route of synthesis.



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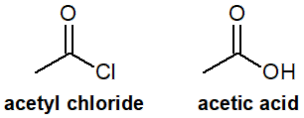
20.14: Solutions to Additional Exercises

General Review

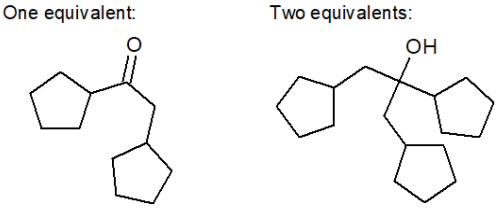
22-1

Possible set of reactants:



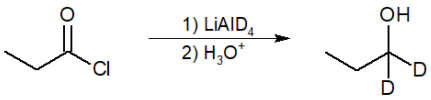
acetyl chloride **acetic acid**

22-2



22-3

a)



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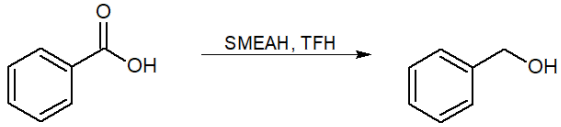
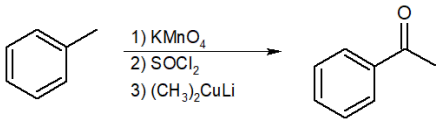


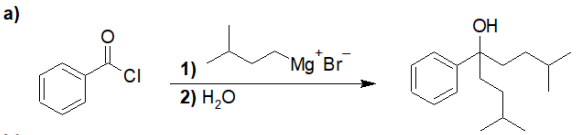
22-4



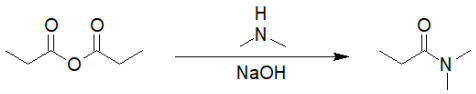
Interconversion of Acid Derivatives by Nucleophilic Acyl Substitution

22-5:

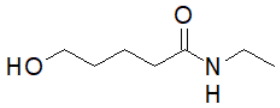
a)



b)



22-6:



***N*-ethyl-5-hydroxypentanamide**

22-7:

Answer: B

Transesterification

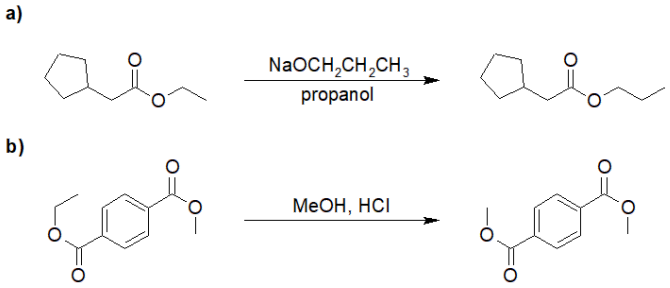
22-8:

Answer: D

22-9:

Under acidic conditions, the carbonyl oxygen atom is protonated, making it a better electrophile for the reaction to occur. Under basic conditions, the alcohol we are trying to add is deprotonated, making it a better nucleophile.

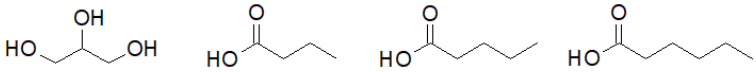
22-10:



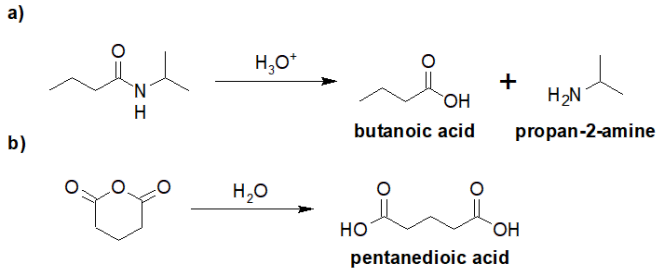
Hydrolysis of Carboxylic Acid Derivatives

22-11:

22-12:



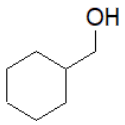
22-13:



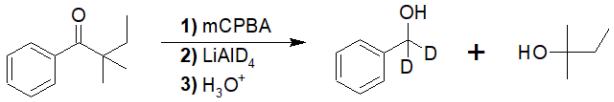
Reduction of Acid Derivatives

22-14:

https://chem.libretexts.org/@go/page/183134



22-15:

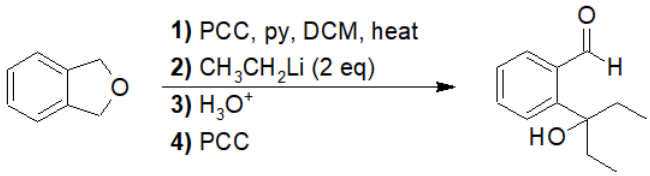


22-16:

Answer: C

Reactions of Acid Derivatives with Organometallic Reagents

22-17:

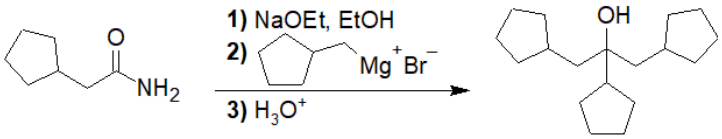


22-18:

Answer: C

22-19:

A possibly better route of synthesis:



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CHAPTER OVERVIEW

21: Alpha Substitutions and Condensations of Carbonyl Compounds
learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- predict the relative acidity of the a-hydrogens on various carbonyl compounds (section 23.1)
- explain or predict the equilibrium of enol-keto tautomers (section 23.2)
- predict the products and specify the reagents for the following reactions
    - Halogenation of the a-carbon of aldehydes and ketones (section 23.3 and 23.4)
    - Halogenation of the a-carbon of carboxylic acids (Hell-Vollhard-Zelinski) (section 23.3 and 23.5)
    - Alkylation of the a-carbon of carbonyl compounds via the LDA pathway (section 23.3 and 23.6)
    - Alkylation of the a-carbon of aldehydes and ketones via the enamine intermediate (section 23.3 and 3.7)
    - Aldol addition and condensation reactions – 2 aldehydes, 2 ketones, 1 aldehyde with 1 ketone (section 23.3 and 23.8)
    - Claisen condensation reactions – 2 esters or 1 ester with 1 ketone (section 23.3 and 23.9)
    - Diekmann condensation reactions (intramolecular Claisen) - (section 23.9)
    - Conjugate Addition a.k.a. Michael reaction (section 23.3 and 23.10)
    - Robinson annulation (section 23.10)
    - Decarboxylation of 3-oxocarboxylic acids (section 23.3 and 23.12)
        - Malonic ester synthesis of carboxylic acids
        - Acetoacetic ester synthesis of methyl ketones

Designing synthesis using all of the reactions through this chapter with an emphasis on increasing the size of the carbon backbone by forming new carbon-carbon bonds

Topic hierarchy

21.1: Relative Acidity of alpha-Hydrogens
21.2: Enols, Enolate Ions and Tautomerization
21.3: Reaction Overview
21.4: Alpha Halogenation of Carbonyls
21.5: Bromination of Acids: The HVZ Reaction
21.6: Alkylation of the alpha-Carbon via the LDA pathway
21.7: Alkylation of the Alpha-Carbon via the Enamine Pathway
21.8: The Aldol Reaction and Condensation of Ketones and Aldehydes
21.9: The Claisen Condensation Reactions of Esters
21.10: Conjugate Additions: The Michael Reaction
21.11: Decarboxylation Reactions
21.12: Additional Exercises
21.13: Solutions to Additional Exercises

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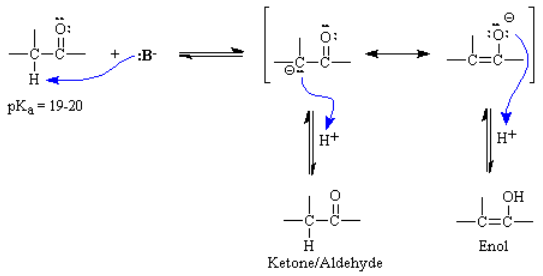
21.1: Relative Acidity of alpha-Hydrogens

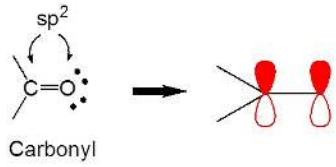
Acidity of Alpha Hydrogens

Alkyl hydrogen atoms bonded to a carbon atom in a a (alpha) position relative to a carbonyl group display unusual acidity. While the pK_a values for alkyl C-H bonds is typically on the order of 40-50, pK_a values for these alpha hydrogens is more on the order of 19-20. This can most easily be explained by resonance stabilization of the product carbanion, as illustrated in the diagram below.

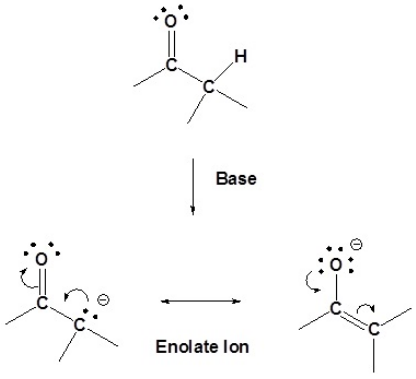


In the presence of a proton source, the product can either revert back into the starting ketone or aldehyde or can form a new product, the enol. The equilibrium reaction between the ketone or aldehyde and the enol form is commonly referred to as "keto-enol tautomerism". The ketone or aldehyde is generally strongly favored in this reaction.

Because carbonyl groups are sp^2 hybridized the carbon and oxygen both have unhybridized p orbitals which can overlap to form the C=O π bond.



The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).

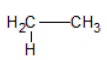
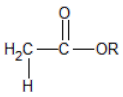
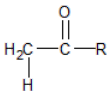
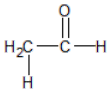
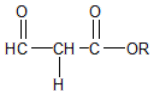
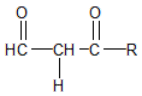
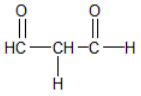


Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

Relative Acidity of Alpha Hydrogens

The acidity of alpha hydrogens varies by carbonyl functional group as shown in the table below. Evaluating the stability of the conjugate bases can explain the differences in the relative acidity of the alpha hydrogens.

The ionizable proton for each compound is bonded to an sp^3 hydbridized carbon.

Compound	pKa
	50
	25
	20
	17
	11
	9
	6

Exercise

1. Draw the bond line structure for each compound in the table above including all relevant resonance forms to explain the relative acidity.

Answer

1.

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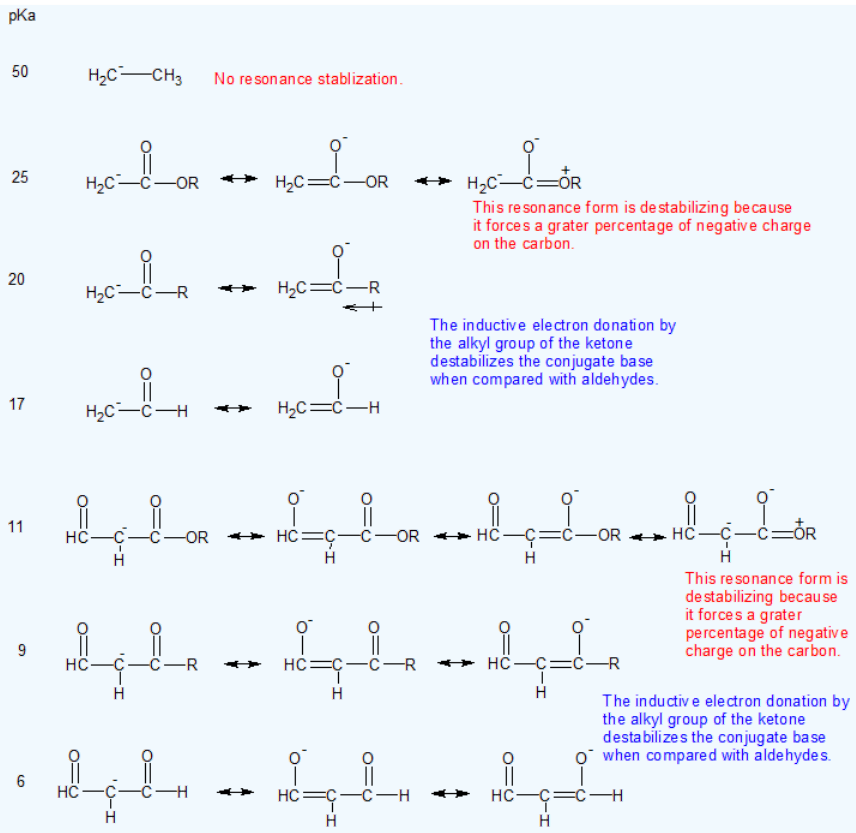

Contributors and Attributions

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- Clarke Earley (Department of Chemistry, Kent State University Stark Campus)

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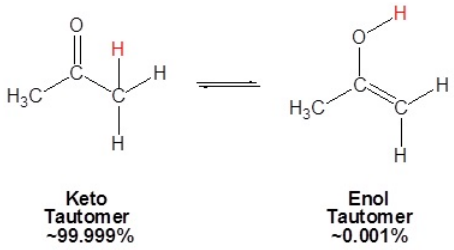
21.2: Enols, Enolate Ions and Tautomerization

Introduction

Because of the acidity of the alpha-hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom 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.

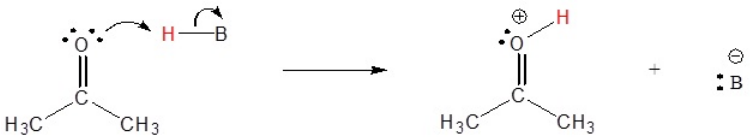


Mechanism for Enol and Enolate Formation

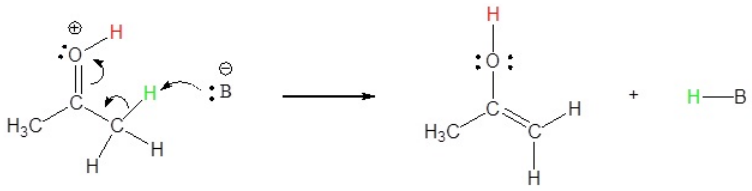
Under acidic conditions, the enol tautomer forms. Under basic conditions, the enolate tautomer forms. Both the enol and enolate are nucleophiles that can undergo subsequent reactions. The mechanism for both acidic and basic reaction conditions are shown below.

Acid conditions

1) Protonation of the Carbonyl

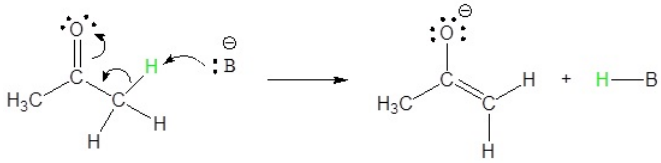


2) Enol formation



Basic conditions

1) Enolate formation



2) Protonation

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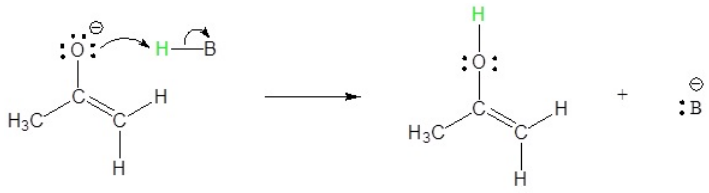
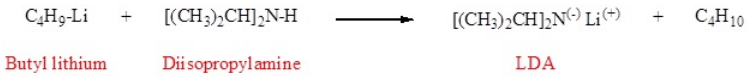
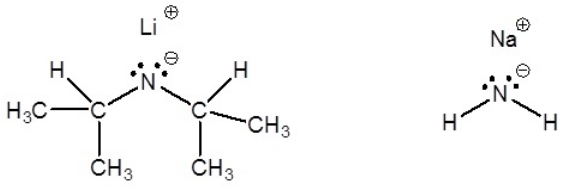


For reactions of enolate anions to be useful, these intermediates must be generated in high concentration in the absence of other strong nucleophiles and bases. The aqueous base conditions used for the aldol condensation are not suitable because the enolate anions of simple carbonyl compounds are formed in very low concentration, and hydroxide or alkoxide bases induce competing S_N2 and E2 reactions of alkyl halides. It is necessary, therefore, to achieve complete conversion of aldehyde or ketone reactants to their enolate conjugate bases by treatment with a very strong base ($pK_a > 25$) in a non-hydroxylic solvent before any alkyl halides are added to the reaction system. Some bases that have been used for enolate anion formation are: NaH (sodium hydride, $pK_a >$ 45), $NaNH_2$ (sodium amide, pK_a = 34), and $LiN[CH(CH_3)_2]_2$ (lithium diisopropylamide, LDA, pK_a 36). Ether solvents like tetrahydrofuran (THF) are commonly used for enolate anion formation. With the exception of sodium hydride and sodium amide, most of these bases are soluble in THF. 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 carbonyl groups. Nevertheless, these very strong bases are useful in making soluble amide bases. In the preparation of lithium diisopropylamide (LDA), for example, the only other product is the gaseous alkane butane.

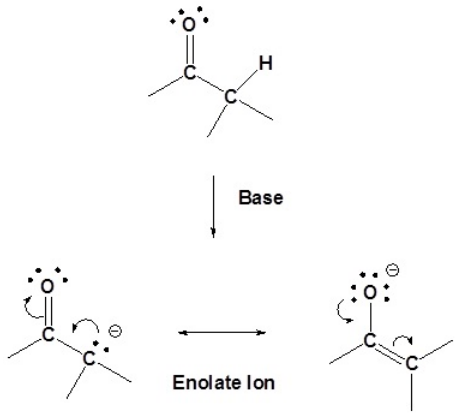




LDA **Sodium Amide**

Because of its solubility in THF, LDA is a widely used base for enolate anion formation. In this application, one equivalent of diisopropylamine is produced along with the lithium enolate, but this normally does not interfere with the enolate reactions and is easily removed from the products by washing with aqueous acid. Although the reaction of carbonyl compounds with sodium hydride is heterogeneous and slow, sodium enolates are formed with the loss of hydrogen, and no other organic compounds are produced.

The presence of these overlapping p orbitals gives α hydrogens (Hydrogens on carbons adjacent to carbonyls) special properties. In particular, α hydrogens are weakly acidic because the conjugate base, called an enolate, is stabilized though conjugation with the π orbitals of the carbonyl. The effect of the carbonyl is seen when comparing the pK_a for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25) to the pK_a of an alkane (~50).

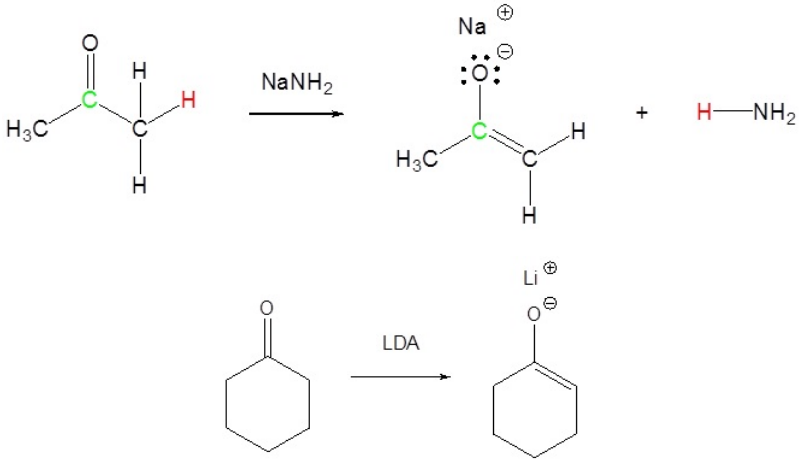


Of the two resonance structures of the enolate ion the one which places the negative charge on the oxygen is the most stable. This is because the negative change will be better stabilized by the greater electronegativity of the oxygen.

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

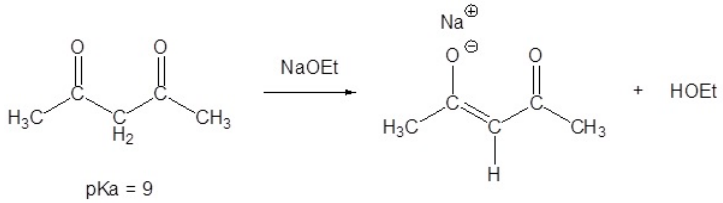
* Note methylene groups bridging between two electron withdrawing groups are more acidic than alpha protons next to only one carbonyl group.

Examples



If the formed enolate is stabilized by more than one carbonyl it is possible to use a weaker base such as sodium ethoxide.

$NaOCH_2CH_3 = Na^+ {}^-OCH_2CH_3 = NaOEt$



Because of the acidity of α hydrogens, carbonyls undergo keto-enol tautomerism. Tautomers are rapidly interconverted constitutional isomers, usually distinguished by a different bonding location for a labile hydrogen atom 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.

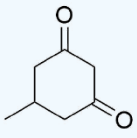
Exercises

2. Draw the enol forms of the following molecules

a. 4-methylcyclohexanone
b. Ethyl thioactetate
c. Methyl acetate
d. Butanal
e. Propionic Acid
f. 1-phenyl-2-butanone

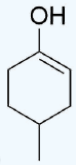
3. How many acid protons do each of the molecules from the previous question have? Label them.

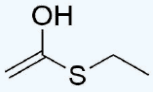
4. Draw all of the monoenol forms for the following molecule. Which ones are most stable? Why?

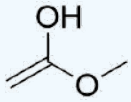


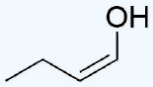
Answers

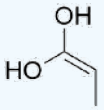
2.

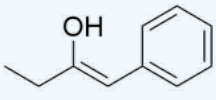
(a) 

(b) 

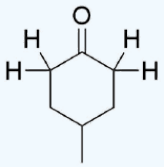
(c) 

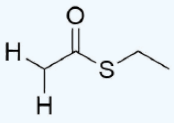
(d) 

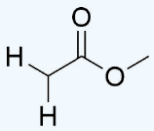
(e) 

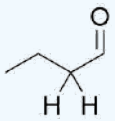
(f) 

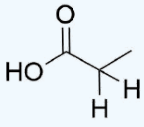
3.

(a) 

(b) 

(c) 

(d) 

(e) 

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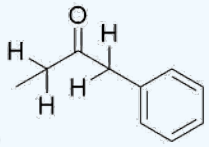
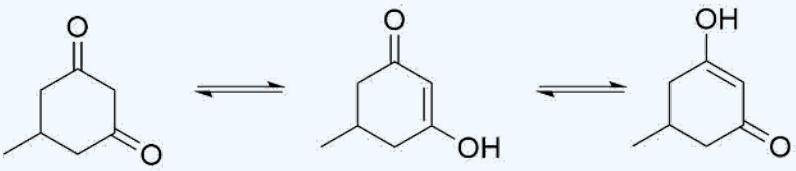
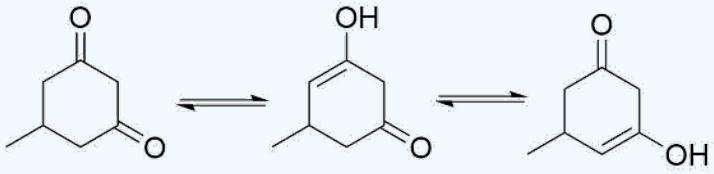


(f)

4.



The ability to resonate stabilizes this enol form.



This enol has no resonance forms and is therefore less stable.

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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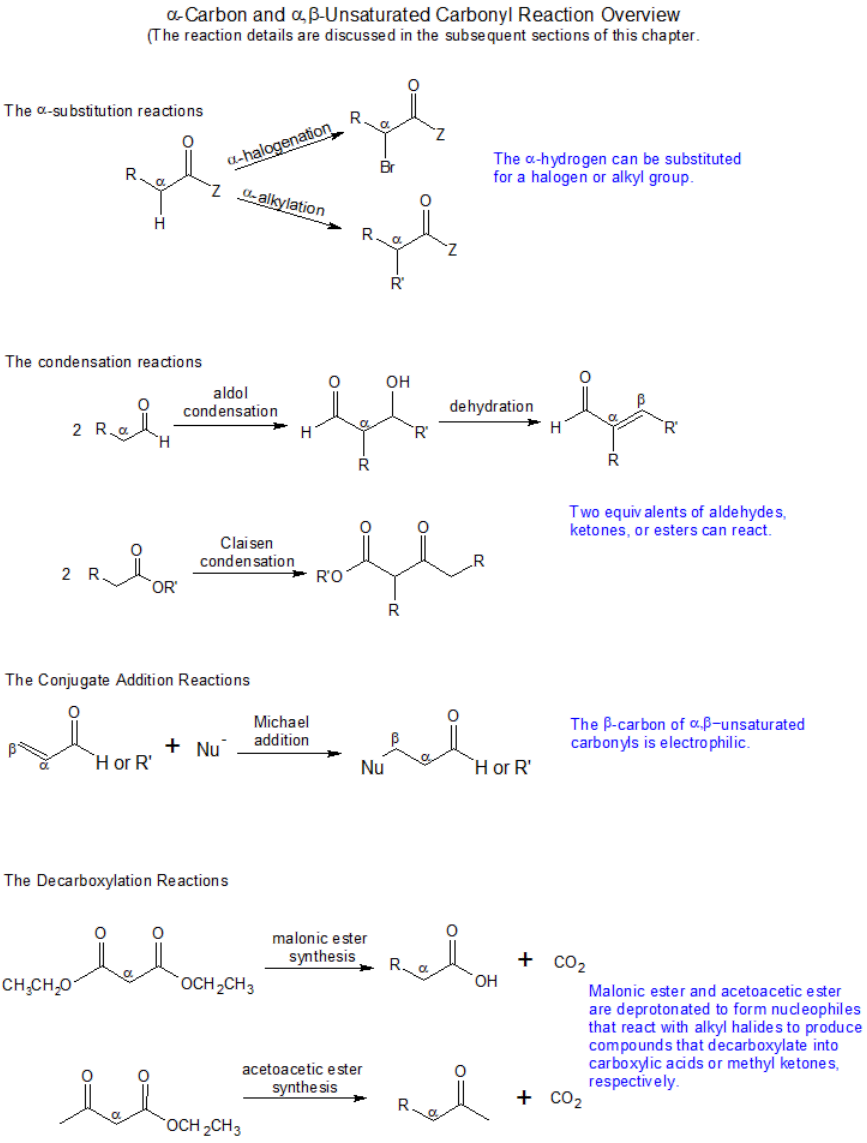
21.3: Reaction Overview

Overview

The reactivity of the alpha-carbon can be grouped into three main categories: alpha-substitution, condensation, and decarboxylation. Alpha,beta-unsaturated carbonyls can undergo conjugate addition reactions that are called Michael Additions when the nucleophile is an alpha-carbon. Because the reactants, reagents and products can contain multiple functional groups, it is helpful to initially focus on the overall conversions between functional groups BEFORE digging into the details of each reaction pathway. It is also useful to label the alpha and beta carbons to help follow the reactivity. An overview of the reactions that will be studied in this chapter are shown below.



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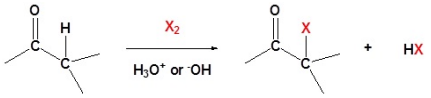
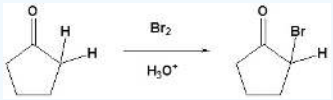
21.4: Alpha Halogenation of Carbonyls

Ketones with alpha hydrogens can undergo a substitution reaction with halogens. This reaction occurs because of the tendency of carbonyl compounds to form enolates in basic condition and enols in acidic condition. In these cases even weak bases, such as the hydroxide anion, is sufficient enough to cause the reaction to occur because it is not necessary for a complete conversion to the enolate. For this reaction Cl_2, Br_2 or I_2 can be used as the halogens.

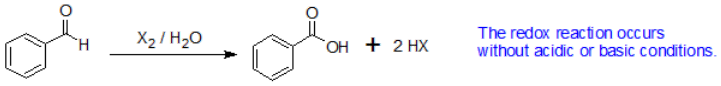
General reaction



Example 1



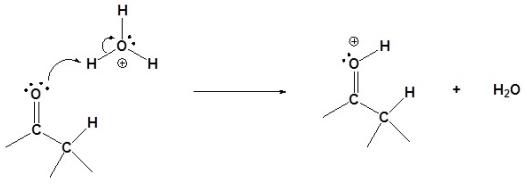
Aldehydes are oxidized by the halogens so this reaction pathway is not synthetically useful. For example, when benzaldehyde is added to either set of reagents described above for ketones, the majore product is benzoic acid.



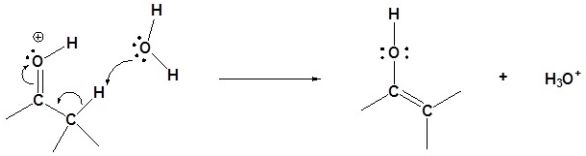
Acid Catalyzed Mechanism

Under acidic conditions the reaction occurs thought the formation of an enol which then reacts with the halogen.

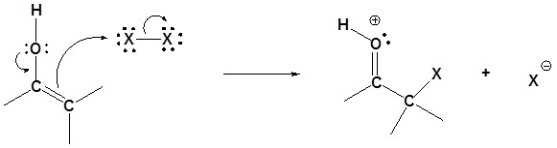
1) Protonation of the carbonyl



2) Enol formation



3) S_N2 reaction



4) Deprotonation

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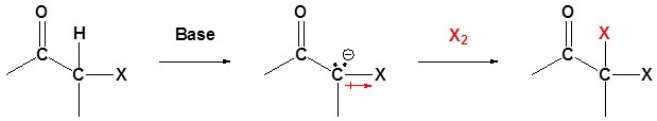
Kinetic studies provide some evidence for the mechanism shown above. The rate law for the alpha-halogenation of a ketone can be given by:

$$\text{rate} = [\text{ketone}][H^+]$$

The implication is that the rate determining step is dependent on the concentrations of the ketone and acid catalyst and therefore associated with the enol formation part of the mechanism. The halogen does not even appear in the rate law. Indeed, the overall rate is completely independent of the concentration of the halogen and suggests the halogenation step occurs rapidly.

Base Promoted Mechanism

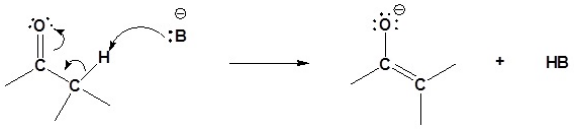
Under basic conditions the enolate forms and then reacts with the halogen.



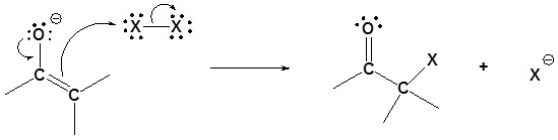
Note! This is base *promoted* and not base *catalyzed* because an entire equivalent of base is required.

It is difficult to stop the base promoted reaction after a single substitution, so acidic conditons are used when a monohalo product is required.

1) Enolate formation

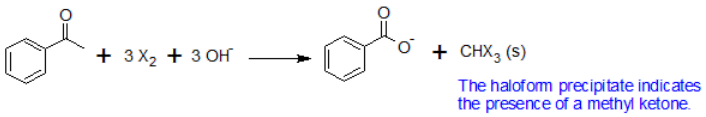


2) S_N2 reaction



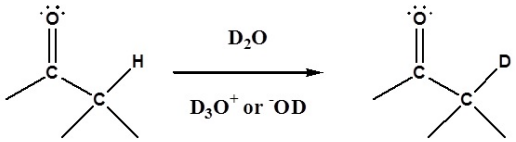
The Haloform Qualitative Reaction to Identify Methyl Ketones

The overreaction during base promotion of alpha halogenation is used as a qualitative test called the haloform reaction to identify methyl ketones. Under basic conditions, subsequent halogenation reactions occur because the halogenated product is more reactive than the starting material due to the electron withdrawing effect of the halogen. The halogen inductively stabilizes the conjugate base and increases the relative acidity of the remaining alpha-carbons. Halogenations occur at the alpha-carbon until the haloform becomes a leaving group and is observed as a precipitate as shown in the example below.

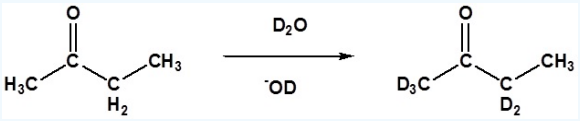


Deuterium Exchange

Due to the acidic nature of α hydrogens they can be exchanged with deuterium by reaction with D_2O (heavy water). The process is accelerated by the addition of an acid or base; an excess of D_2O is required. The end result is the complete exchange of all α hydrogens with deuteriums.

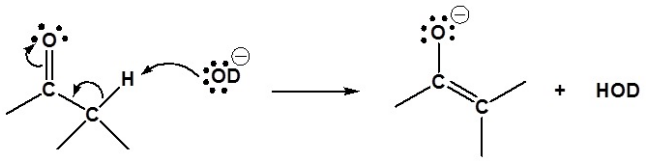


Example 2

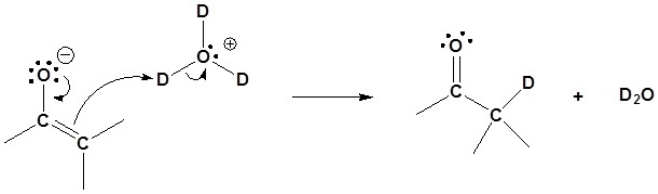


Mechanism in basic conditions

1) Enolate Formation

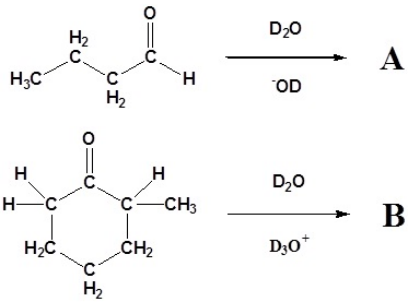


2) Deuteration

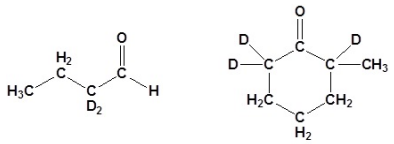


Example Question

Draw the product for the following reactions.



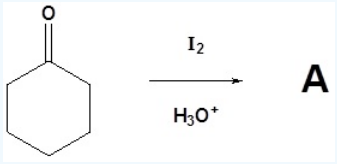
Solutions to example question



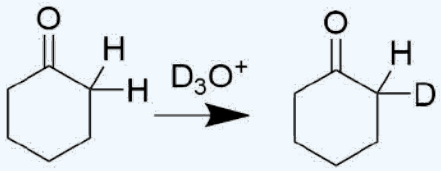
A B

Exercises

5. Draw the products of the following reactions



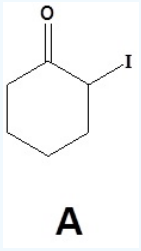
6. Draw out the mechanism for the following reaction.



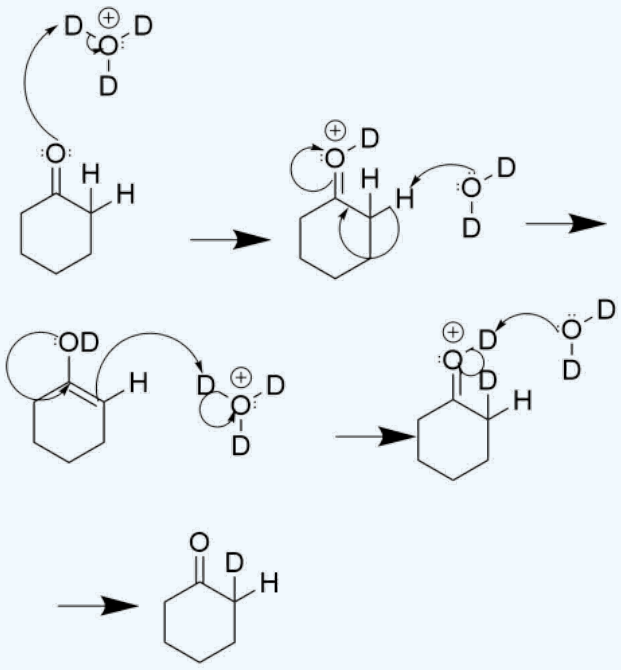
7. How might you form 2-hepten-4-one from 4-heptanone?

Answer

5.



6.



7. 1) Br_2, H_3O^+; 2) Pyridine, Heat

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Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)

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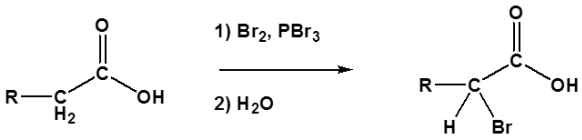
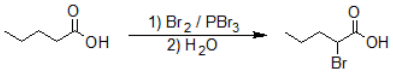
21.5: Bromination of Acids: The HVZ Reaction

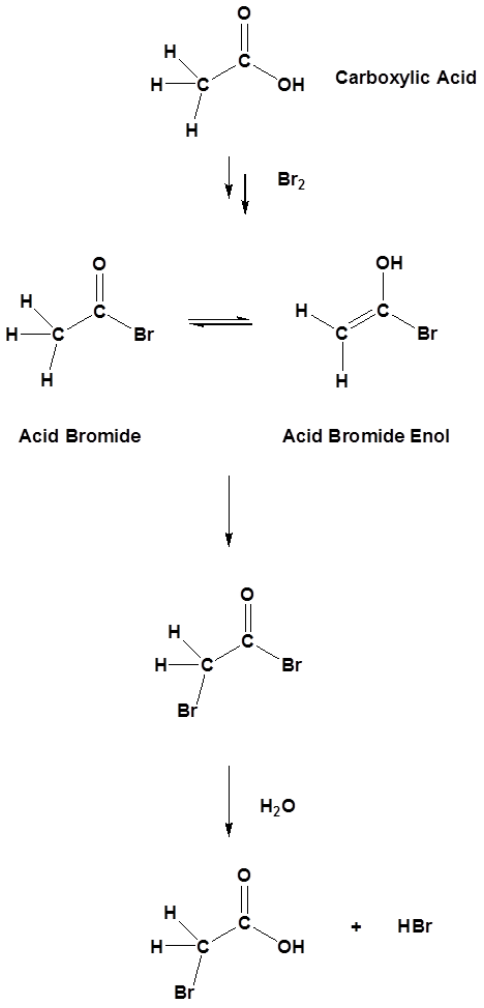
Although the alpha bromination of some carbonyl compounds, such as aldehydes and ketones, can be accomplished with Br_2 under acidic conditions, the reaction will generally not occur with acids, esters, and amides. This is because only aldehydes and ketones enolize to a sufficient extent to allow the reaction to occur. However, carboxylic acids, can be brominated in the alpha position with a mixture of Br_2 and PBr_3 in a reaction called the Hell-Volhard-Zelinskii (HVZ) reaction.



For example, pentanoic acid can be converted to 2-bromopentanoic acid as shown in the example below.

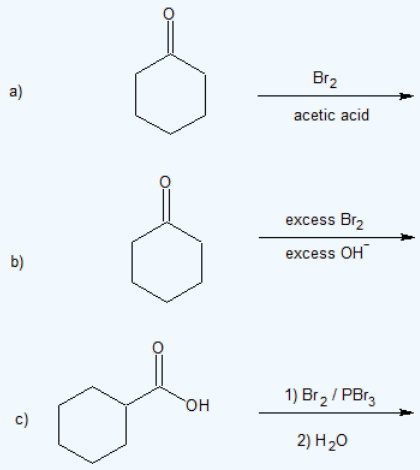


The mechanism of this reaction involves an acid bromide enol instead of the expected carboxylic acid enol. The reaction starts with the reaction of the carboxylic acid with PBr_3 to form the acid bromide and HBr. The HBr then catalyzes the formation of the acid bromide enol which subsequently reacts with Br_2 to give alpha bromination. Lastly, the acid bromide reacts with water to reform the carboxylic acid.



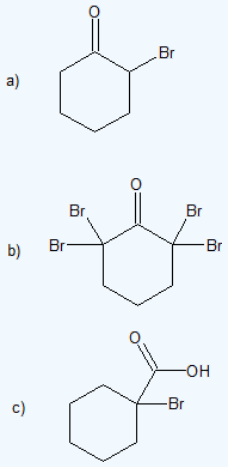
Exercise

8. Draw the bond-line structure for the product of each reaction below.



Answer

8.



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- Prof. Steven Farmer (Sonoma State University)

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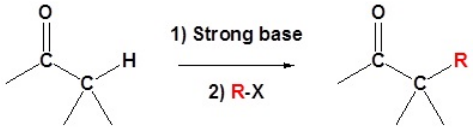
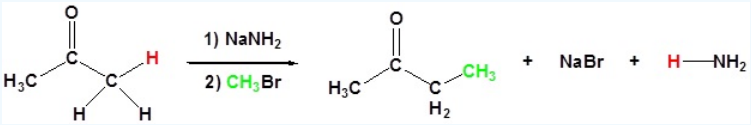
21.6: Alkylation of the alpha-Carbon via the LDA pathway

Alpha Alkylation

A strong base, such as lithium diisopropyl amide (LDA), sodium hydride, or sodium amide, creates the nucleophilic enolate ion which reacts with an alkyl halide suitable for the S_N2 reactivity to form an alpha-alkylated product.



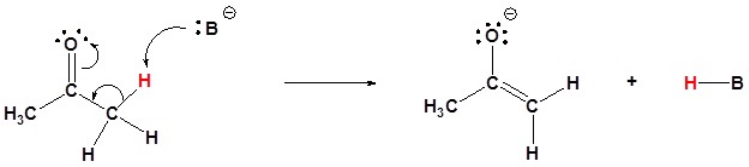
Example 1: Alpha Alkylation



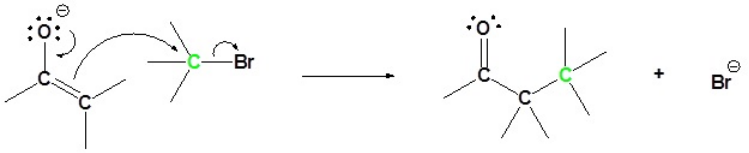
Mechanism

The mechanism begins with enolate formation. The resulting enolate is the nucleophile in an S_N2 reaction with a suitable alkyl halide.

1) Enolate formation

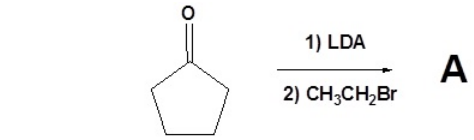


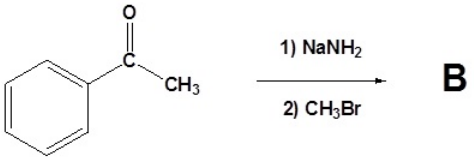
2) S_N2 reaction



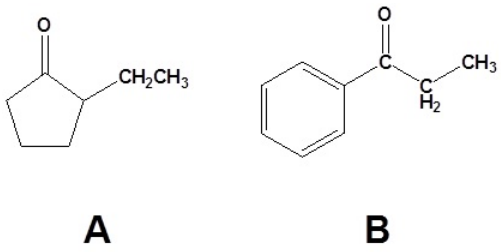
Example Question

Write the structure of the product for the following reactions.



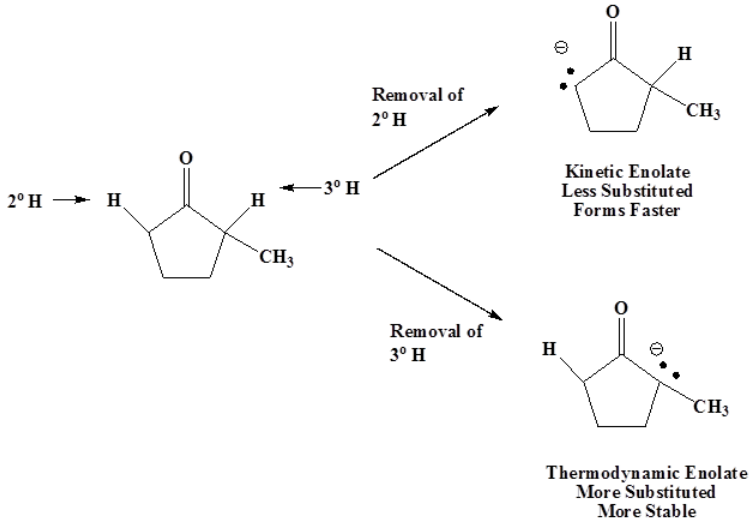


Solution to Example Question



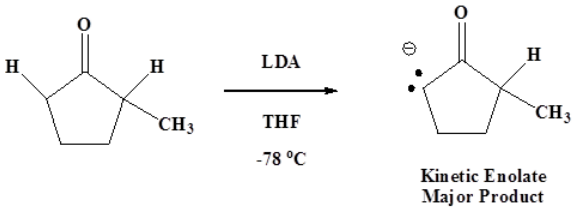
Enolate of Unsymmetrical Carbonyl Compounds

Now let's consider what happens when an unsymmetrical carbonyl is treated with a base. In the case displayed below there are two possible enolates which can form. The removal of the 2o hydrogen forms the kinetic enolate and is formed faster because it is less substituted and thereby less sterically hindered. The removal of the 3o hydrogen forms the thermodynamic enolate which is more stable because it is more substituted.



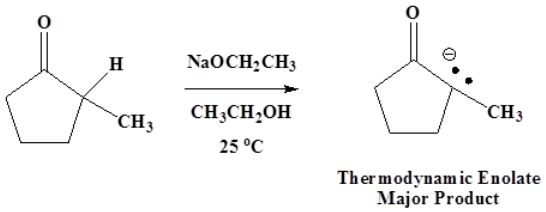
Kinetic Enolates

Kinetic enolates are formed when a strong bulky base like LDA is used. The bulky base finds the 2o hydrogen less sterically hindered and preferable removes it. Low temperature are typically used when forming the kinetic enolate to prevent equilibration to the more stable thermodynamic enolate. Typically a temperature of -78 oC is used.



Thermodynamic Enolates

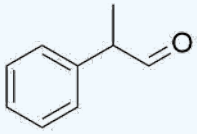
The thermodynamic enolate is favored by conditions which allow for equilibration. The thermodynamic enolate is usually formed by using a strong base at room temperature. At equilibrium the lower energy of the thermodynamic enolate is preferred, so that the more stable, more stubstituted enolate is formed.

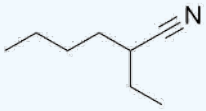


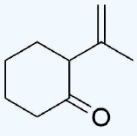
Thermodynamic Enolate
Major Product

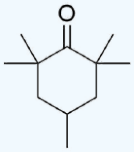
Exercises

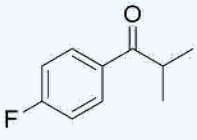
9. How might you prepare the following compounds from an alkylation reaction?

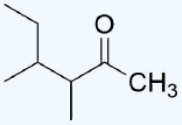
(a) 

(b) 

(c) 

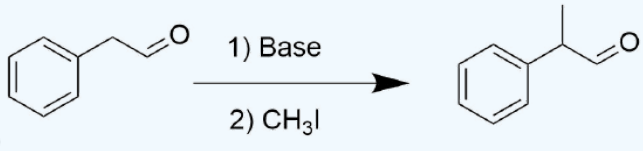
(d) 

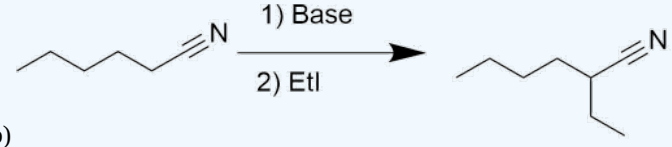
(e) 

(f) 

Answer

9.

(a) 

(b) 

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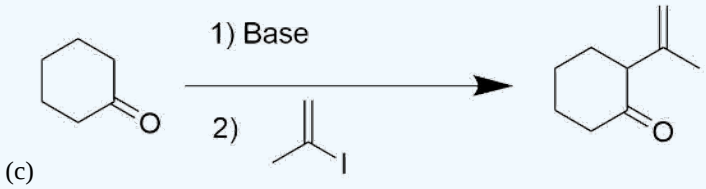

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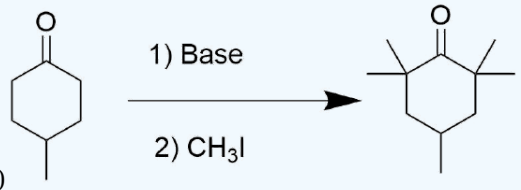

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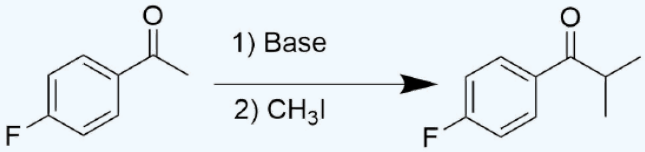
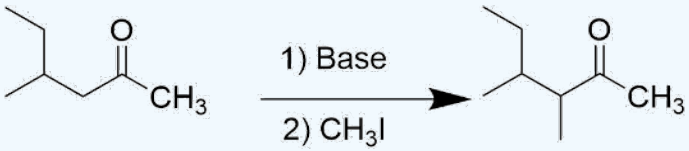


(e)



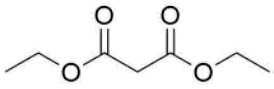
(f)

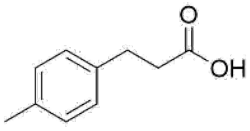
Exercises

Questions

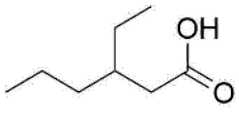
Q22.7.1

Propose a synthesis for each of the following molecules from this malonic ester.





(a)



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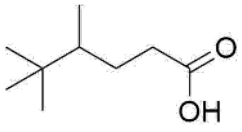


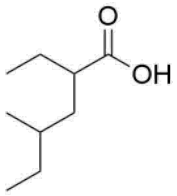
(c)

Q22.7.2

Why can't you prepare tri substituted acetic acids from a malonic ester?

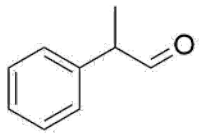
Q22.7.3

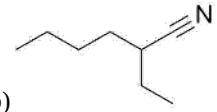
Propose a synthesis for the following molecule via a malonic ester.

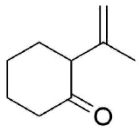


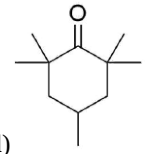
Q22.7.4

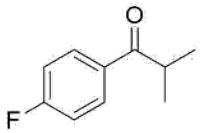
How might you prepare the following compounds from an alkylation reaction?

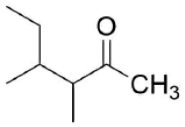
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Solutions

S22.7.1

(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

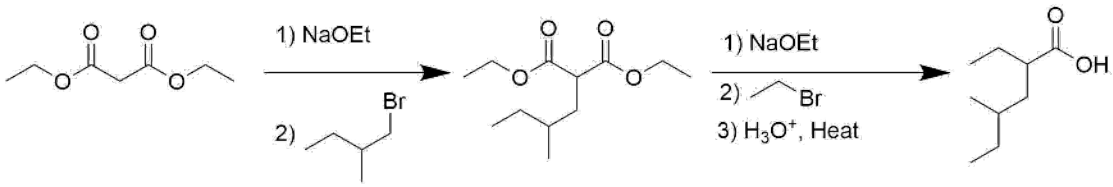
(b) 1) Malonic Ester, NaOEt, 2) 3-bromohexane, 3) Base, 4) Acid, Eat

(c) 1) Malonic Ester, NaOEt, 2) 1-Bromo-2,3,3-trimethylbutane, 3) Base, 4) Acid, Heat

S22.7.2

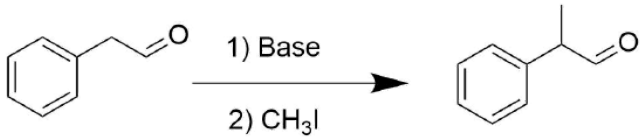
Malonic esters only contain two acid protons.

S22.7.3

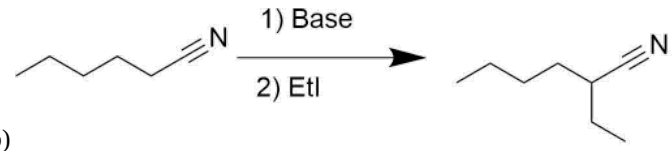


S22.7.4

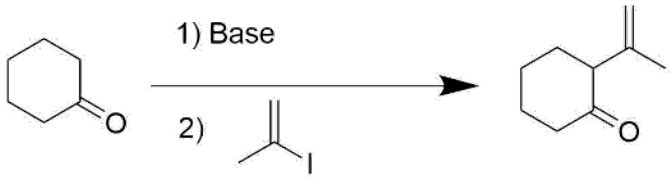
(a)



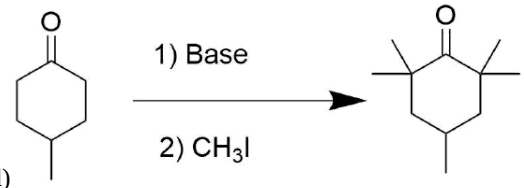
(b)



(c)



(d)



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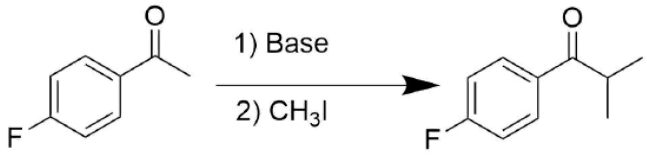

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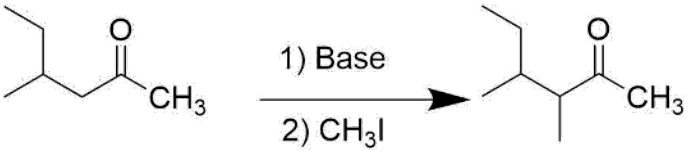

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Prof. Steven Farmer (Sonoma State University)

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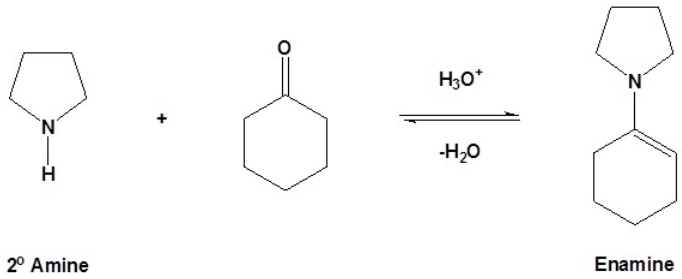
21.7: Alkylation of the Alpha-Carbon via the Enamine Pathway

Overview of the Stork Enamine Reaction

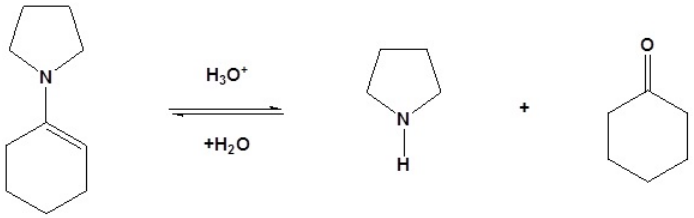
The reaction conditions for the direct alkylation of the alpha carbon with LDA or other very strong base are quite harsh. Many organic compounds cannot withstand the reaction environment at synthetically useful amounts. Therefore, an alternate synthetic pathway was developed by Gilbert Stork of Columbia University. Some of the advantages of using an enamine over an enolate are that enamines are neutral, easier to prepare, and usually prevent the overreaction problems plagued by enolates. As shown in the example below, the aldehyde or ketone can be recovered from the enamine via a hydrolysis reaction.

Example

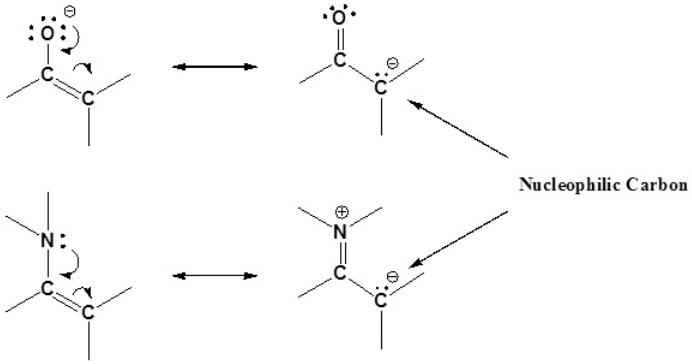


2° Amine Enamine

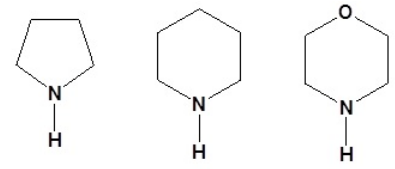
Reversible



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 eletrophile to form an iminium salt, 3) Hydrolysis of the iminium salt to reform the aldehyde or ketone.



Typically we use the following 2° amines for enamine reactions



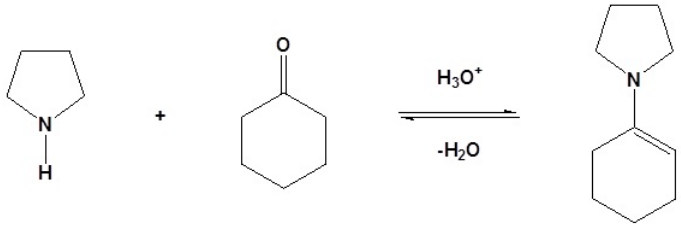
Pyrrolidine Piperidine Morpholine

Alkylation of an Enamine

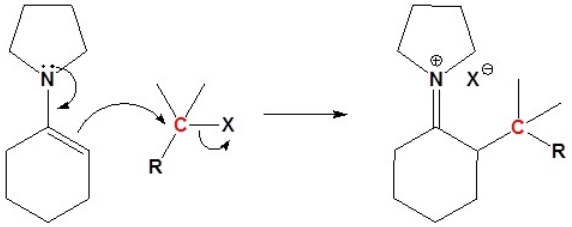
Enamined undergo an S_N2 reaction with reactive alkyl halides to give the iminium salt. The iminium salt can be hydrolyzed back into the carbonyl.

Individual steps

1) Formation of an enamine

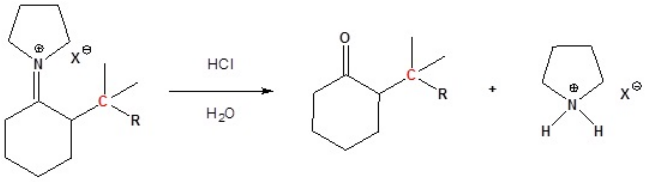


2) S_N2 Alkylation

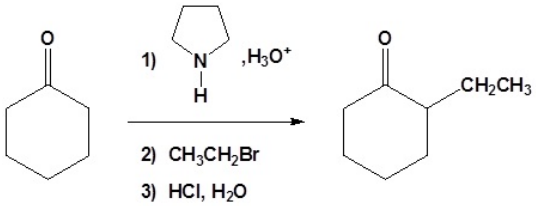


Iminium Salt

3) Reform the carbonyl by hydrolysis



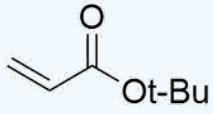
All three steps together:



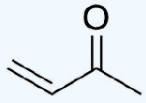
Exercises

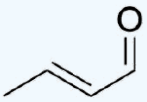
10. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

(a)

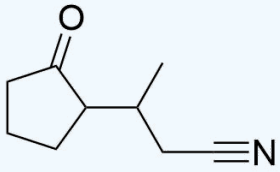


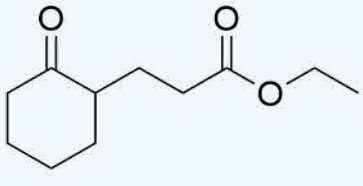
(b)



(c) 

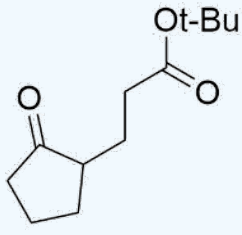
11. Propose a synthesis for the following compounds via an enamine.

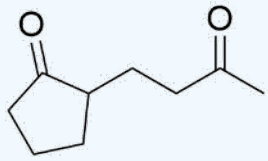
(a) 

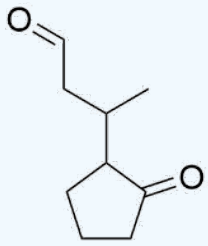
(b) 

Answers

10.

(a) 

(b) 

(c) 

11.

(a) cyclopentanone enamine + 2-cyanopropene

(b) cyclohexanone enamine + ethyl acrylate

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)

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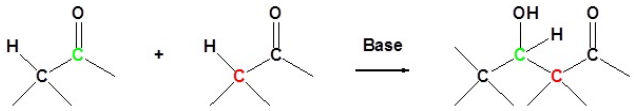
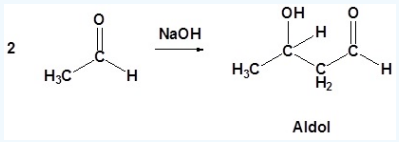
21.8: The Aldol Reaction and Condensation of Ketones and Aldehydes

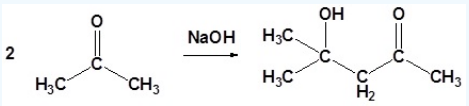
A useful carbon-carbon bond-forming reaction known as the **Aldol Reaction** is yet another example of electrophilic substitution at the alpha carbon in enolate anions. The fundamental transformation in this reaction is a dimerization of an aldehyde (or ketone) to a beta-hydroxy aldehyde (or ketone) by alpha C–H addition of one reactant molecule to the carbonyl group of a second reactant molecule. Due to the carbanion like nature of enolates they can add to carbonyls in a similar manner as Grignard reagents. For this reaction to occur at least one of the reactants must have alpha hydrogens.



The aldol reactions for acetaldehyde and acetone are shown as examples.

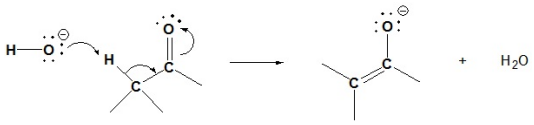
Example: Aldol Reactions



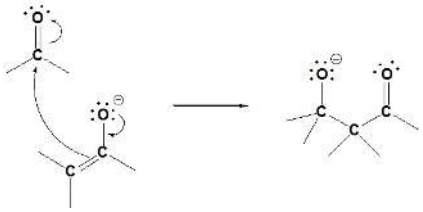


Aldol Reaction Mechanism

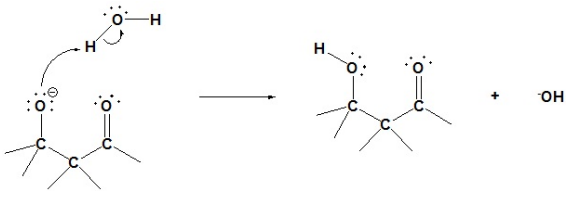
Step 1: Enolate formation



Step 2: Nucleophilic reaction by the enolate



Step 3: Protonation



Aldol Condensation: the dehydration of aldol products to synthesize α, β unsaturated carbonyls (enones)

The products of aldol reactions often undergo a subsequent elimination of water, made up of an alpha-hydrogen and the beta-hydroxyl group. The product of this ***β*-elimination** reaction is an α,β-unsaturated aldehyde or ketone. Base-catalyzed elimination

occurs with heating. The additional stability provided by the conjugated carbonyl system of the product makes some aldol reactions thermodynamically driven and mixtures of stereoisomers (*E* & *Z*) are obtained from some reactions. 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**. Overall the general reaction involves a dehydration of an aldol product to form an alkene:

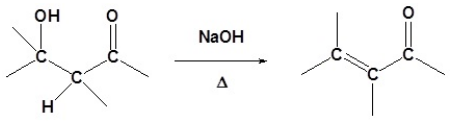


Figure: General reaction for an aldol condensation

Going from reactants to products simply

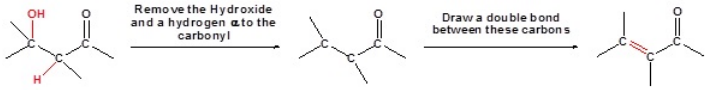
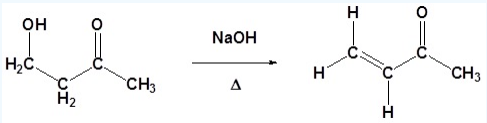


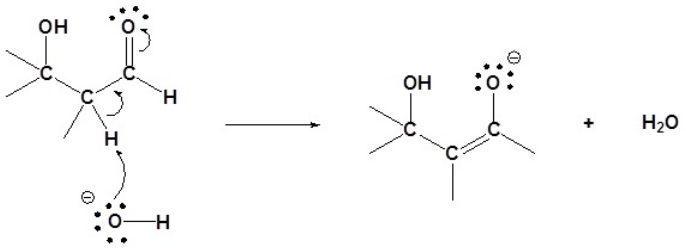
Figure: The aldol condensatio example

Example: Aldol Condensation from an Aldol Reaction Product

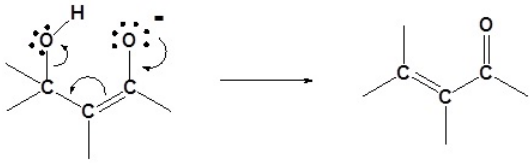


Aldol Condensation Base Catalyzed Mechanism

1) Form enolate

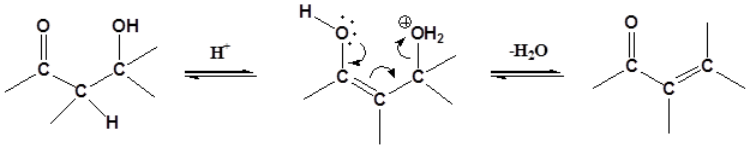


2) Form enone



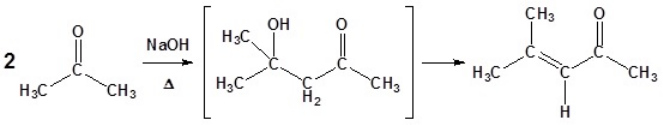
Aldol Condensation Acid Catalyzed Mechanism

Under acidic conditions an enol is formed and the hydroxy group is protonated. Water is expelled by either and E1 or E2 reaction.



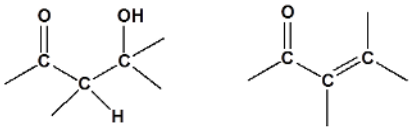
When performing both reactions together always consider the aldol product first then convert to the enone. Note! The double bond always forms in conjugation with the carbonyl.

Example: Aldol Condensation Directly from the Ketones or Aldehydes



Aldol Reactions in Multiple Step Synthesis

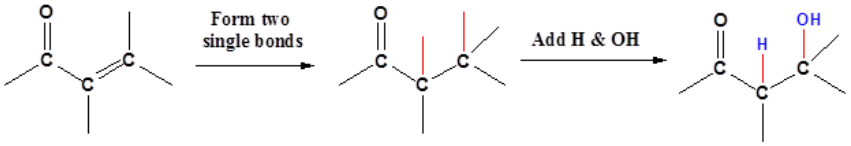
Aldol reactions are excellent methods for the synthesis of many enones or beta hydroxy carbonyls. Because of this, being able to predict when an aldol reaction might be used in a synthesis in an important skill. This accomplished by mentally breaking apart the target molecule and then considering what the starting materials might be.



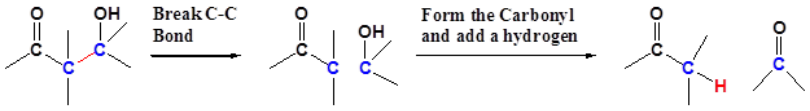
Fragments which are easily made by an aldol reaction

Steps to 'reverse' the aldol reaction (from the final aldol product towards identifying the starting compounds).

1) From an enone break the double bond and form two single bonds. Place and OH on the bond furthest from the carbonyl and an H on the bond closest to the carbonyl.

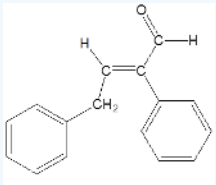


2) From the aldol product break the C-C bond between the alpha carbon and the carbon attached to the OH. Then turn the OH into a carbonyl and add an hydrogen to the other carbon.

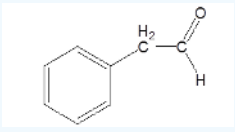


Example: Determining the Reactant when given the Aldol Condensation Product

What reactant must be used to make the following molecule using an aldol condensation?



Solution

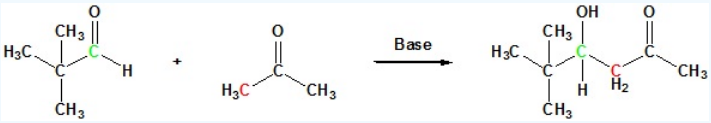


Mixed Aldol Reactions and Condensations

The previous examples of aldol reactions and condensations used a common reactant as both the enolic 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.

Example: Mixed Aldol Reaction (One Product)

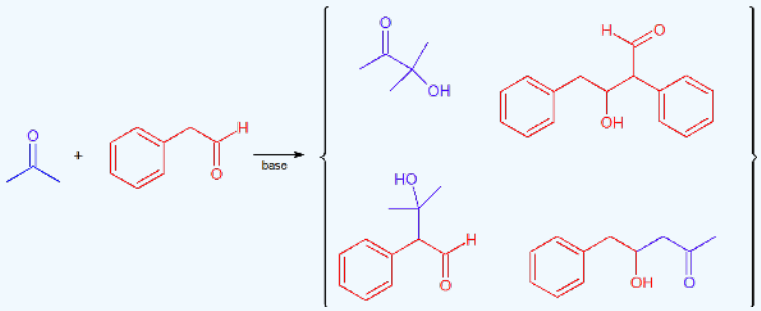


The success of these mixed aldol reactions is due to two factors. First, aldehydes are more reactive acceptor electrophiles than ketones, and formaldehyde is more reactive than other aldehydes. Second, aldehydes lacking alpha-hydrogens can only function as acceptor reactants, and this reduces the number of possible products by half. 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 alpha hydrogens.

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.

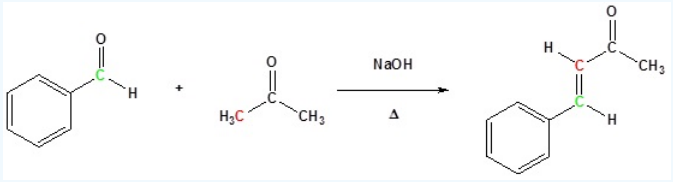
$\mathbf{A}CH_2CHO + \mathbf{B}CH_2CHO + NaOH \longrightarrow A–A + B–B + A–B + B–A$

Example: Products of a Mixed Aldol Reaction



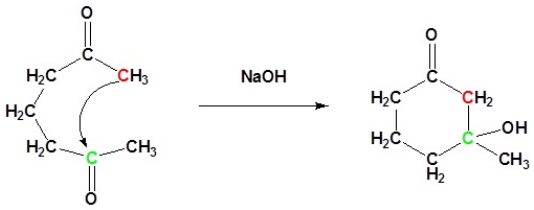
The aldol condensation of ketones with aryl aldehydes to form α,β-unsaturated derivatives is called the **Claisen-Schmidt** reaction.

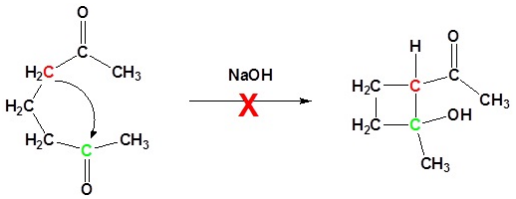
Example: Claisen-Schmidt Reaction



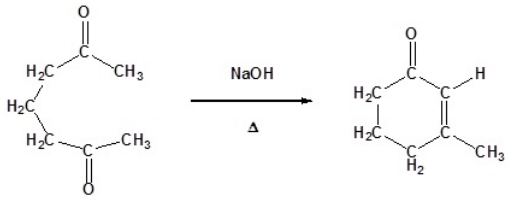
Intramolecular aldol reaction

Molecules which contain two carbonyl functionalities have the possibility of forming a ring through an intramolecular aldol reaction. In most cases two sets of α hydrogens need to be considered. As with most ring forming reaction five and six membered rings are preferred (less ring strain).



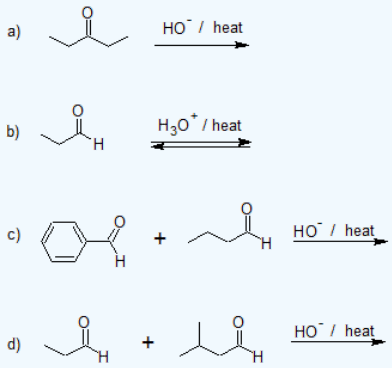


As with other aldol reaction the addition of heat causes an aldol condensation to occur.



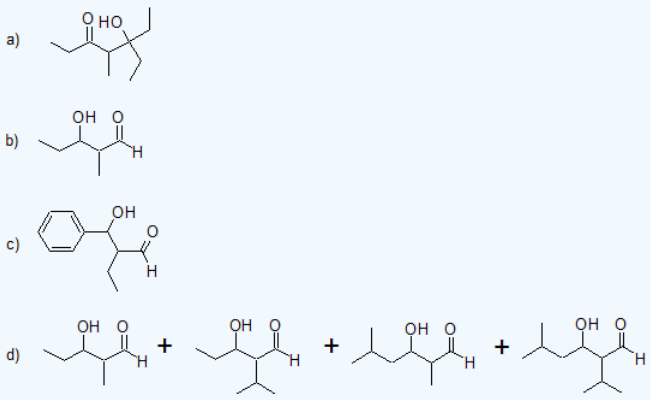
Exercise

12. Draw the bond-line structures for the products of the reactions below. Note: One of the reactions is a poorly designed aldol condensation producing four different products.



Answer

12.



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Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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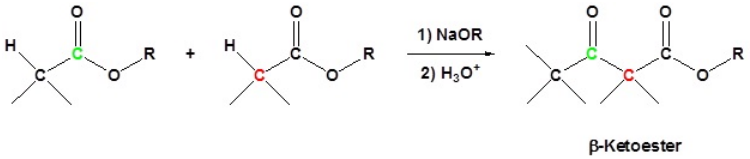
21.9: The Claisen Condensation Reactions of Esters

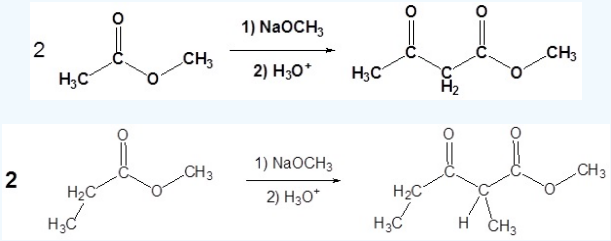
Because esters can contain alpha hydrogens, they can undergo a condensation reaction similar to the aldol reaction called a **Claisen Condensation**. In a fashion similar to the aldol, one ester acts as a nucleophile while a second ester acts as the electrophile. During the reaction a new carbon-carbon bond is formed. The product is a β-keto ester. A major difference with the aldol reaction is the fact that hydroxide cannot be used as a base because it could possibly react with the ester. Instead, an alkoxide version of the alcohol used to synthesize the ester is used to prevent transesterification side products.

Claisen Condensation



The Claisen condensation reactions of methyl acetate and methyl propanoate are shown as examples.

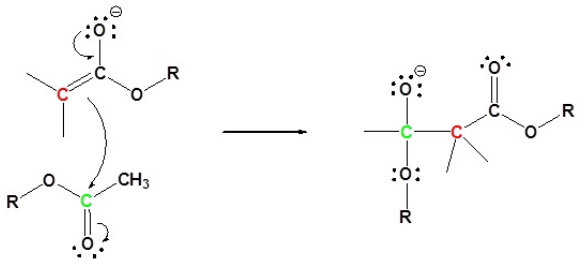
Example: Claisen Condensation



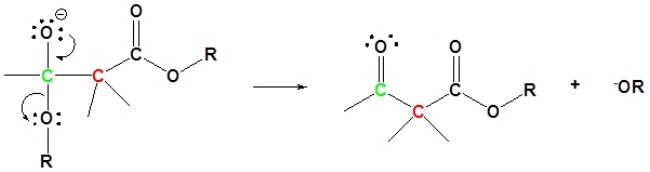
Claisen Condensation Mechanism

1) Enolate formation

2) Nucleophilic reaction

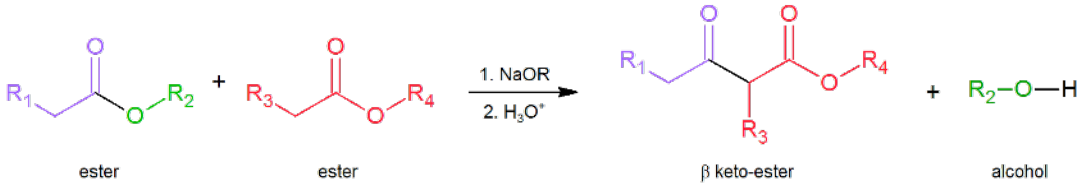


3) Removal of leaving group

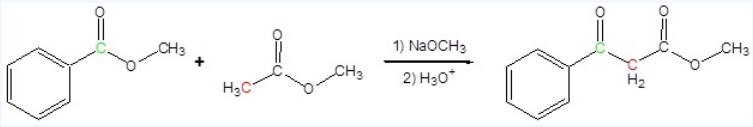


Crossed Claisen Condensation

Claisen condensations between different ester reactants are called **Crossed Claisen** reactions. Crossed Claisen reactions in which both reactants can serve as 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.



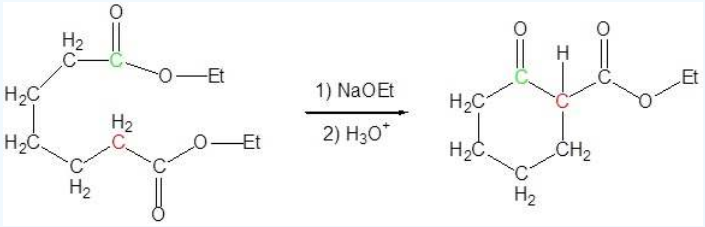
Example: Crossed Claisen Condensation



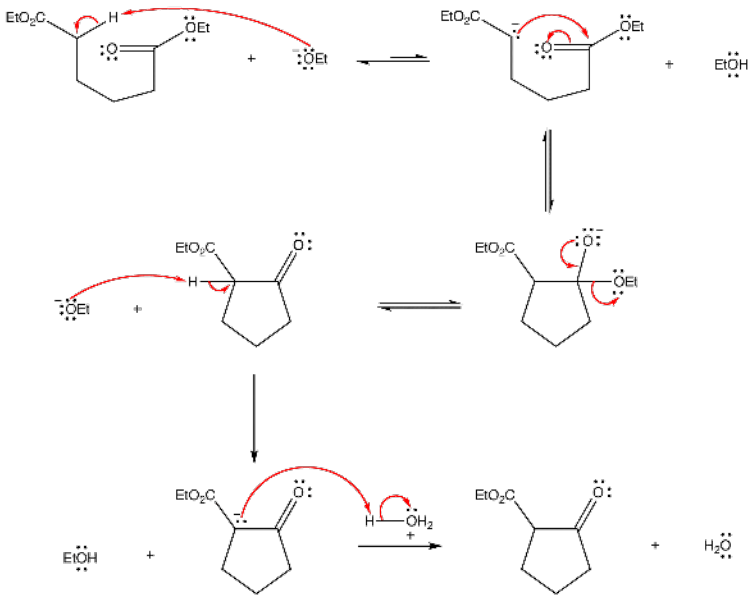
Dieckmann Condensation

A diester can undergo an intramolecular reaction called a Dieckmann condensation.

Example: Dieckman Condensation



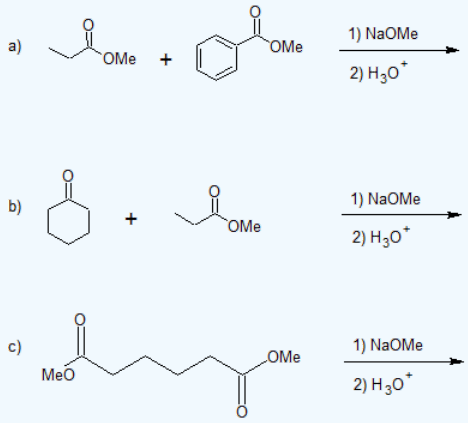
Mechanism



1. Dieckmann, W. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 102–103.

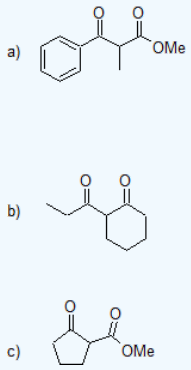
Exercise

13. Draw the bond-line structures for the products of the following reactions.



Answer

13.



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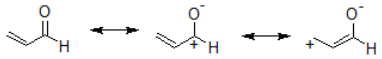
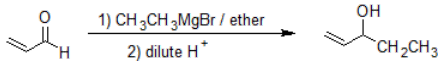
21.10: Conjugate Additions: The Michael Reaction

1,2 (Direct) versus 1,4 (Conjugate) Addition

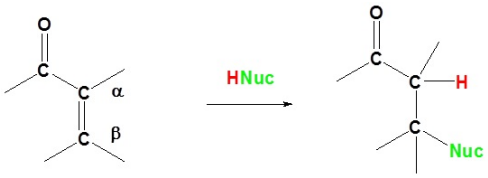
There are two electrophilic sites in alpha,beta-unsaturated carbonyls: the carbonyl carbon and the beta carbon. The second electrophilic site is created through resonance as shown below.



It is the strength of the nucleophile that determines the dominant reaction pathway. Strong nucleophiles like Grignard reagents and hydrides will react directly at the carbonyl carbon following the reactivity previously studied. The strong nucleophile reacts with the carbonyl carbon to produce a tetrahedral intermediate that is protonated to form an alcohol. The 1,2 direct addition reaction of prop-2-enal with a Grignard reagent is shown as an example below.

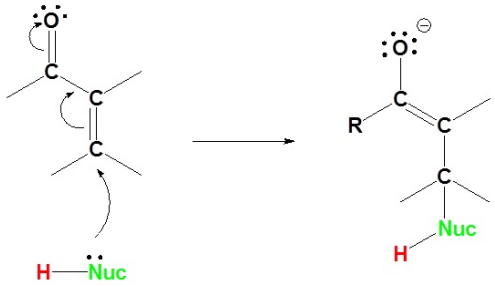


In 1,4 conjugate addition, the nucleophile reacts with the carbon β to the carbonyl driving the formation of an enolate ion that tautermerizes back to the carbonyl upon protonation.while the hydrogen is added to the carbon alpha to the carbonyl.

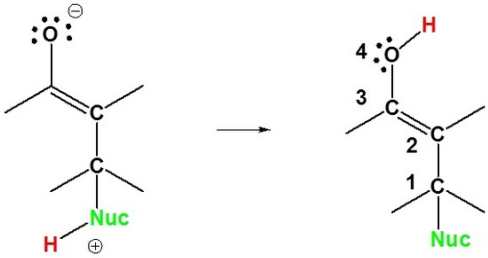


Mechanism for 1,4 conjugate addition

1) Nucleophilic reaction at the carbon β to the carbonyl

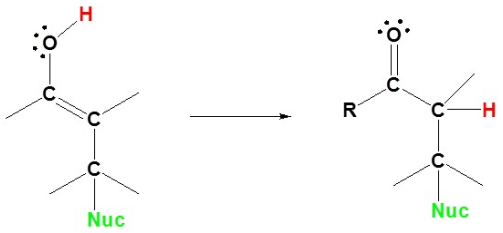


2) Proton Transfer



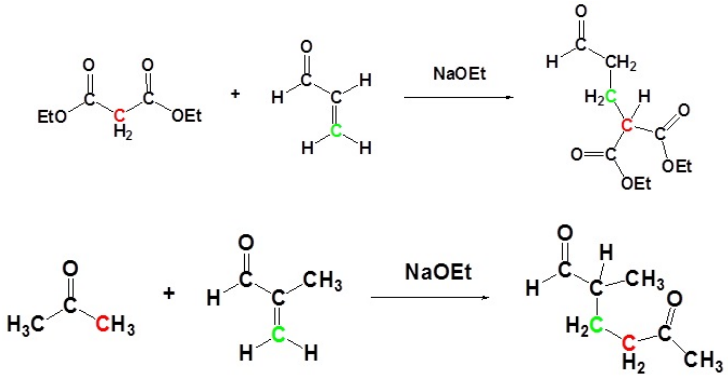
Here we can see why this addition is called 1,4. The nucleophile bonds to the carbon in the one position and the hydrogen adds to the oxygen in the four position.

3) Tautomerization

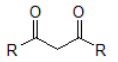
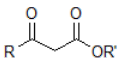
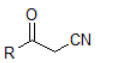
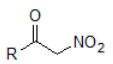


Michael Additions

Enolates are weak nucleophiles and undergo 1,4 addition to α, β-unsaturated carbonyl compounds in a process called a Michael addition. The reaction is named after American chemist Arthur Michael (1853-1942). Two examples are shown below.



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 nucleophile is called the Michael Donor and the electrophile (the alpha,beta-unsaturated carbonyl) is called the Michael Acceptor. The table below shows common reagents used for Michael addition reactions.

Michael Donors (aka nucleophile)		Michael Acceptors (aka electrophile)	
R_2CuLi	Gilman reagent		α,β-unsaturated aldehyde
	enamine		α,β-unsaturated ketone
	β-diketone		α,β-unsaturated ester
	β-ketoester		α,β-unsaturated amide
	β-keto nitrile		α,β-unsaturated nitrile
	α-nitro ketone		nitroethylene

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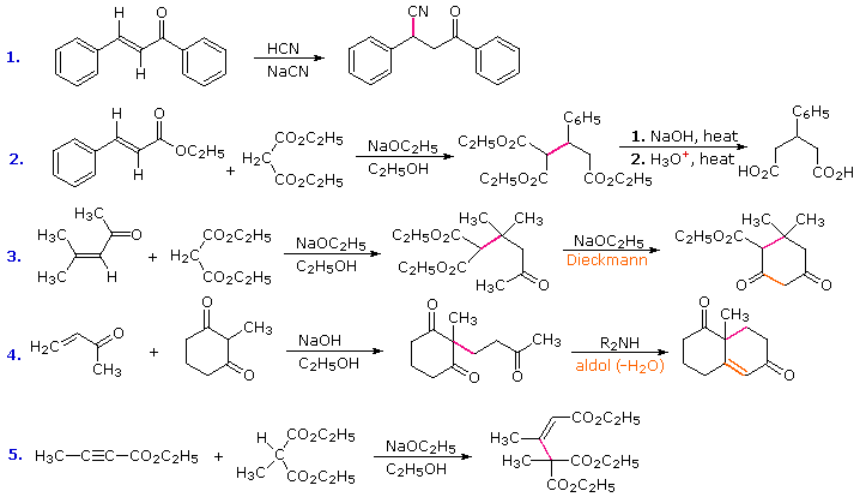
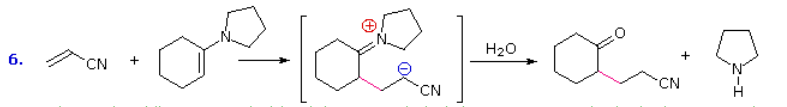
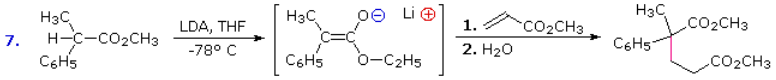
There are several examples shown below including cyanide as another potential Michael donor. These anions are sufficiently stable that their addition reactions may be presumed reversible. If this is so, the thermodynamic argument used for hetero-nucleophile additions would apply here as well, and would 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.

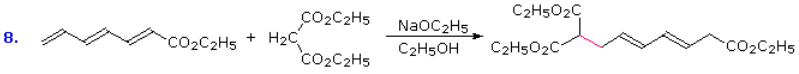




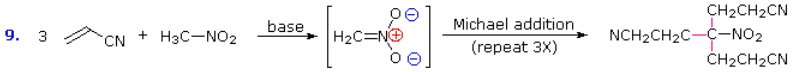
Enamine nucleophiles are good Michael donors. Hydrolysis is necessary to obtain the ketone product.



Weak carbon acids may be converted to their enolate anions prior to addition of the Michael acceptor.



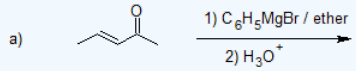
Extended vinylagous Michael acceptors have been used. This is a 1,6-addition (1,8 if the enol is counted).



Nitroalkanes have acidic α-hydrogens and make excellent Michael donors.

Exercise2

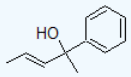
14. Draw the bond-line structures for the products of the reactions below.



15. Specify the reagents needed to perform the following chemical transformation.

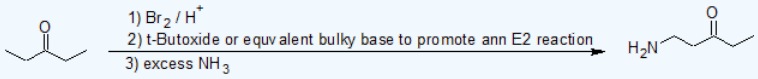
Answers

14.

a) 

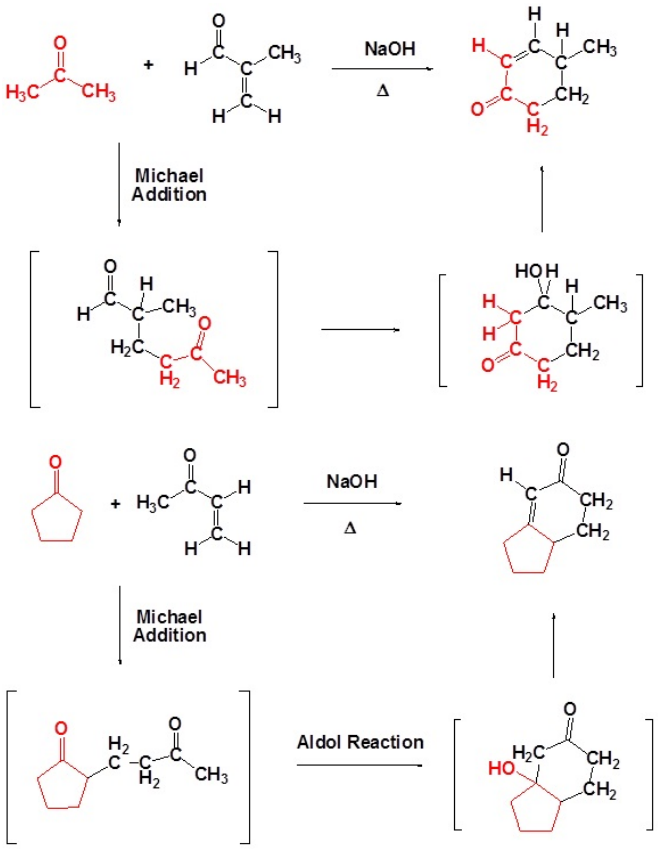
b)

15.



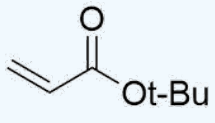
Robinson Annulations

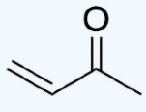
Many times the product of a Michael addition produces a dicarbonyl which can then undergo an intramolecular aldol reaction. These two processes together in one reaction creates two new carbon-carbon bonds and also creates a ring. Ring-forming reactions are called annulations after the Latin work for 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.

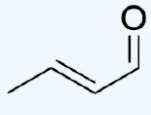


Exercise

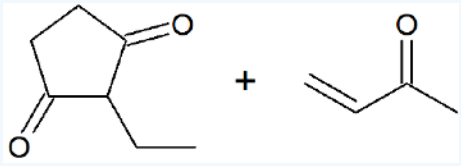
16. Draw the product of the reaction with the enamine prepared from cyclopentanone and pyrrolidine, and the following molecules.

(a) 

(b) 

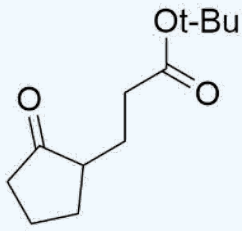
(c) 

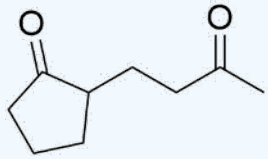
17. Draw the product of the following reaction.

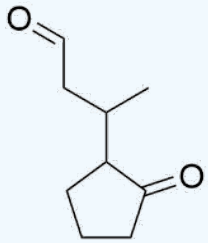


Answer

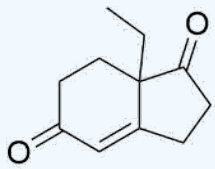
16.

(a) 

(b) 

(c) 

17.



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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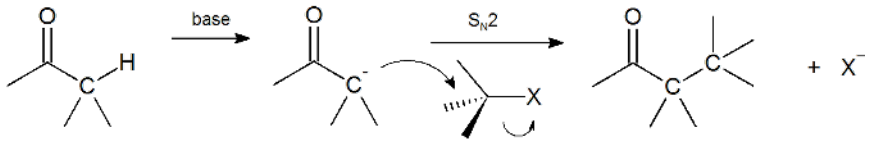
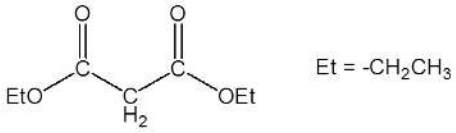
21.11: Decarboxylation Reactions

Enolates can act as a nucleophile in S_N2 type reactions. Overall an α hydrogen is replaced with an alkyl group. This reaction is one of the more important for enolates because a carbon-carbon bond is formed. These alkylations are affected by the same limitations as S_N2 reactions previously discussed. A good leaving group, X= chloride, bromide, iodide, tosylate, should be used. Also, secondary and tertiary leaving groups should not be used because of poor reactivity and possible competition with elimination reactions. Lastly, it is important to use a strong base, such as LDA or sodium amide, for this reaction. Using a weaker base such as hydroxide or an alkoxide leaves the possibility of multiple alkylation's occurring.



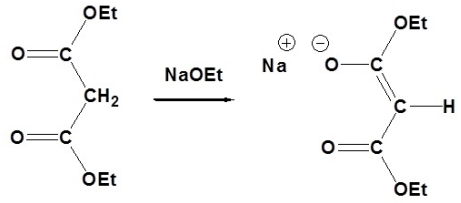
Malonic Ester Synthesis

Malonic ester is a reagent specifically used in a reaction which converts alkyl halides to carboxylic acids called the Malonic Ester Synthesis. Malonic ester synthesis is a synthetic procedure used to convert a compound that has the general structural formula 1 into a carboxylic acid that has the general structural formula 2.



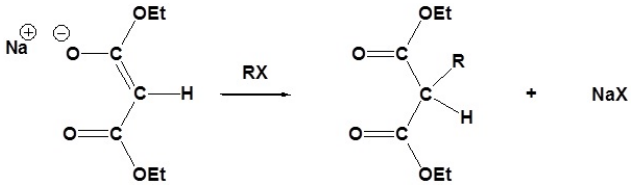
Malonic Ester

Due to the fact that Malonic ester's α hydrogens are adjacent to two carbonyls, they can be deprotonated by sodium ethoxide (NaOEt) to form Sodio Malonic Ester.

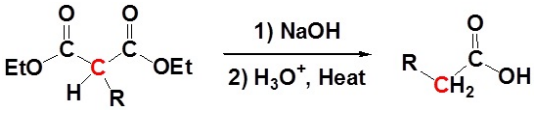


Malonic Ester **Sodio Malonic Ester**

Because Sodio Malonic Ester is an enolate, it can then be alkylated with alkyl halides.

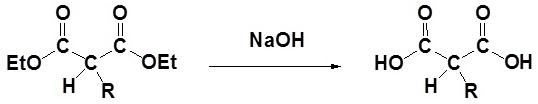


After alkylation the product can be converted to a dicarboxylic acid through saponification and subsequently one of the carboxylic acids can be removed through a decarboxylation step.

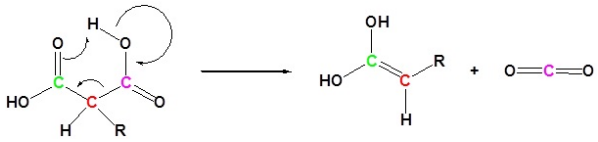


Mechanism

1) Saponification



2) Decarboxylation

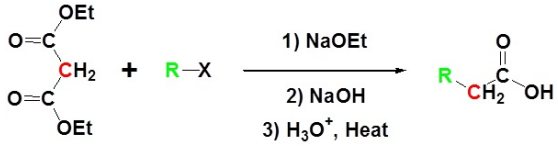


3) Tautomerization

All of the steps together form the Malonic ester synthesis.

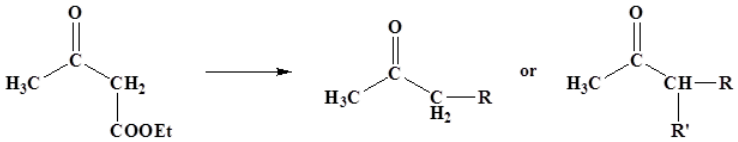
$$RX \rightarrow RCH_2CO_2H \tag{21.11.1}$$

Example



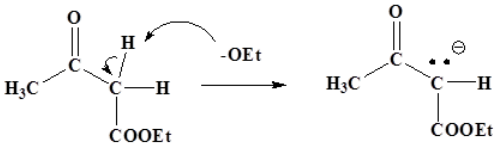
The Acetoacetic Ester Synthesis

The acetoacetic ester synthesis allows for the conversion of ethyl acetoacetate into a methyl ketone with one or two alkyl groups on the alpha carbon.

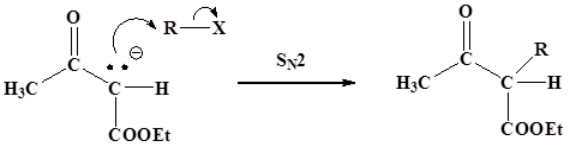


Steps

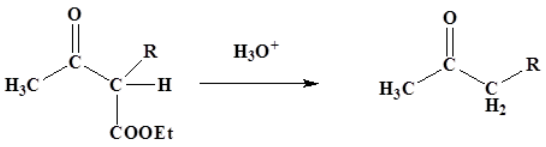
1) Deprotonation with ethoxide



2) Alkylation via and SN2 Reaction

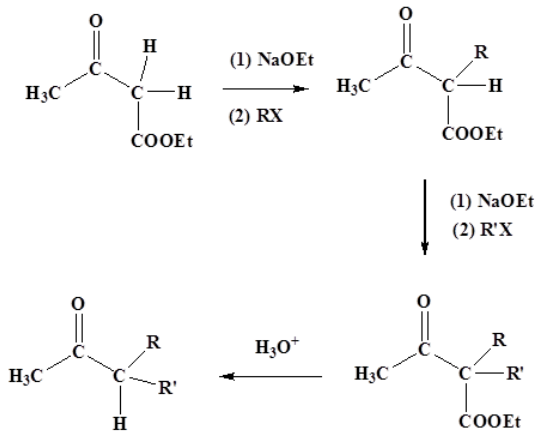


3) Hydrolysis and decarboxylation



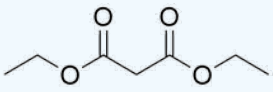
Addition of a second alky group

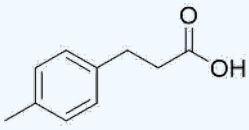
After the first step and additional alkyl group can be added prior to the decarboxylation step. Overall this allows for the addition of two different alkyl groups.

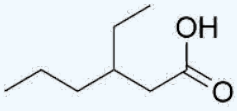


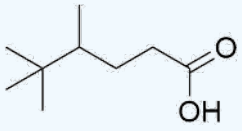
Exercise

18. Propose a synthesis for each of the following molecules from this malonic ester.



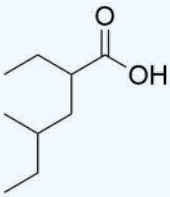
(a) 

(b) 

(c) 

19. Why can't we prepare tri substituted acetic acids from a malonic ester?

20. Propose a synthesis for the following molecule via a malonic ester.



Answer

18.

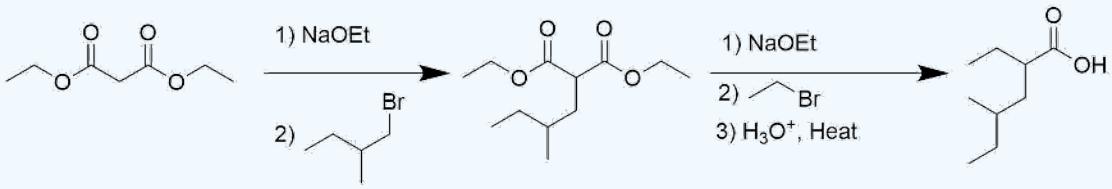
(a) 1) Malonic Ester, NaOEt, 2) 4-Methylbenzyl Bromide, 3) Base, 4) Acid, Heat

(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

19. Malonic esters only contain two acid protons.

20.



Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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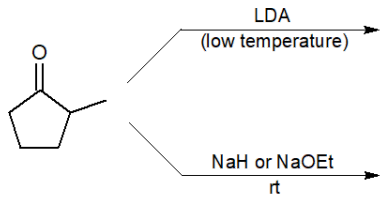
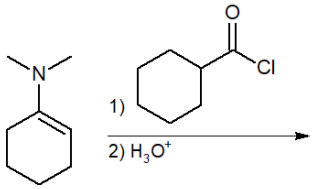
21.12: Additional Exercises

General Review

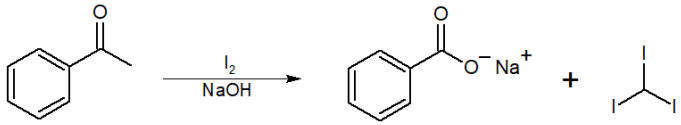
23-1 For each of the following reactions, predict the product. Then identify which one gives the kinetic product and which one gives the thermodynamic product. Explain your reasoning.



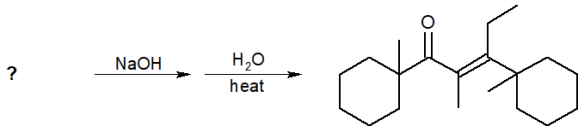
23-2 Predict the final product of the following reaction.



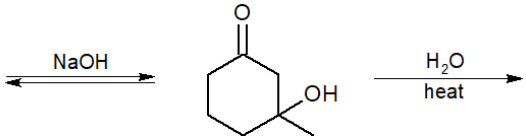
23-3 Explain why we obtain the products shown below as a result of the base catalyzed α-halogenation reaction, instead of a single or double halogenated product.



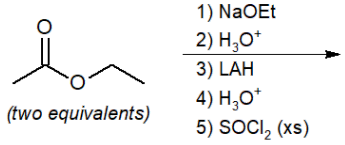
23-4 Identify the starting molecule of the aldol addition-condensation reaction that resulted in the final product below.



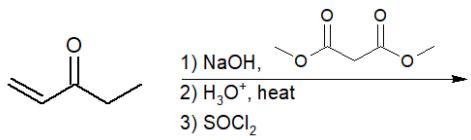
23-5 The following reaction is an example of an intramolecular aldol addition-condensation reaction. Given the aldol product, identify the starting molecule and the condensation product.



23-6 Provide the final product of the following reaction (for now, ignore any stereochemistry).

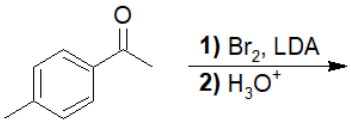


23-7 Predict the final product of the following reaction.



Enols and Enolate Ions

23-8 Choose the correct IUPAC nomenclature of the product of the following reaction and provide its structure.



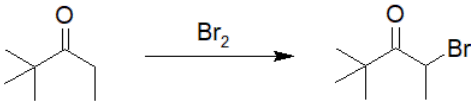
a) dibromo(4-methylphenyl)methanol

b) 4-methylbenzoic acid

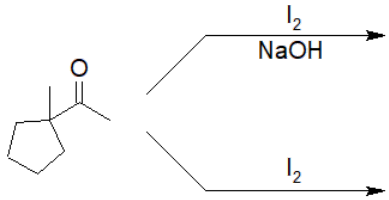
c) 4-methylbenzoyl bromide

d) bromo(4-methylphenyl)methanol

23-9 Draw the mechanism for the following self-catalyzed halogenation reaction.

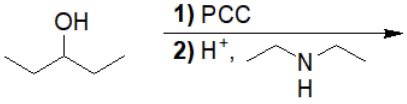


23-10 Predict the product of the following reaction.



Formation and Alkylation of Enamines

23-11 Choose the correct IUPAC nomenclature for the product of the following reaction.



a) (2Z)-N,N-diethylpent-2-en-3-amine

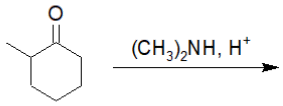
b) N,N-diethylpentan-3-amine

c) 3-(diethylamino)pentan-3-ol

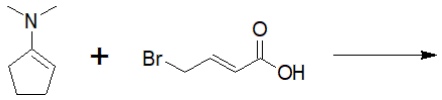
d) Tetraethylhydrazine

23-12 Predict the major products of the following reactions.

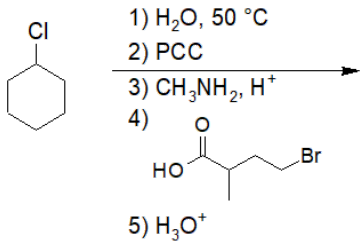
a)



b)

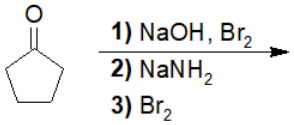


23-13 Predict the product of the following reaction.



Alpha Halogenation of Ketones

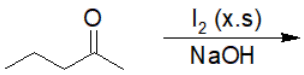
23-14 Predict the product of the following reaction.



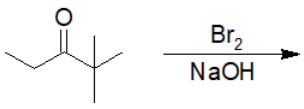
23-15 Draw the mechanism for the α-halogenation step of the ketone in problem **23-14**.

23-16 Provide the structures of the products of the following reactions.

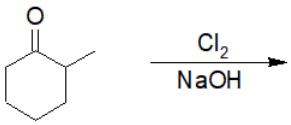
a)



b)

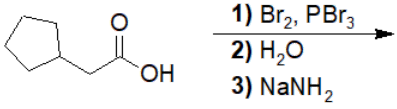


c)

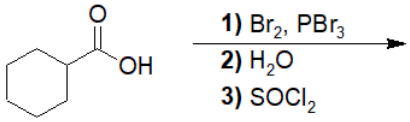


Alpha Bromination of Acids: The HVZ Reaction

23-17 Give the product of the following reaction.



23-18 Choose the correct IUPAC nomenclature of the product of the following reaction.



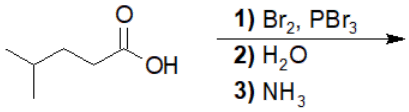
a) 1-chlorocyclohexane-1-carboxylic acid

b) 1-bromocyclohexane-1-carbonyl chloride

c) 1-chlorocyclohexane-1-carbonyl chloride

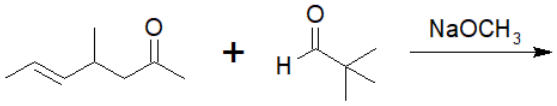
d) 1-hydroxycyclohexane-1-carbonyl bromide

23-19 Provide the structure and IUPAC nomenclature of the product of the following reaction.

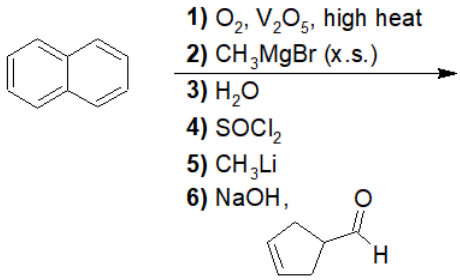


The Aldol Condensation of Ketones and Aldehydes

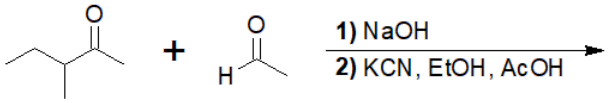
23-20 Give the structure of the product of the following aldol condensation reaction.



23-21 Predict the structure of the product of the following reaction.

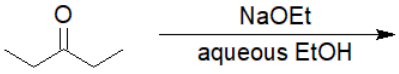


23-22 Provide the structure of the product of the following reaction.



Dehydration of Aldol Products

23-23 Choose the correct IUPAC nomenclature for the product of the following aldol condensation reaction.



a) 5-ethyl-4-methylheptan-3-one

b) 5-ethyl-4-methylhept-4-en-3-one

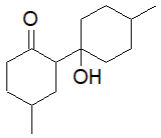
c) 5-ethyl-5-hydroxy-4-methylheptan-3-one

d) (5Z)-5-ethyl-4-methylhept-5-en-3-one

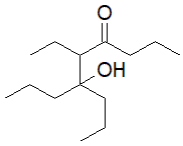
23-24 Provide the mechanism for the reaction to the answer for the previous question.

23-25 For the following compounds, draw a possible product of the condensation step.

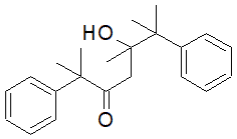
a)



b)

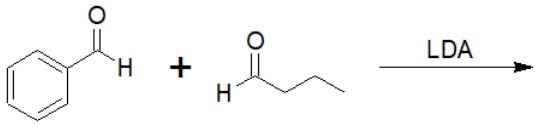


c)

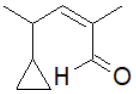


Crossed Aldol Condensations

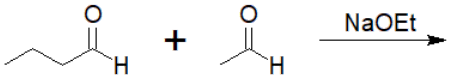
23-26 Provide the structure of the product of the following reaction.



23-27 Suggest the structures of the starting compounds that were reacted to create this final crossed aldol condensation product.



23-28 Provide the structures of all possible products of the following crossed aldol condensation reaction.

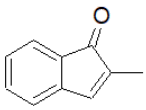


Aldol Cyclizations

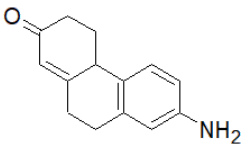
23-29 Provide the IUPAC name for the product of the following intramolecular aldol condensation reaction.

23-30 Identify the starting material used to create the following products of aldol cyclization.

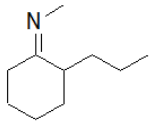
a)



b)



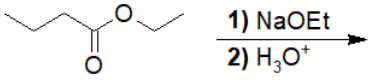
23-31 Starting with a single diketone molecule, propose a method of synthesis for the following compound that includes an aldol cyclization step.



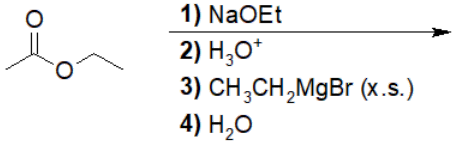
(1*Z*)-*N*-methyl-2-propylcyclohexan-1-imine

Claisen Condensations

23-32 Predict the product of the following Claisen condensation reaction.

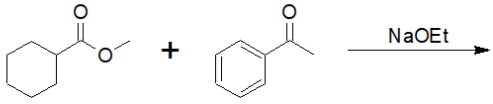


23-33 Predict the final product of the following reaction.

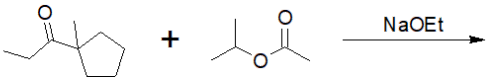


23-34 Provide the structure of the products of the following crossed Claisen condensation reactions.

a)

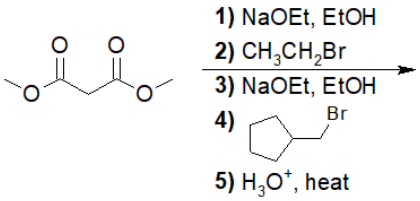


b)

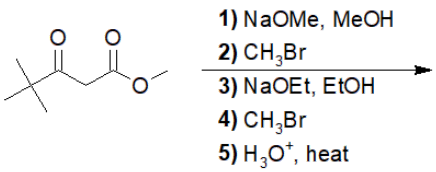


Syntheses Using *β*-Dicarbonyl Compounds

23-35 Give the structure and IUPAC nomenclature of the product of the following reaction.



23-36 Choose the correct IUPAC nomenclature of the product of the following reaction.



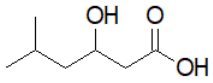
a_ 2,2,4,4-tetramethylpentan-3-one

b) 2,2,4-trimethylpentan-3-one

c) 2,4,4-trimethylpent-1-en-3-one

d) 2,4,4-trimethyl-3-oxopentanoic acid

23-37 Suggest a way to make (5-methylhexyl)benzene from 3-hydroxy-5-methylhexanoic acid.



3-hydroxy-5-methylhexanoic acid

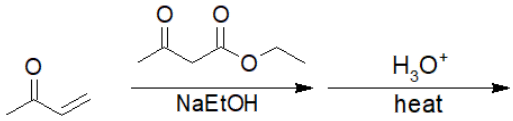
Conjugate Additions: The Michael Reaction

23-38 For the following pairs of compounds, identify the Michael acceptor and the Michael donor.

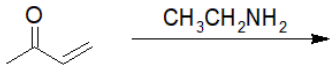
a)

b)

23-39 Predict the product of the following reaction chain.



23-40 Pick the answer that correctly names the product of the following Michael addition reaction.



a) 3-(ethylamino)butan-2-one

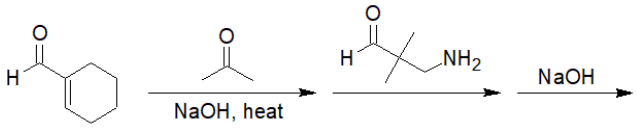
b) 2-(ethylamino)butan-2-ol

c) 4-(ethylamino)butan-2-one

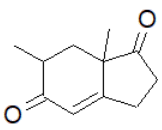
d) 4-(methylamino)butan-2-one

The Robinson Annulation

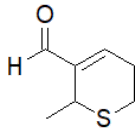
23-41 Predict a possible product of the following reactions.



23-42 Given the following compound, predict the Michael acceptor and donor that initially reacted to allow for the aldol condensation to occur.



23-43 Given the following Robinson annulation product, identify the intermediate compound that results from the Michael addition and exists before the aldol condensation.



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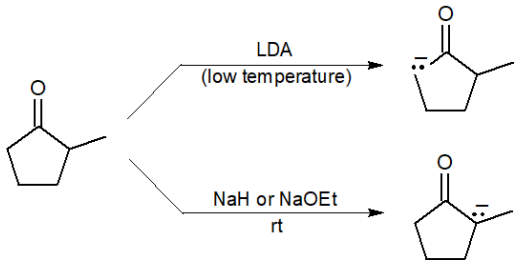
21.13: Solutions to Additional Exercises

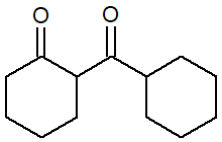
General Review

23-1



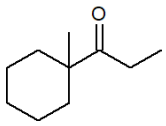
When a bulky base, such as LDA, is used, it will almost always deprotonate the least hindered position. In this case, the reaction is performed under low temperatures (to prevent the thermodynamic product from forming) and we get the kinetic product. When we use a strong base that is not bulky, it will favor deprotonating the position that will provide the most stable product at equilibrium. As a result, the enolate that forms when using NaH or NaOEt is more substituted and more stable.

23-2

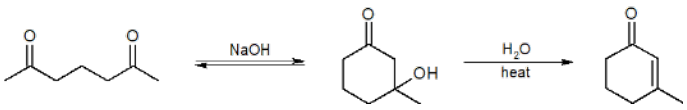


23-3 When acetophenone is halogenated at the α-position, the α-carbon becomes more acidic as a result of the electron-withdrawing halogen. This makes it more likely to go through α-halogenation again, until it no longer has any α-protons. When the base performs a nucleophilic attack on the ketone, the triiodomethyl group becomes a good leaving group. The resulting products are sodium benzoate and triiodomethane.

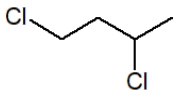
23-4



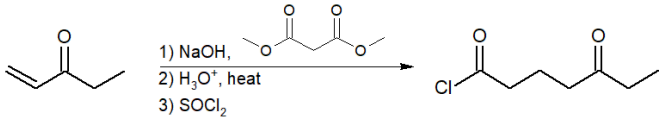
23-5



23-6



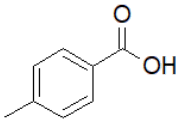
23-7



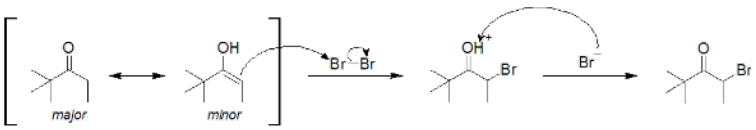
Enols and Enolate Ions

23-8:

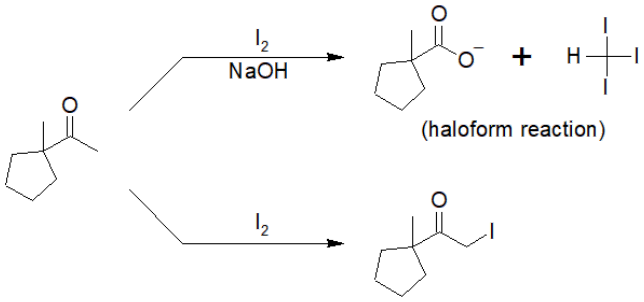
Answer: B



23-9:



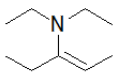
23-10:



Formation and Alkylation of Enamines

23-11:

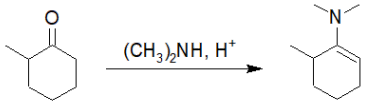
Answer: A



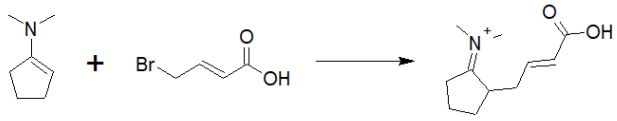
(2*Z*)-*N*,*N*-diethylpent-2-en-3-amine

23-12:

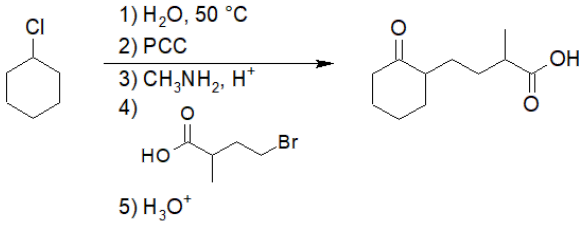
a)



b)

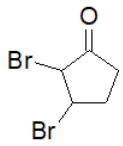


23-13:

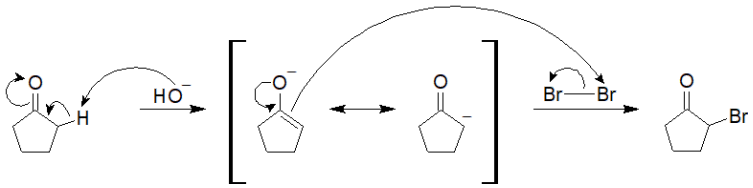


Alpha Halogenation of Ketones

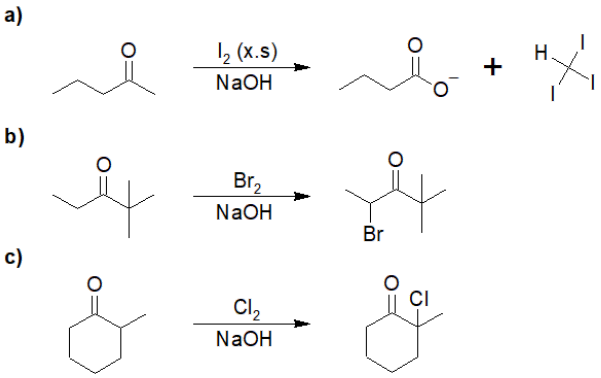
23-14:



23-15:

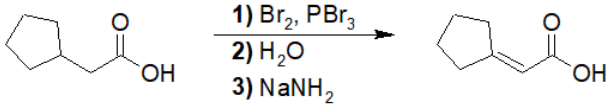


23-16:



Alpha Bromination of Acids: The HVZ Reaction

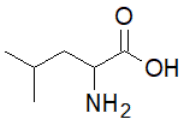
23-17:



23-18:

Answer: B

23-19:

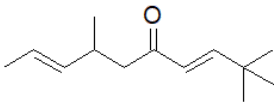


2-amino-4-methylpentanoic acid
(also known as the amino acid Leucine)

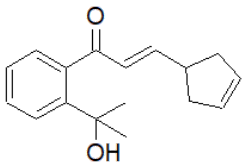
The Aldol Condensation of Ketones and Aldehydes

23-20:

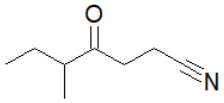
https://chem.libretexts.org/@go/page/183148



23-21:



23-22:

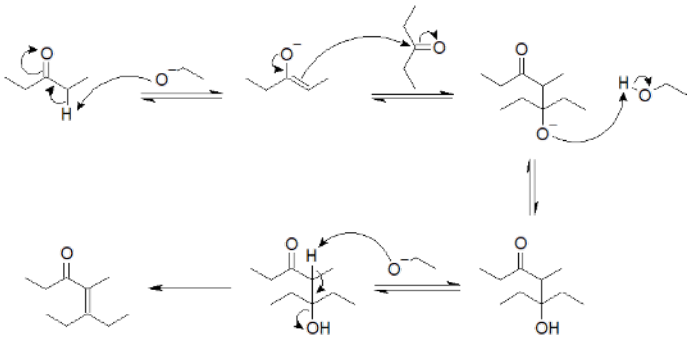


Dehydration of Aldol Products

23-23:

Answer: B

23-24:



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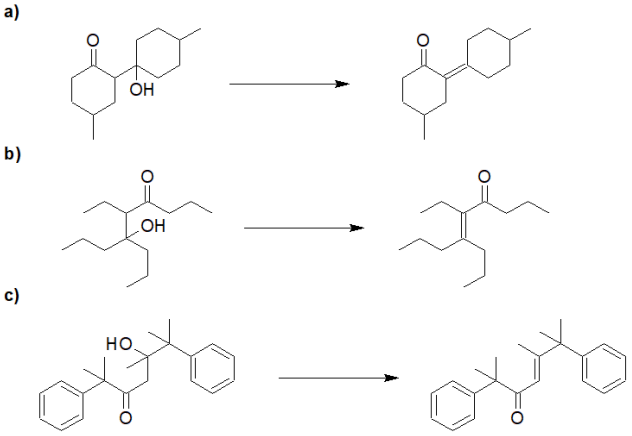
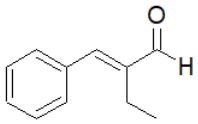


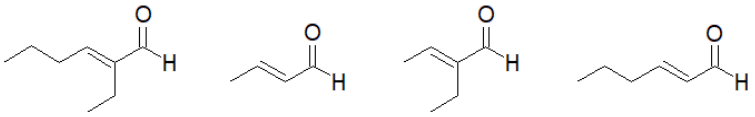
Crossed Aldol Condensations

23-26:



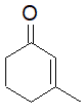
23-27:

23-28:



Aldol Cyclizations

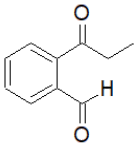
23-29:



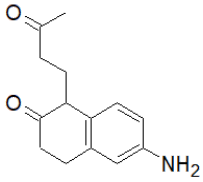
3-methylcyclohex-2-en-1-one

23-30:

a)

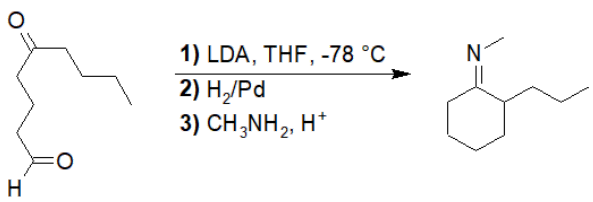


b)



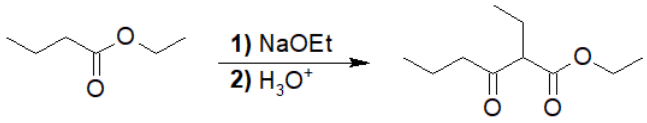
23-31:

Several answers possible. One plausible method of synthesis:

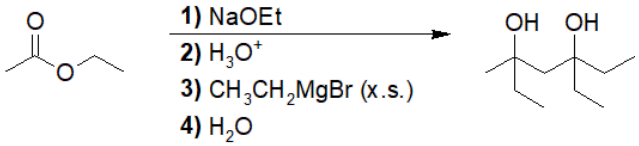


Claisen Condensations

23-32:

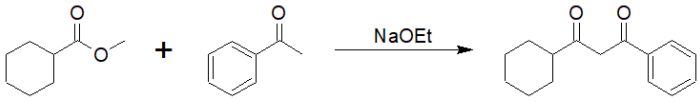


23-33:

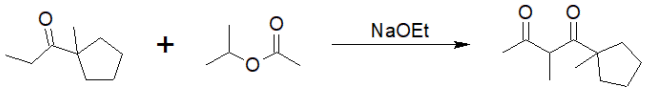


23-34:

a)

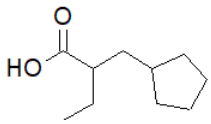


b)



Syntheses Using *β*-Dicarbonyl Compounds

23-35:



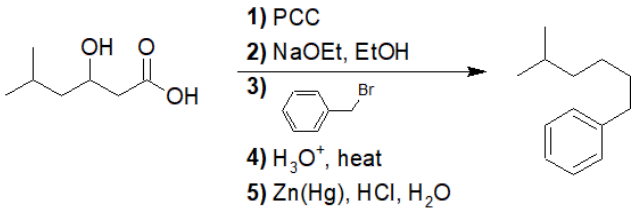
2-(cyclopentylmethyl)butanoic acid

23-36:

Answer: B

23-37:

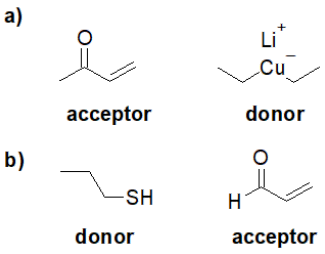
Possible route of synthesis:



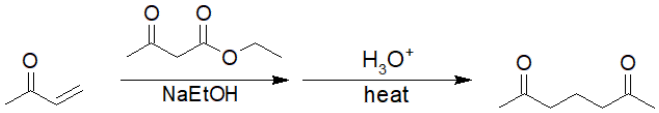
Conjugate Additions: The Michael Reaction

23-38:

Michael acceptors are generally α,β-unsaturated ketones; however, aldehydes or acid derivatives can also function as acceptors. Michael donors are weak bases/strong nucleophiles.

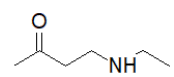


23-39:



23-40

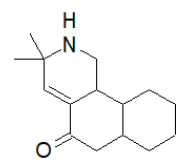
Answer: C



4-(ethylamino)butan-2-one

The Robinson Annulation

23-41:



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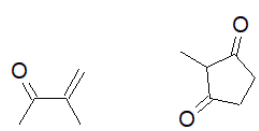

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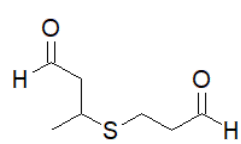

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CHAPTER OVERVIEW

22: Amines

learning objectives

After reading this chapter and completing ALL the exercises, a student can be able to

- describe the structure and physical properties of amines and ammonium salts (section 20.1)
- explain and predict the relative basicity of amines using resonance, hybridization, substituent effects, and aromaticity (section 20.2)
- determine the structure of amines from their elemental analysis and spectral data (MS, IR ^{1}H NMR & ^{13}C NMR) (section 20.3)
- predict the products and specify the reagents to synthesize amines (section 20.4)
- predict the products and specify the reagents to synthesize primary amines (section 20.5)
- predict the products and specify the reagents for reactions of amines with
  - aldehydes & ketones (section 20.6)
  - alkyl halides and tosylates (section 20.6)
  - acyl chlorides (section 20.6)
  - sulfonyl chlorides (section 20.6)
  - nitrous acid (section 20.7)
  - oxidizing agents via Cope Elimination (section 20.9)
- explain the activating effects of aryl amines during electrophilic aromatic substitution reactions (section 20.7)
- use amides as protecting groups in multiple step synthesis (section 20.7)
- use diazonium salts to design multiple step syntheses using the Sandmeyer reactions (section 20.7)
- specify the reagents and predict the products for Hofmann Elimination reactions (section 20.8)
- Specify reagents for chemical transformations using all of the reactions studied to date
- combine the reactions studied to date to develop efficient and effective multiple-step synthesis including the use of amides as protecting groups

Please note: IUPAC nomenclature and important common names of amines were explained in Chapter 3.

Topic hierarchy

22.1: Structure and Physical Properties of Amines
22.2: Basicity of Amines and Ammonium Salt Formation
22.3: Spectroscopy of Amines
22.4: Synthesis of Amines
22.5: Synthesis of Primary Amines
22.6: Reactions of Amines
22.7: Reactions of Arylamines
22.8: The Hofmann Elimination: Amines as Leaving Groups
22.9: Oxidation of Amines - The Cope Elimination
22.10: Sulfa Drugs - a closer look
22.11: Additional Exercises
22.12: Solutions to Additional Exercises

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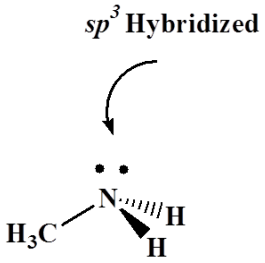
22.1: Structure and Physical Properties of Amines

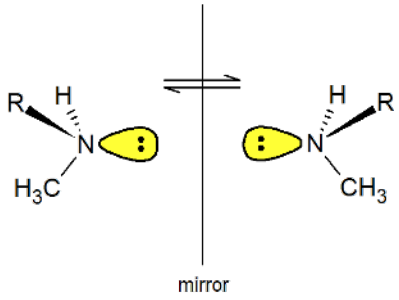
Structure

Amines typically have three bonds and one pair of lone pair electrons. This makes the nitrogen sp^3 hybridized, trigonal pyramidal, with a bond angle of roughly 109.5°.

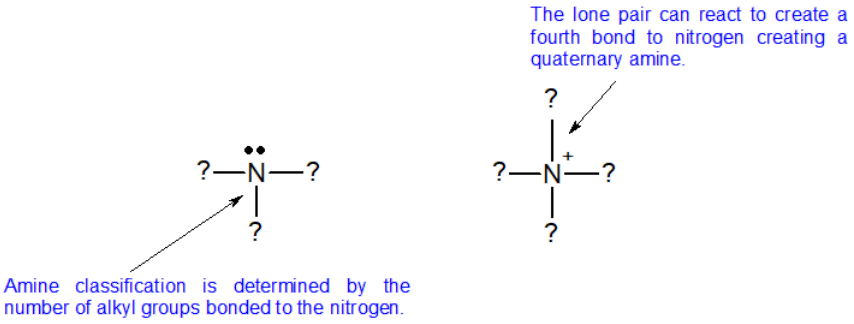


Stereochemistry

Single-bonded nitrogen is pyramidal in shape, with the non-bonding electron pair pointing to the unoccupied corner of a tetrahedral region. Since the nitrogen in these compounds is bonded to three different groups, it is stereogenic and its configuration is chiral. The non-identical mirror-image configurations are illustrated in the following diagram (the remainder of the molecule is represented by *R*, and the electron pair is colored yellow). If these configurations were stable, there would be four additional stereoisomers of ephedrine and pseudoephedrine. However, pyramidal nitrogen is normally not configurationally stable. 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. If the nitrogen atom were the only chiral center in the molecule, a 50:50 (racemic) mixture of *R* and *S* configurations would exist at equilibrium. If other chiral centers are present, as in the ephedrin isomers, a mixture of diastereomers will result. The take-home message is that nitrogen does not contribute to isolable stereoisomers.



Amines are classified according to the number of alkyl or aryl groups attached to nitrogen. Amines are classified differently from alkyl halides and alcohols because nitrogen has a neutral bonding pattern of three bonds with a single lone pair. To classify amines, we look at the nitrogen atom of the amine and count the number of alkyl groups bonded to it. This number is the classification of the amine.



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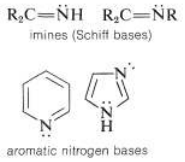
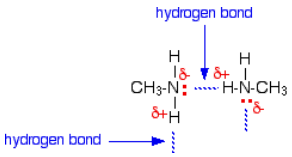
There are two additional classifications of amines. When the nitrogen is double bonded to carbon, then it is call am imine. When nitrogen is part of a ring that includes double bonds, then it is classified as heterocyclic, as seen in the aromatic nitrogen bases shown below.



Boiling Point and Water Solubility

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 (light green columns) 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.



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

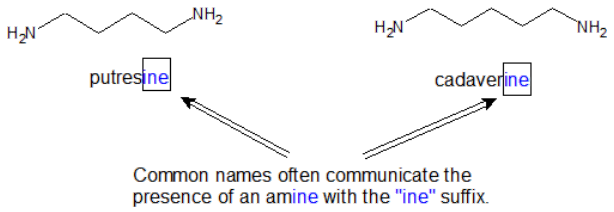
The second table illustrates differences associated with isomeric 1º, 2º & 3º-amines, as well as the influence of chain branching. Since 1º-amines have two hydrogens available for hydrogen bonding, we expect them to have higher boiling points than isomeric 2º-amines, which in turn should boil higher 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

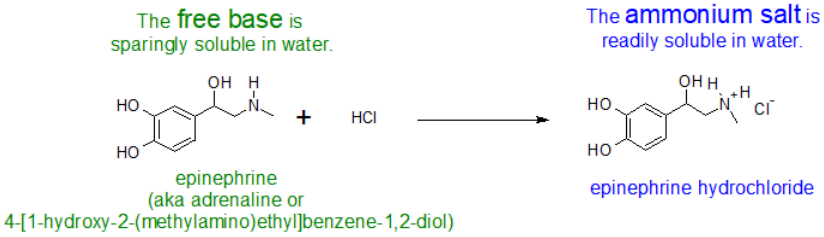
The water solubility of 1º and 2º-amines is similar to that of comparable alcohols. As expected, the water solubility of 3º-amines and ethers is also similar. These comparisons, however, are valid only for pure compounds in neutral water. The basicity of amines (next section) allows them to be dissolved 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.

Odor

The free base form of amines can be quite odiferous. The foul smell of dying flesh is primarily from the amines released during decomposition of the proteins in an organism. The common names for the amines below emphasize this aspect of amines. It is also useful to note that common names frequently indicate the presence of an amine with the "ine" suffix.



The smell of amines can be reduced by reacting them with strong acids to form the ammonium salts. For example, the acid from lemons can be used to disguise the smell of fish that is past optimum freshness. While the free base forms of amines can be thermally unstable and smelly, the ammonium salt formed from the conjugate acid of the amine have increased thermal stability and reduced odor. If the amine is not soluble as a free base, its ammonium salt will be water soluble.

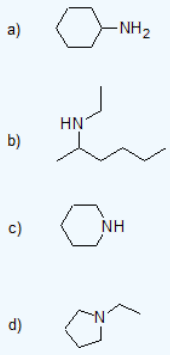


Exercise

1. Draw the structures for the following amines in order of decreasing water solubility: methanamine, 2-octanamine, 2-butanamine.

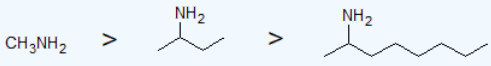
2. Draw the for the following amines in order of decreasing boiling point: cyclohexanamine, 2-octanamine, 2-butanamine.

3. Classify the following amines.

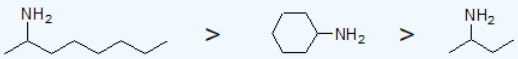


Answer

1.



2.



3. a) primary b) secondary c) secondary d) tertiary

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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22.2: Basicity of Amines and Ammonium Salt Formation

Basicity of nitrogen groups

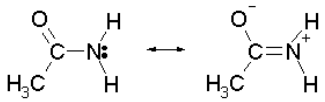
When evaluating the relative basicity of several nitrogen-containing functional groups: amines, amides, anilines, imines, and nitriles, the central question is: how reactive (and thus how basic) is the lone pair on the nitrogen? In other words, how much does that lone pair want to break away from the nitrogen nucleus and form a new bond with a hydrogen?

Comparing the basicity of alkyl amines to ammonia

Alkyl groups donate electrons to the more electronegative nitrogen. This inductive effect makes the electron density on the alkylamine's nitrogen greater than the nitrogen of ammonium. Correspondingly, primary, secondary, and tertiary alkyl amines are more basic than ammonia. Inductive effects are also moderated by the increased steric hindrance of alkyl groups (R grps).

Comparing the basicity of alkylamines to amides

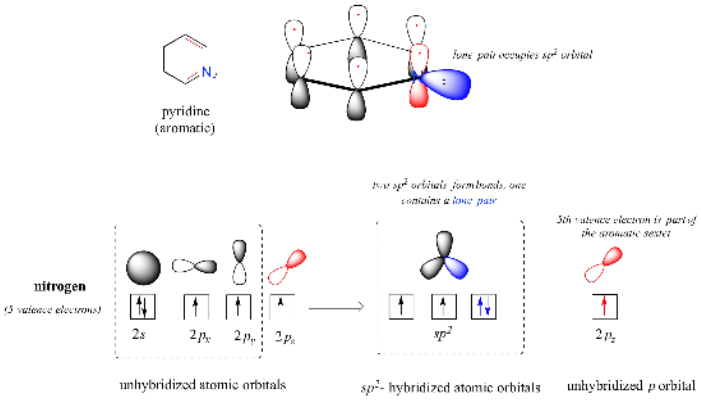
With an alkyl amine the lone pair electron is localized on the nitrogen. However, the lone pair electron on an amide are delocalized between the nitrogen and the oxygen through resonance. This makes amides much less basic compared to alkylamines.



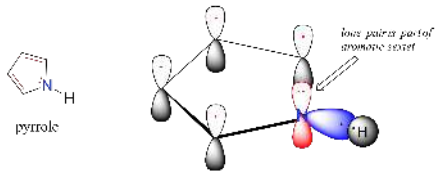
When an amide reacts with an acid, the protonation occurs at the carbonyl oxygen and not the nitrogen. The cation resulting from oxygen protonation is resonance stabilized., while the cation resulting for the protonation of nitrogen is not resonance stabilized.

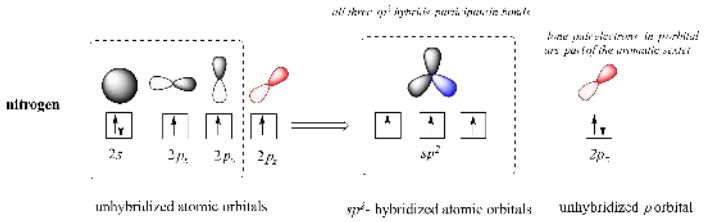
Basicity of heterocyclic amines

When a nitrogen atom is incorporated directly into an aromatic ring, its basicity depends on the bonding context. In a pyridine ring, for example, the nitrogen lone pair occupies an sp^2-hybrid orbital, and is *not* part of the aromatic sextet - it is essentially an imine nitrogen. Its electron pair is available for forming a bond to a proton, and thus the pyridine nitrogen atom is somewhat basic.

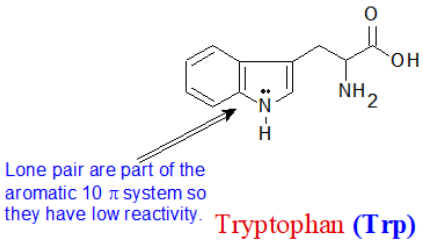


In a pyrrole ring, in contrast, the nitrogen lone pair *is* part of the aromatic sextet. This means that these electrons are very stable right where they are (in the aromatic system), and are much less available for bonding to a proton (and if they *do* pick up a proton, the aromic system is destroyed). For these reasons, pyrrole nitrogens are not strongly basic.





The aniline, pyridine, and pyrrole examples are good models for predicting the reactivity of nitrogen atoms in more complex ring systems (a huge diversity of which are found in nature). The tryptophan side chain, for example, contains a non-basic 'pyrrole-like' nitrogen, while adenine (a DNA/RNA base) contains all three types.



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 means that the electrons are close to the nucleus and therefore not significantly basic.

Base Strength and pKa Values

Like ammonia, most amines are Brønsted and Lewis bases, but their base strength can be changed enormously by substituents. 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. 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).

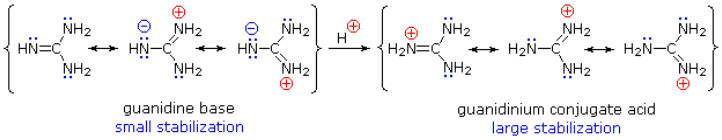
Compound	NH_3	pyridine	aniline	4-nitroaniline	pyrrole	R–C(=O)–NH2	$CH_3C{\equiv}N$ acetonitrile
pK_a	9.3	5.2	4.6	1.0	0.0	-1.0	-10.

The first four compounds in the table above are all weak bases. The last five compounds are significantly less basic to neutral and even acidic as a consequence of two possible factors:

- orbital hybridization
- electron delocalization through resonance.

In pyridine, the nitrogen is sp^2 hybridized, and in nitriles (last entry) an sp hybrid nitrogen is part of the triple bond. In each of these compounds, the non-bonding electron pair is localized on the nitrogen atom, but increasing s-character brings it closer to the nitrogen nucleus, reducing its tendency to bond to a proton. For aniline and 4-nitroaniline, the nitrogen lone pair is stabilized through hyperconjugation with the aromatic ring. Pyrrole exhibits exceptional delocalization of the nitrogen electron pair because of its incorporation into the aromatic ring.

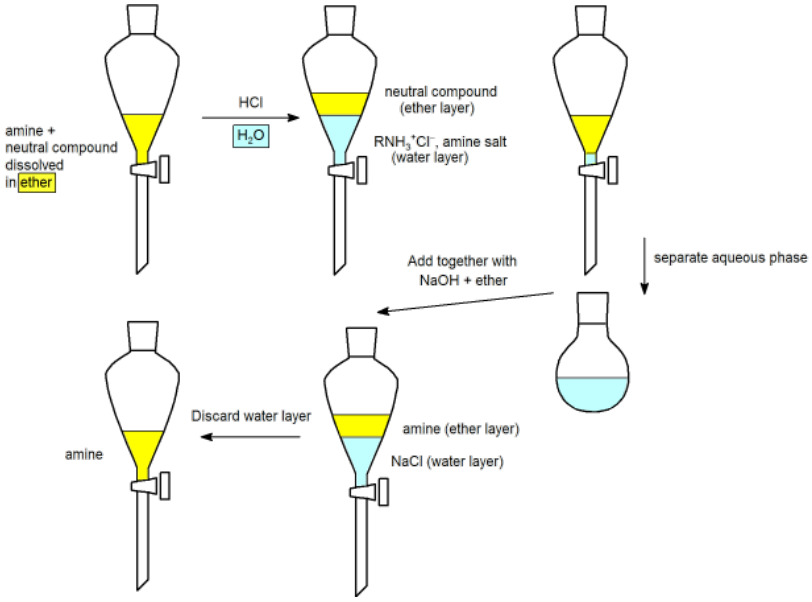
Although resonance delocalization generally reduces the basicity of amines, a dramatic example of the reverse effect is found in the compound guanidine (pK_a = 13.6). Here, as shown below, resonance stabilization of the base is small, due to charge separation, while the conjugate acid is stabilized strongly by charge delocalization. Consequently, aqueous solutions of guanidine are nearly as basic as are solutions of sodium hydroxide.



> *Strong bases have weak conjugate acids, and weak bases have strong conjugate acids.*

Amine Extraction in the Laboratory

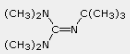
Extraction is often employed in organic chemistry to purify compounds. Liquid-liquid extractions take advantage of the difference in solubility of a substance in two immiscible liquids (e.g. ether and water). The two immiscible liquids used in an extraction process are (1) the solvent in which the solids 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.

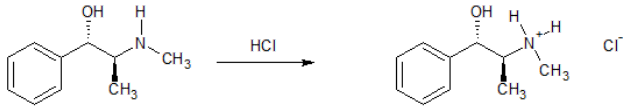
Since alcohols are much stronger acids than amines, their conjugate bases are weaker than amide bases, and fill the gap in base strength between amines and amide salts. In the following table, pK_a again refers to the conjugate acid of the base drawn above it.

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	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 like DBU 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 DBU or 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.

Ammonium Salt Formation and Water Solubility

Many pharmaceuticals include amine functional groups. Sometimes the basicity of these amine groups is used to increase the water solubility of a drug so that it can be administered orally or intravenously. Ammonium salts are also thermally more stable and have less odor than their "free base" conjugates. The antihistamine, pseudoephedrine, reacts with hydrochloric acid to form the water soluble ammonium salt as shown below.

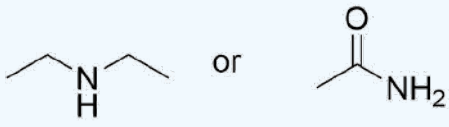


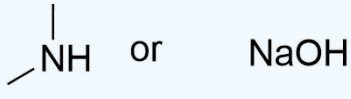
pseudoephedrine
H_2O solubility: 7 mg/L

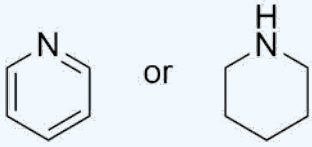
pseudoephedrine hydrochloride
H_2O solubility: 1.06×10^5 mg/L
over 15,000 x more water soluble

Exercise

4. Select the more basic compound from each of the following pairs of compounds.

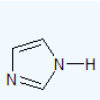
(a) 

(b) 

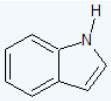
(c) 

5. 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?

6. The structures for indole and imidazole are shown below. One compound has a pKa of -2 while the other compound has a pKa of 7. Assign the pKa values to the corresponding compound and explain your reasoning.



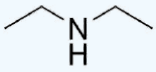
imidazole



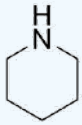
indole

Answer

4.

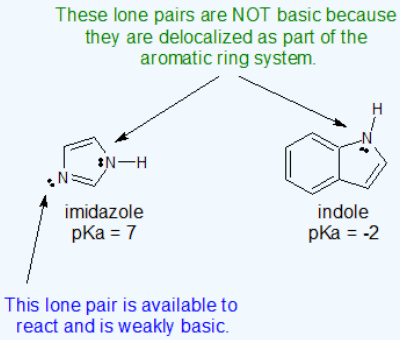
(a) 

(b) NaOH

(c) 

5. The butylammonium is more basic. The pKb for butylammonium is 3.41, the pKb for 4-methylbenzylammonium is 4.49.

6.



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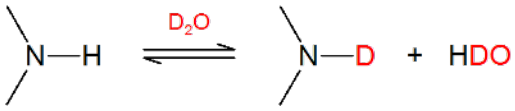
22.3: Spectroscopy of Amines

NMR

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.

Addition of D_2O will normally cause all hydrogens on non-carbon atoms to exchange with deuteriums, 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.

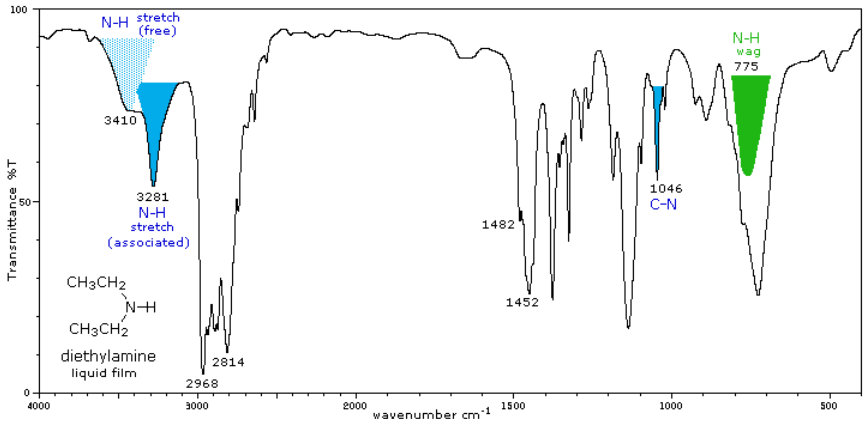


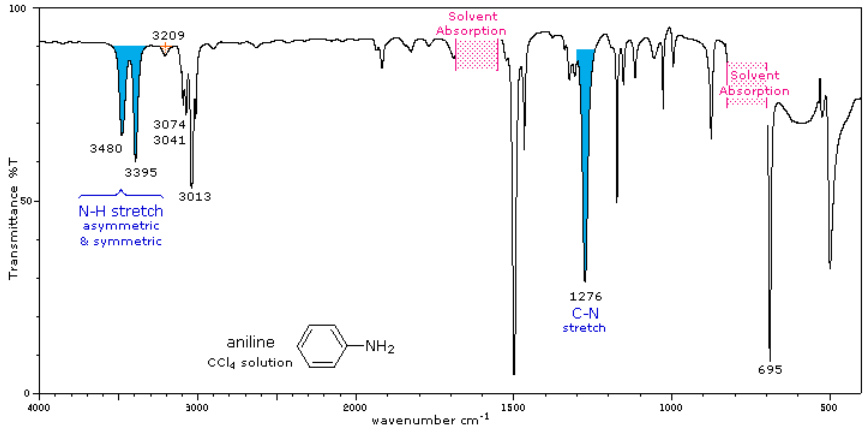
IR

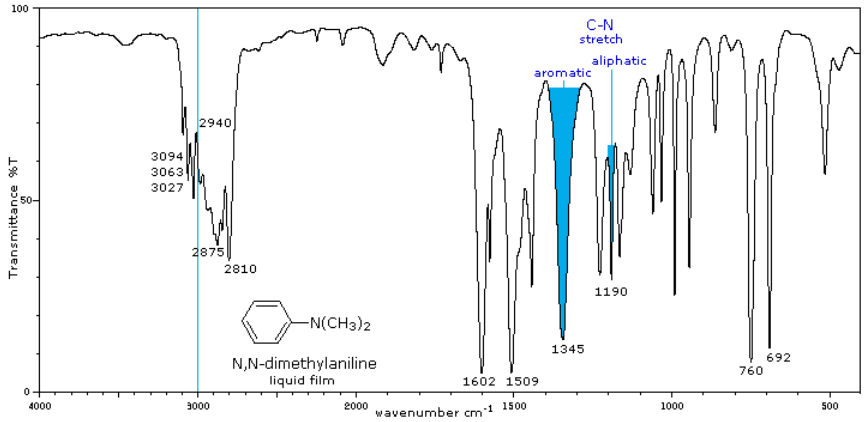
The infrared spectrum of aniline is shown beneath the following table. Some of the characteristic absorptions for C-H stretching and aromatic ring substitution are also marked, but not colored.

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.







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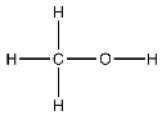
Mass Spectrometry and the Nitrogen Rule

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.

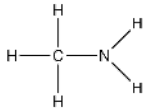
eg. 1:



molecular formula = CH_4O
nominal mass = (1x12) + (4x1) + (1x16)
= 32

N atoms = 0
nominal mass = 32 (even #)

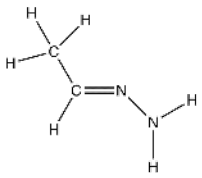
eg. 2:



molecular formula = CH_5N
nominal mass = (1x12) + (5x1) + (1x14)
= 31

N atoms = 1 (odd #)
nominal mass = 31 (odd #)

eg. 3:



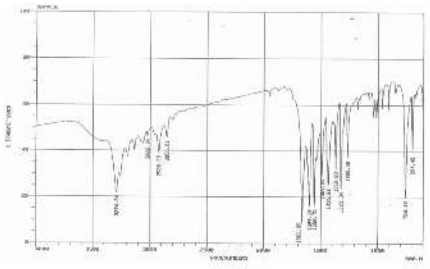
molecular formula = $C_2H_6N_2$
nominal mass = (2x12) + (6x1) + (2x14)
= 58

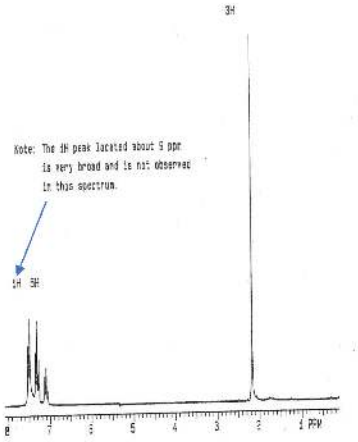
N atoms = 2 (even #)
nominal mass = 58 (even #)

Exercise

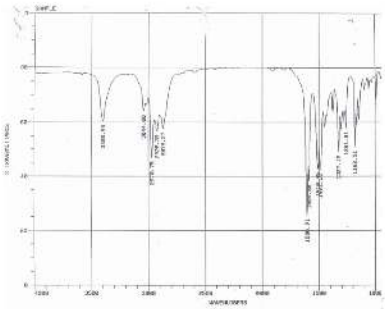
7. Oh no! The labels have fallen off two samples: Q and R. The elemental analysis for the samples indicated the following composition: compound Q is 81.15% C, 8.34% H, and 10.52% O and compound R is 71.08% C, 6.72% H, 10.36% N, and 11.84% O. Fortunately, we can analyze the samples using IR and ^{1}H NMR spectroscopy. Name and draw the bond-line structures for compounds Q and R using the information provided. Support your answer by correlating the spectral data to the compound structures.

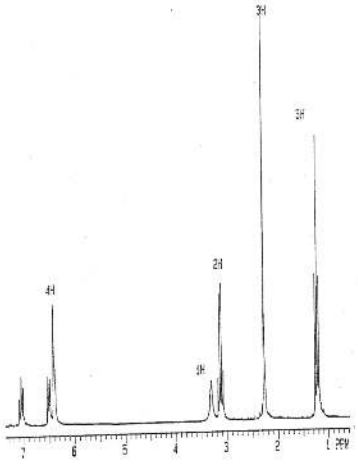
Vial 1





Vial 2





Answer

7. Vial 1 contains compound R which is acetanilide. Vial 2 contains compound Q which is N-ethyl-3-methylaniline.

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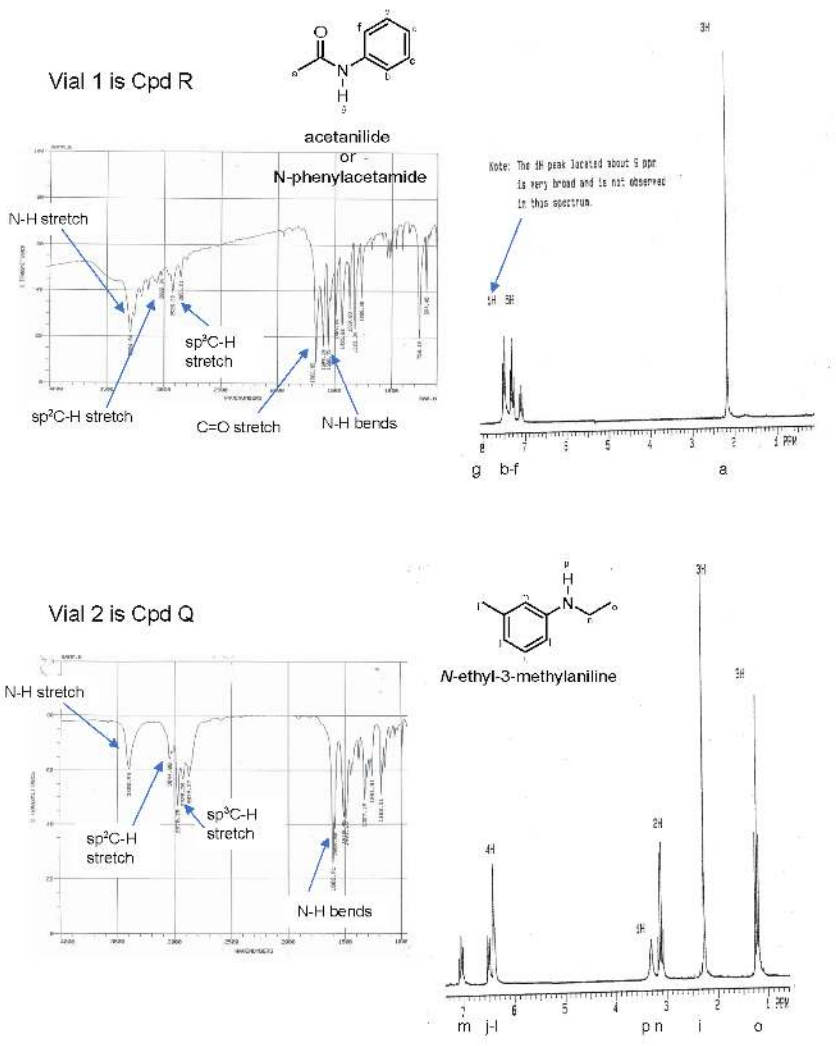

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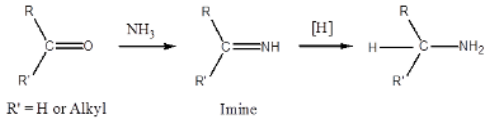
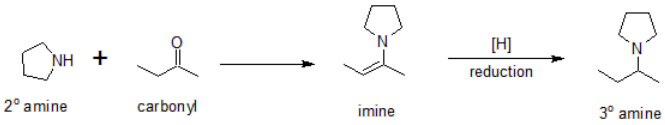
22.4: Synthesis of Amines

Reductive Amination of Aldehydes and Ketones (Carbonyls)

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 the carbonyl group to form an imine. The second step is the reduction of the imine to an amine using an reducing agent. A reducing agent commonly used for this reaction is sodium cyanoborohydride ($NaBH_3CN$).

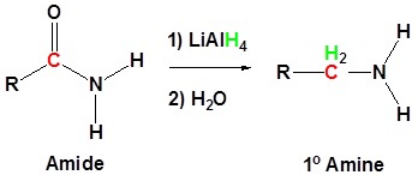


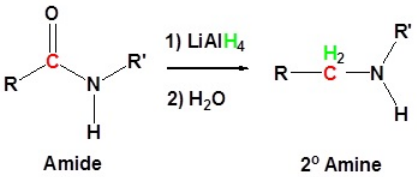
The nitrogen gains a bond to carbon during this reaction sequence. When carbonyls react with ammonia, a primary amine is produced. The reaction pattern continues for each amine classification. For example, pyrrolidine reacts with 2-butanone to produce the imine, which can be reduced by $LiAlH_4$, sodium cyanoborohydride ($NaBH_3CN$), or H_2 with an active metal catalyst to produce a tertiary amine.

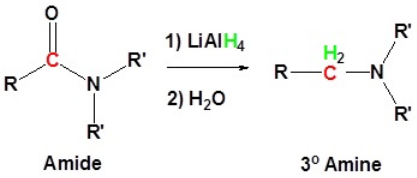


Amide Reduction to 1°, 2° or 3° Amines using $LiAlH_4$

There is a direct correlation between the structure of the amide and the structure of the amine produced. Primary amides are reduced to primary amines. Secondary amides are reduced to secondary amines. Tertiary amides are reduced to tertiary amines. Lithium aluminum hydride is a stronger reducing agent than sodium borohydride, which is not strong enough for this reaction.

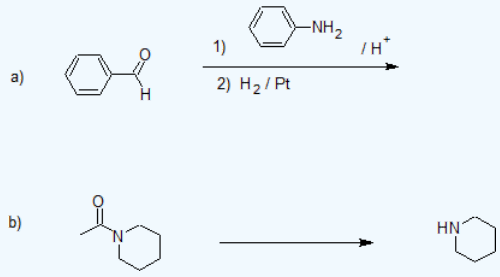






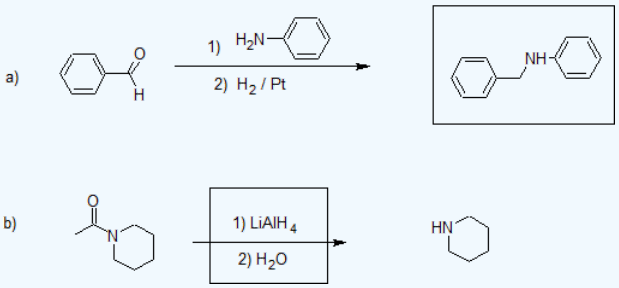
Exercise

8. Add the missing reactants/products to the following reactions.



Answer

8.



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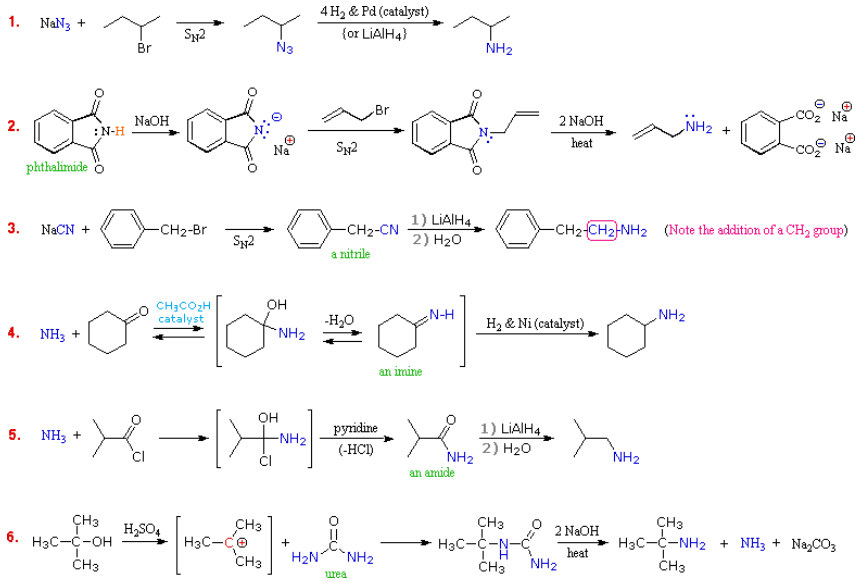
22.5: Synthesis of Primary Amines

Preparation of Primary Amines

Although direct alkylation of ammonia by alkyl halides leads to 1°-amines, alternative procedures are preferred in many cases. These methods require two steps, but they provide pure product, usually in good yield. The general strategy is to first form a carbon-nitrogen bond by reacting a nitrogen nucleophile with a carbon electrophile. The following table lists several general examples of this strategy in the rough order of decreasing nucleophilicity of the nitrogen reagent. In the second step, extraneous nitrogen substituents that may have facilitated this bonding are removed to give the amine product.

Nitrogen Reactant	Carbon Reactant	1st Reaction Type	Initial Product	2nd Reaction Conditions	2nd Reaction Type	Final Product
$N_3^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-N_3 or R_2CH-N_3	$LiAlH_4$ or 4 H_2 & Pd	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$C_6H_5C_2O_2NH$ / OH^-	RCH_2-X or R_2CH-X	S_N2	RCH_2-$NC_2O_2C_6H_5$ or R_2CH-$NC_2O_2C_6H_5$	NaOH / heat	Hydrogenolysis	RCH_2-NH_2 or R_2CH-NH_2
$CN^{(-)}$	RCH_2-X or R_2CH-X	S_N2	RCH_2-CN or R_2CH-CN	$LiAlH_4$	Reduction	RCH_2-CH_2NH_2 or R_2CH-CH_2NH_2
NH_3	RCH=O or R_2C=O	Addition / Elimination	RCH=NH or R_2C=NH	H_2 & Ni or $NaBH_3CN$	Reduction	RCH_2-NH_2 or R_2CH-NH_2
NH_3	RCOX	Addition / Elimination	RCO-NH_2	$LiAlH_4$	Reduction	RCH_2-NH_2
NH_2CONH_2 (urea)	$R_3C^{(+)}$	S_N1	R_3C-$NHCONH_2$	NaOH soln.	Hydrolysis	R_3C-NH_2

A specific example of each general class is provided in the diagram below. In the first two, an anionic nitrogen species undergoes an S_N2 reaction with a modestly electrophilic alkyl halide reactant. For example #2, the Gabriel synthesis is shown. The alkaline conditions deprotonate phthalmide to create a strong nucleophile for S_N2 reactions with alkyl halides. Example #3 also starts with an S_N2 reaction of cyanide with an alkyl halide following by reduction of the cyano group to form a primary amine that extends the carbon system of the alkyl halide by a methylene group (CH_2). In all three of these methods 3°-alkyl halides cannot be used because the major reaction path is an E2 elimination.

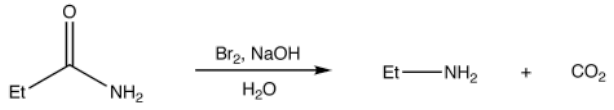


The methods illustrated by examples #4 and #5 proceed by the reaction of ammonia, or equivalent nitrogen nucleophiles, with the electrophilic carbon of a carbonyl group. A full discussion of carbonyl chemistry is presented in an independent chapter, but for present purposes it is sufficient to recognize that the C=O double bond is polarized so that the carbon atom is electrophilic. Nucleophilic addition to aldehydes and ketones is often catalyzed by acids. Acid halides and anhydrides are even more electrophilic, and do not normally require catalysts to react with nucleophiles. The reaction of ammonia with aldehydes or ketones occurs by a reversible addition-elimination pathway to give **imines** (compounds having a C=N function). These intermediates are not usually isolated, but are reduced as they are formed (i.e. *in situ*). Acid chlorides react with ammonia to give amides, also by an addition-elimination path, and these are reduced to amines by $LiAlH_4$.

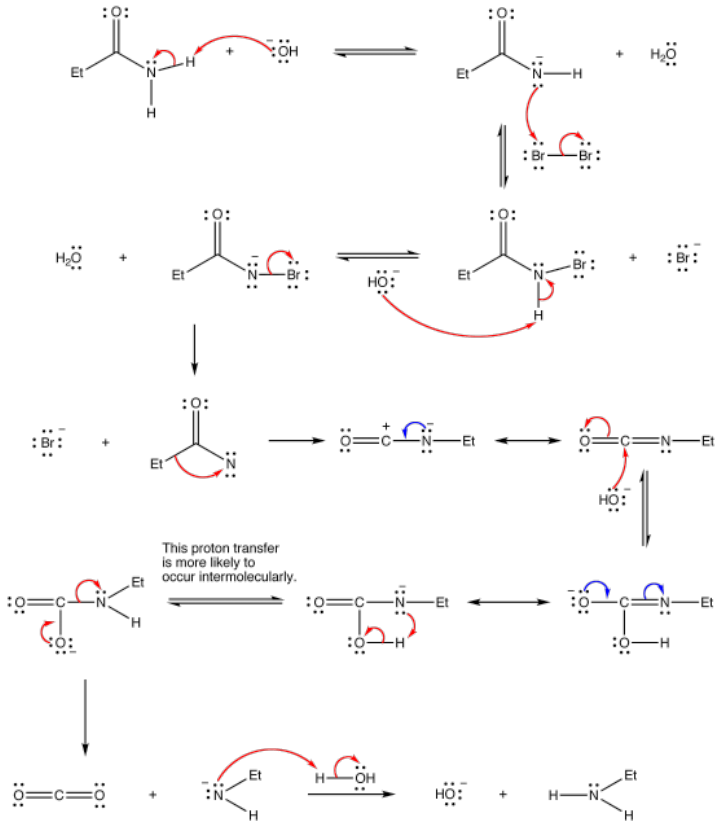
The 6th example is a specialized procedure for bonding an amino group to a 3º-alkyl group (none of the previous methods accomplishes this). Since a carbocation is the electrophilic species, rather poorly nucleophilic nitrogen reactants can be used. Urea, the diamide of carbonic acid, fits this requirement nicely. The resulting 3º-alkyl-substituted urea is then hydrolyzed to give the amine. One important method of preparing 1º-amines, especially aryl amines, uses a reverse strategy. Here a strongly electrophilic nitrogen species ($NO_2^{(+)}$) bonds to a nucleophilic carbon compound. This nitration reaction gives a nitro group that can be reduced to a 1º-amine by any of several reduction procedures.

Hofmann rearrangement

Hofmann rearrangement, also known as Hofmann degradation and not to be confused with Hofmann elimination, is the reaction of a primary amide with a halogen (chlorine or bromine) in strongly basic (sodium or potassium hydroxide) aqueous medium, which converts the amide to a primary amine. For example:

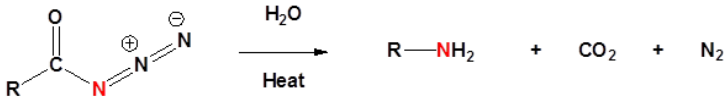


Mechanism:

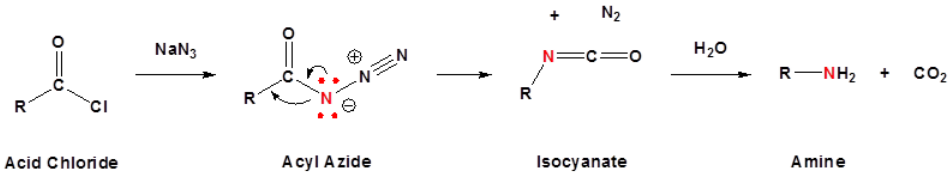


Curtius Rearrangement

The Curtius rearrangement involves an acyl azide.



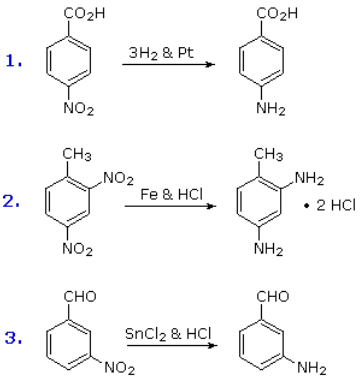
The mechanism of the Curtius rearrangement involves the migration of an -R group form the carbonyl carbon to the the neighboring nitrogen.



Reduction of Nitro Groups

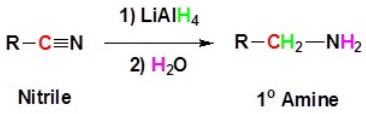
Several methods for reducing nitro groups to amines are known. These include catalytic hydrogenation (H_2 + catalyst), zinc or tin in dilute mineral acid, and sodium sulfide in ammonium hydroxide solution. The procedures described above are sufficient for most case

Nitro Group Reduction



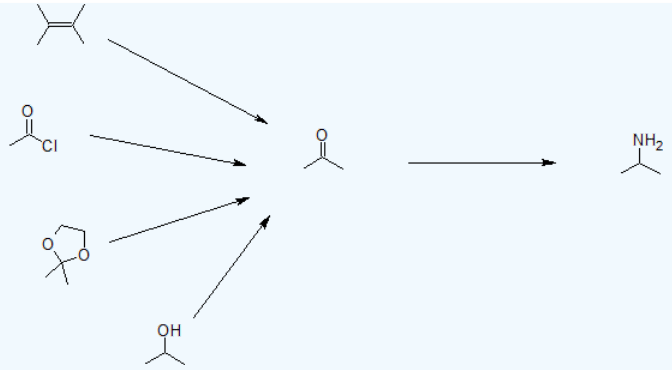
Reduction of Nitriles

Nitriles can be converted to primary amines by reaction with lithium aluminum hydride. During this reaction the hydride nucleophile reacts with the electrophilic carbon in the nitrile to form an imine anion. Once stabilized by a Lewis acid-base complexation the imine salt can accept a second hydride to form a dianion. The dianion can then be converted to an amine by addition of water.



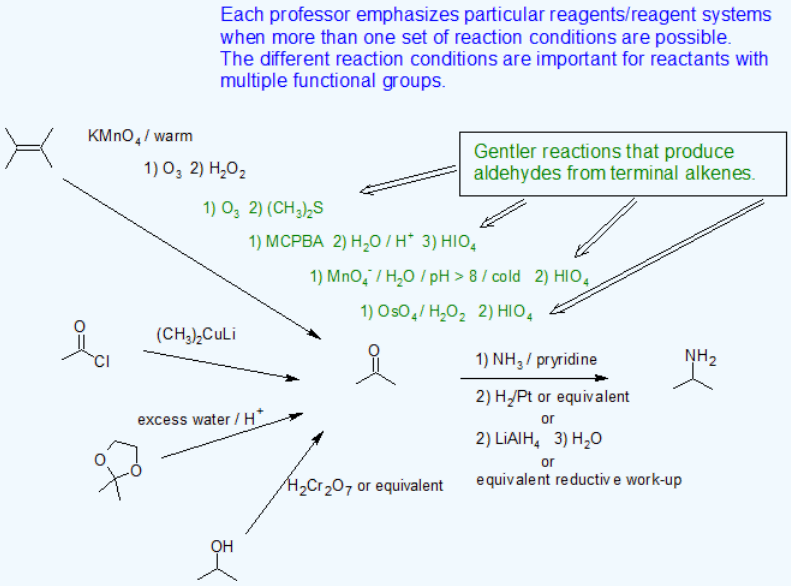
Exercise

9. Complete the reaction map below to build reaction patterns for multiple step synthesis.



Answer

9.



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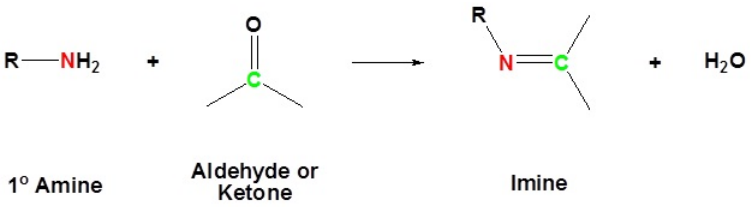
22.6: Reactions of Amines

Amines as Nucleophiles

Amines 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. While we will see another section that it is possible to coax the amine to serve as a leaving group. As weak bases, amines are good nucleophiles.

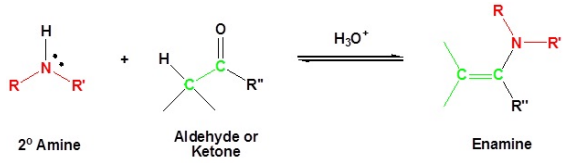
Amines and Carbonyls

The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases (compounds having a C=N function). Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation. 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.

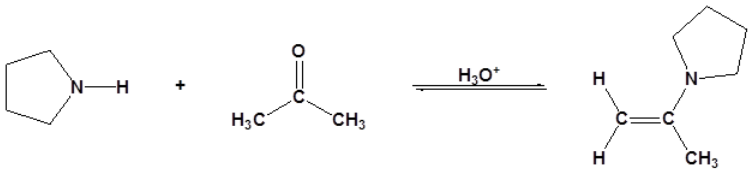


Imine formation is reversible. Imines can be hydrolyzed back to the corresponding primary amine under acidic aqueous conditions.

Most aldehydes and ketones react with 2º-amines to give products known as **enamines**.

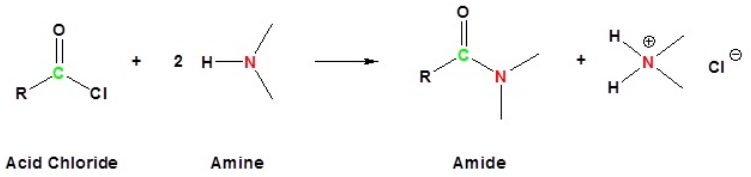


It should be noted that, like acetal and imine formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis.

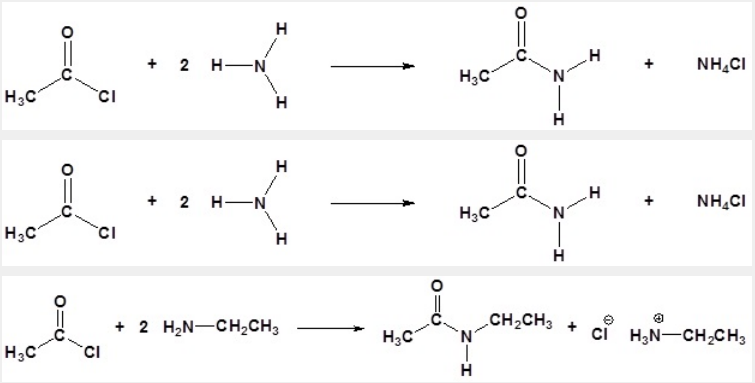


Amines and Acid Chlorides

Acid chlorides react with ammonia, 1º amines and 2º amines to form amides.

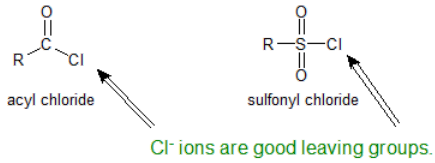


Examples:

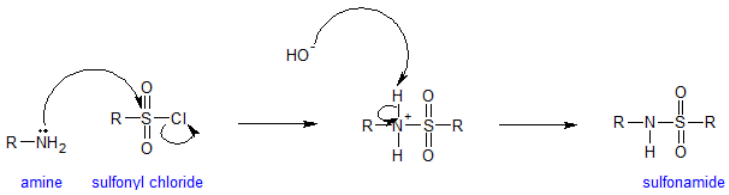


Amines and Sulfonyl Chloride

The sulfonyl group is the sulfur-analog to the carbonyl group. Both groups contain an electrophilic carbonyl carbon with chloride as an excellent leaving group. Because sulfur is a third shell element it can form "expanded octets".



Amines react with sulfonyl groups to form sulfonamides. Sulfonamides are used as antimicrobial agents therapeutically and called sulfa drugs. The reaction to form sulfonamides occurs under alkaline conditions to keep the amine nucleophilic. Any time amines are present in an aqueous solution, measurable hydroxide is present. The mechanism for the sulfonation reaction is analogous to the acylation mechanism as is shown below.



The end of this chapter includes some additional information on sulfonamides.

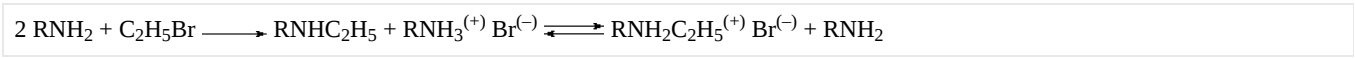
Alkylations

It is instructive to examine nitrogen substitution reactions using common alkyl halides as the electrophiles. Thus, reaction of a primary alkyl bromide with a large excess of ammonia yields the corresponding 1º-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 1º-alkyl halides to give alcohols, so the enhanced nucleophilicity of nitrogen relative to oxygen is clearly demonstrated.

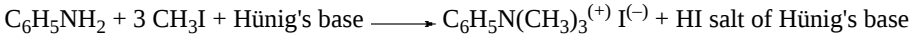
$$2\ RCH_2Br + NH_3\ (\text{large excess}) \longrightarrow RCH_2NH_2 + NH_4^{(+)}\ Br^{(-)}$$

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 co-product, hydrobromide salts of the alkylated amine or unreacted starting amine (in equilibrium) will also be formed.



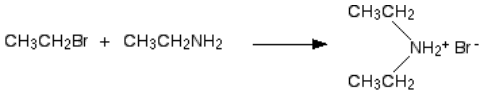
Unfortunately, the direct alkylation of 1º or 2º-amines to give a more substituted product does not proceed cleanly. If a 1:1 ratio of amine to alkyl halide is used, only 50% of the amine will react because the remaining amine will be tied up as an ammonium halide salt (remember that one equivalent of 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 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.



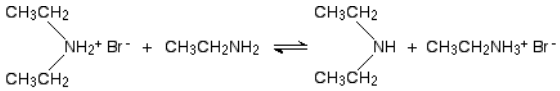
You get a complicated series of reactions on heating primary amines with halogenoalkanes to give a mixture of products - probably one of the most confusing sets of reactions you will meet at this level. The products of the reactions include secondary and tertiary amines and their salts, and quaternary ammonium salts.

Making secondary amines and their salts

In the first stage of the reaction, you get the salt of a secondary amine formed. For example if you started with ethylamine and bromoethane, you would get diethylammonium bromide



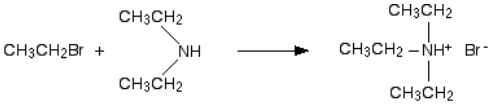
In the presence of excess ethylamine in the mixture, there is the possibility of a reversible reaction. The ethylamine removes a hydrogen from the diethylammonium ion to give free diethylamine - a secondary amine.



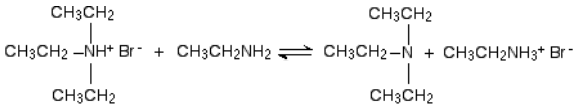
Making tertiary amines and their salts

But it doesn't stop here! The diethylamine also reacts with bromoethane - in the same two stages as before. This is where the reaction would start if you reacted a secondary amine with a halogenoalkane.

In the first stage, you get triethylammonium bromide.



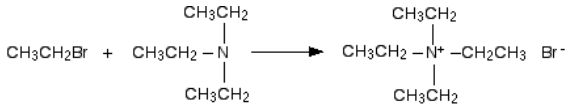
There is again the possibility of a reversible reaction between this salt and excess ethylamine in the mixture.



The ethylamine removes a hydrogen ion from the triethylammonium ion to leave a tertiary amine - triethylamine.

Making a quaternary ammonium salt

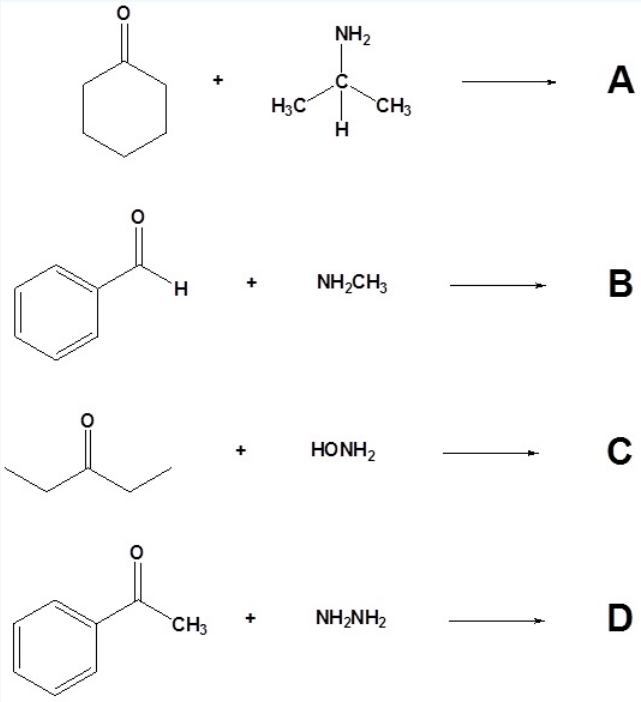
The final stage! The triethylamine reacts with bromoethane to give tetraethylammonium bromide - a quaternary ammonium salt (one in which all four hydrogens have been replaced by alkyl groups).



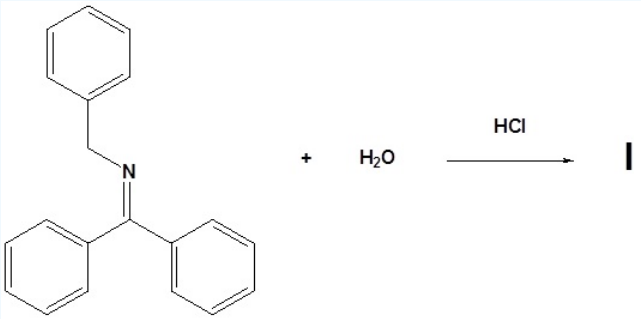
This time there isn't any hydrogen left on the nitrogen to be removed. The reaction stops here.

Exercise

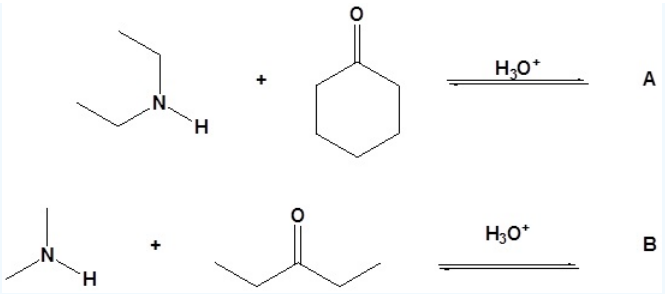
10. Draw the products of the following reactions.



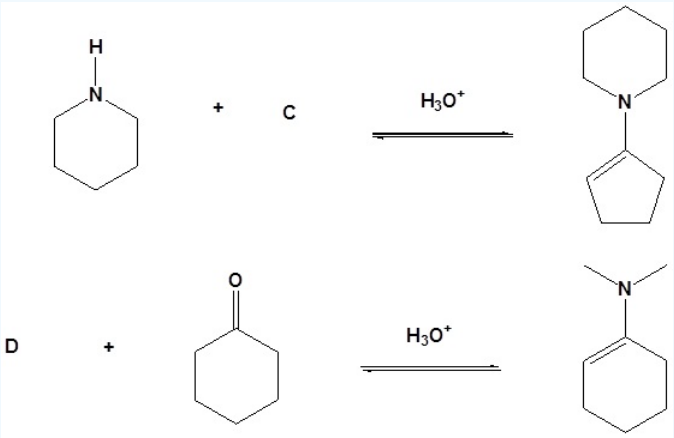
11. Draw the structure of the reactant needed to produce the indicated product.



12. Draw the products for the following reactions.



13. Draw the missing reactant to complete each reaction below.



Answer

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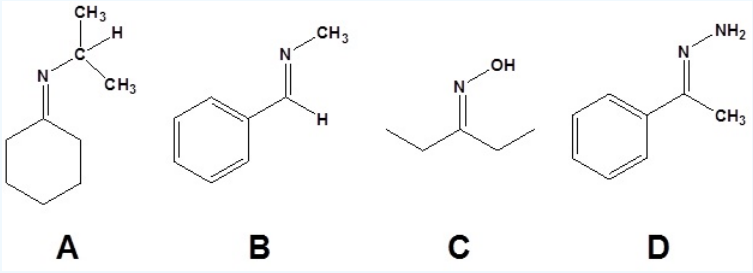

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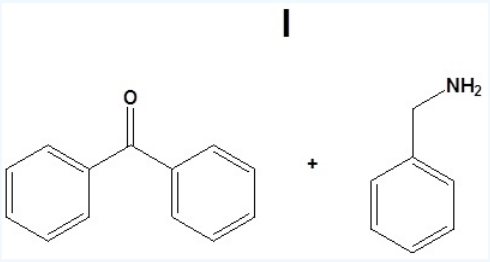

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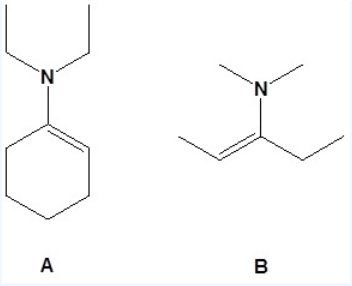

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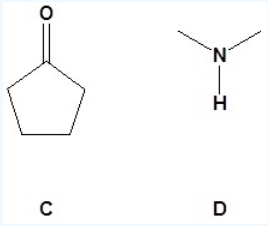

Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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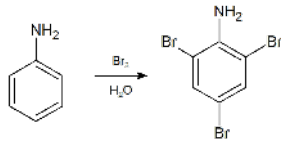
22.7: Reactions of Arylamines

Overreaction of Aniline

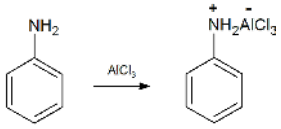
Arylamines are very reactive towards electrophilic aromomatic substitution. The strongest activating and ortho/para-directing substituents are the amino (-NH_2) and hydroxyl (-OH) groups. Direct nitration of phenol (hydroxybenzene) by dilute nitric acid gives modest yields of nitrated phenols and considerable 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.

$C_6H_5–NH_2 + I_2 + NaHCO_3$		⟶	p-I–$C_6H_4–NH_2 + NaI + CO_2 + H_2O$

In addition to overreactivity, we have previously seen that Friedel-Crafts reactions employing $AlCl_3$ catalyst do not work with aniline. A salt complex forms and prevents electrophilic aromatic substitution.



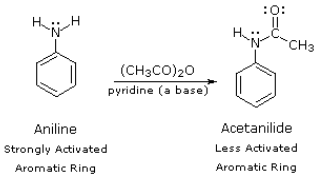
Both this problem and the aniline overreactivity can be circumvented by first going through the corresponding amide.

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.

$C_6H_5–NH_2 + (CH_3CO)_2O$	pyridine (a base) ⟶	$C_6H_5–NHCOCH_3$	HNO_3 , 5 ºC ⟶	p-$O_2N–C_6H_4–NHCOCH_3$	$H_3O^{(+)}$ & heat ⟶	p-$O_2N–C_6H_4–NH$

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.



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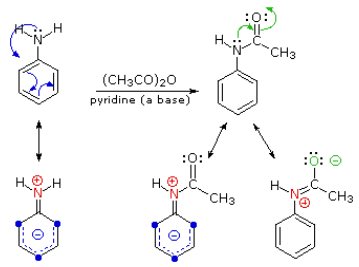
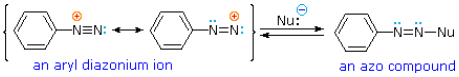


Diazonium Ions and their Salts

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.

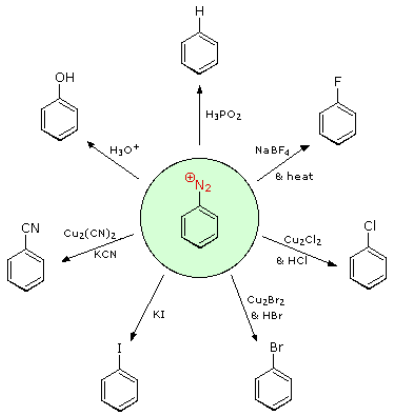
$C_6H_5N_2^{(+)}$ $HSO_4^{(-)}$ + NaOH (cold solution)		$C_6H_5N_2$–OH + NaOH (cold)	⟷	$C_6H_5N_2$–$O^{(-)}$ $Na^{(+)}$
phenyldiazonium bisulfate		phenyldiazoic acid		sodium phenyldiazoate

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.

$NaHSO_3$ $Ar\text{-}N_2^{(+)}$ $X^{(-)}$	Ar-N=N-SO_3H	$NaHSO_3$ ⟶	Ar-NH-NH-SO_3H	H_2O ⟶	A

Diazonium Salts: The Sandmeyer Reactions

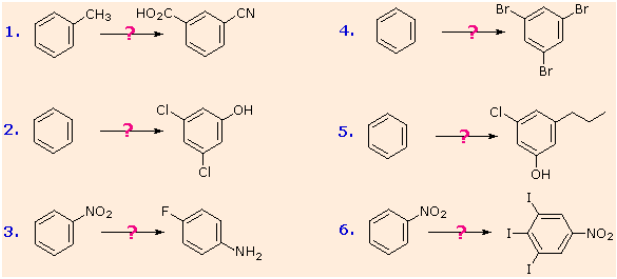
Aryl diazonium salts are important intermediates. They are prepared in cold (0 º to 10 ºC) aqueous solution, and generally react with nucleophiles with loss of nitrogen. Some of the more commonly used substitution reactions are shown in the following diagram. Since the leaving group (N_2) is thermodynamically 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:

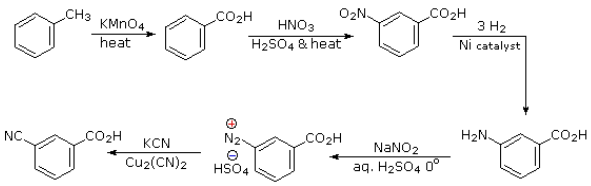
I. The usual precursor to an aryl amine is the corresponding nitro compound. A nitro substituent deactivates an aromatic ring and directs electrophilic substitution to meta locations.
II. Reduction of a nitro group to an amine may be achieved in several ways. The resulting amine substituent strongly 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.



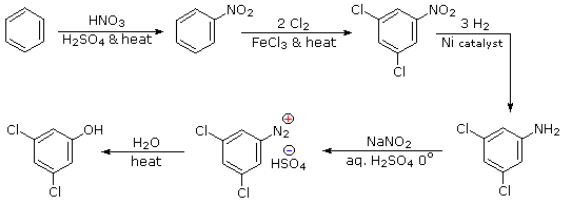
Answer 1:

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:

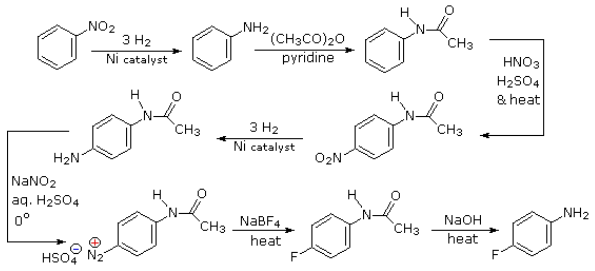
The hydroxyl group is a strong activating substituent and would direct aromatic ring chlorination to locations ortho & para to itself, leading to the wrong product. As an alternative, the nitro group is not only meta-directing, it can be converted to a hydroxyl group by way of a diazonium intermediate. The resulting strategy is self evident.



Answer 3:

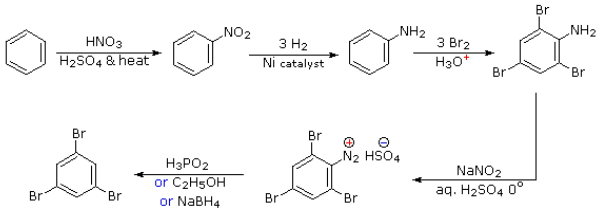
Selective introduction of a fluorine is best achieved by treating a diazonium intermediate with boron tetrafluoride anion. To get the necessary intermediate we need to make p-nitroaniline. Since the nitro substituent on the starting material would direct a new substituent to a meta-location, we must 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.



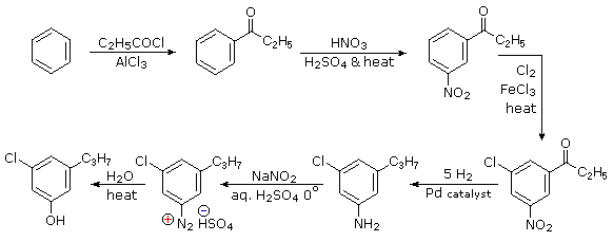
Answer 4:

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).



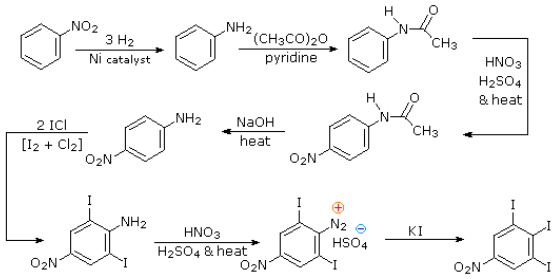
Answer 5:

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.



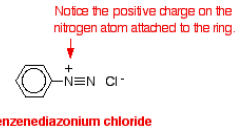
Answer 6:

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.



Substitution reactions of diazonium ions

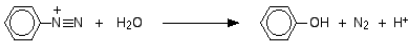
Diazonium ions are present in solutions such as benzenediazonium chloride solution. They contain an $-N_2^+$ group. In the case of benzenediazonium chloride, this is attached to a benzene ring. Benzenediazonium chloride looks like this:



In this set of reactions of the diazonium ion, the $-N_2^+$ group is replaced by something else. The nitrogen is released as nitrogen gas.

Substitution by an -OH group

To get this reaction, all you need to do is warm the benzenediazonium chloride solution. The diazonium ion reacts with the water in the solution and phenol is formed - either in solution or as a black oily liquid (depending on how much is formed). Nitrogen gas is evolved.

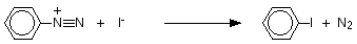


This is the same reaction that you get if you react phenylamine with nitrous acid in the warm. The diazonium ion is formed first and then immediately reacts with the water in the solution to give phenol.

Substitution by an iodine atom

This is a good example of the use of diazonium salts to substitute things into a benzene ring which are otherwise quite difficult to attach. (That's equally true of the previous reaction, by the way.) If you add potassium iodide solution to the benzenediazonium chloride solution in the cold, nitrogen gas is given off, and you get oily droplets of iodobenzene formed.

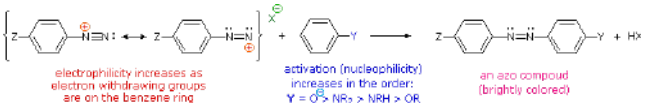
There is a simple reaction between the diazonium ions and the iodide ions from the potassium iodide solution.



Coupling reactions of diazonium ions

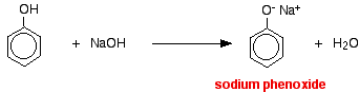
In the substitution reactions above, the nitrogen in the diazonium ion is lost. In the rest of the reactions on this page, the nitrogen is retained and used to make a bridge between two benzene rings.

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.

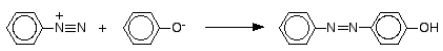


The reaction with phenol

Phenol is dissolved in sodium hydroxide solution to give a solution of sodium phenoxide.



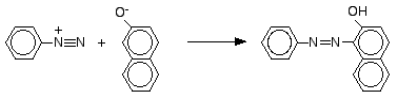
The solution is cooled in ice, and cold benzenediazonium chloride solution is added. There is a reaction between the diazonium ion and the phenoxide ion and a yellow-orange solution or precipitate is formed. The product is one of the simplest of what are known as azo compounds, in which two benzene rings are linked by a nitrogen bridge.



The reaction with naphthalen-2-ol

Naphthalen-2-ol is also known as 2-naphthol or beta-naphthol. It contains an -OH group attached to a naphthalene molecule rather than to a simple benzene ring. Naphthalene has two benzene rings fused together. The reaction is done under exactly the same conditions as with phenol. The naphthalen-2-ol is dissolved in sodium hydroxide solution to produce an ion just like the phenol one. This solution is cooled and mixed with the benzenediazonium chloride solution.

An intense orange-red precipitate is formed - another azo compound.



The reaction with phenylamine (aniline)

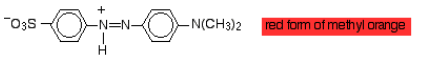
Some liquid phenylamine is added to a cold solution of benzenediazonium chloride, and the mixture is shaken vigorously. A yellow solid is produced.

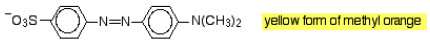
These strongly coloured azo compounds are frequently used as dyes known as azo dyes. The one made from phenylamine (aniline) is known as "aniline yellow" (amongst many other things - see note above). Azo compounds account for more than half of modern dyes.

The use of an azo dye as an indicator - methyl orange

Azo compounds contain a highly delocalized system of electrons which takes in both benzene rings and the two nitrogen atoms bridging the rings. The delocalization can also extend to things attached to the benzene rings as well. If white light falls on one of these molecules, some wavelengths are absorbed by these delocalized electrons. The colour you see is the result of the non-absorbed wavelengths. The groups which contribute to the delocalization (and so to the absorption of light) are known as a chromophore.

Modifying the groups present in the molecule can have an effect on the light absorbed, and so on the color you see. You can take advantage of this in indicators. Methyl orange is an azo dye which exists in two forms depending on the pH:





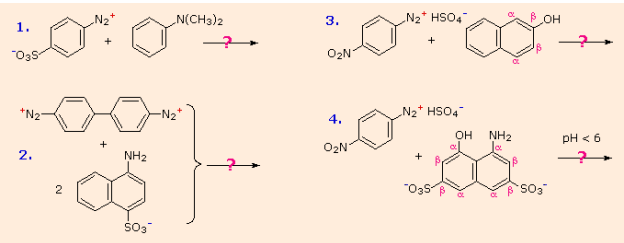
As the hydrogen ion is lost or gained there is a shift in the exact nature of the delocalisation in the molecule, and that causes a shift in the wavelength of light absorbed. Obviously that means that you see a different colour. When methyl orange is added, a hydrogen ion attaches to give the red form. Methyl orange is red in acidic solutions (in fact solutions of pH less than 3.1). If an alkali is added or hydrogen ions are removed, then the yellow form if generated. Methyl orange is yellow at pH's greater than 4.4.

In between, at some point there will be equal amounts of the red and yellow forms and so methyl orange looks orange.

Some examples of azo coupling reactions are shown below. A few simple rules are helpful in predicting the course of such reactions:

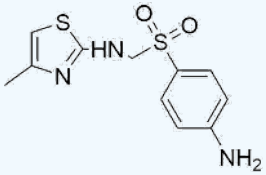
I. At acid pH (< 6) an amino group is a stronger activating substituent than a hydroxyl group (i.e. a phenol). At alkaline pH (> 7.5) phenolic functions are stronger activators, due to increased phenoxide base concentration.
II. Coupling to an activated benzene ring occurs preferentially para to the 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

14. Propose a synthesis for the following compound via benzene and any amine you may require.



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15. Proposes synthesis for each of the following compounds via benzene.

(a) *N*,*N*-Diethylaniline

(b) *p*-Bromoaniline

(c) *m*-Bromoaniline

(d) 2,4-Diethylaniline

16. 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

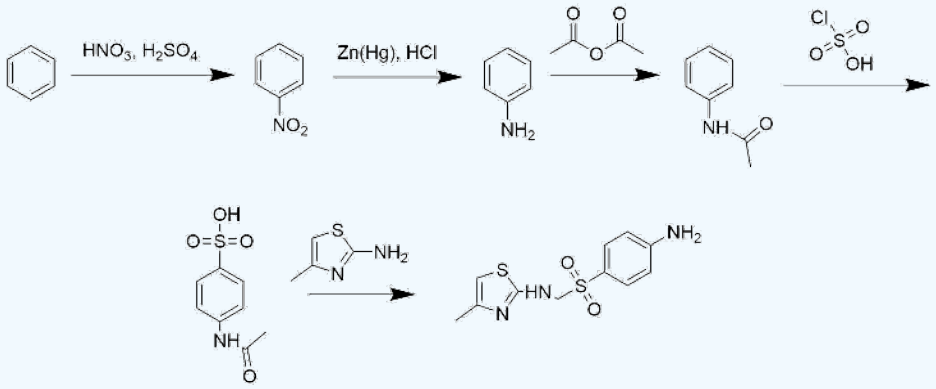
(d) *p*-Ethylbenzoic acid

(e) 1,2,4-Trichlorobenzene

Classify the following alcohols as primary, secondary, or tertiary.

Answer

14.



15.

(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

16.

(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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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Jim Clark (Chemguide.co.uk)

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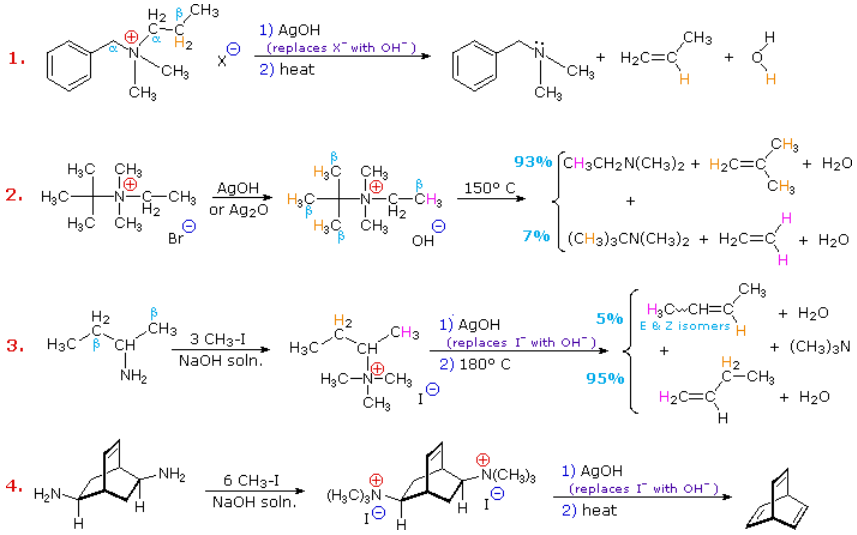
22.8: The Hofmann Elimination: Amines as Leaving Groups

Hofmann Elimination

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 effect the E2-like elimination of a 3º-amine. Example #1 below shows a typical Hofmann elimination. Obviously, for an elimination to occur one of the alkyl substituents on nitrogen must have one or more beta-hydrogens, as noted earlier in examining elimination reactions of alkyl halides.



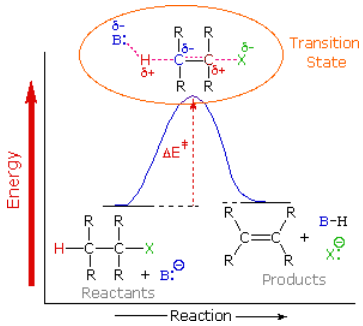
In example #2 above, two of the alkyl substituents on nitrogen have beta-hydrogens, all of which are on methyl groups (colored orange & magenta). The chief product from the elimination is the alkene having the more highly substituted double bond, reflecting not only the 3:1 numerical advantage of those beta-hydrogens, but also the greater stability of the double bond.

Example #3 illustrates two important features of the Hofmann elimination:

1. 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). Exhaustive methylation is shown again in example #4.
2. When a given alkyl group has two different sets of beta-hydrogens available to the elimination process (colored orange & magenta here), the major product is often the alkene isomer having the less substituted double bond.

The tendency of Hofmann eliminations to give the less-substituted double bond isomer is commonly referred to as the **Hofmann Rule**, and contrasts strikingly with the Zaitsev Rule formulated for dehydrohalogenations and dehydrations. In cases where other activating groups, such as phenyl or carbonyl, are present, the Hofmann Rule may not apply. Thus, if 2-amino-1-phenylpropane is treated in the manner of example #3, the product consists largely of 1-phenylpropene (E & Z-isomers).

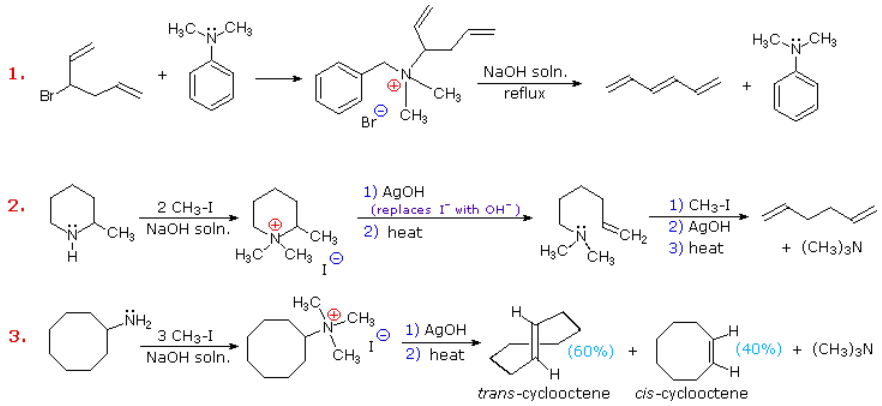
To understand why the base-induced elimination of 4º-ammonium salts behaves differently from that of alkyl halides it is necessary to reexamine the nature of the E2 transition state, first described for dehydrohalogenation. The energy diagram shown earlier for a single-step bimolecular E2 mechanism is repeated below.



The E2 transition state is less well defined than is that of S_N2 reactions. More bonds are being broken and formed, with the possibility of a continuum of states in which the extent of C–H and C–X bond-breaking and C=C bond-making varies. For example, if the bond to the leaving group (X) is substantially broken relative to the other bond changes, the transition state approaches that for an E1 reaction (initial ionization followed by a fast second step). At the other extreme, if the acidity of the beta-hydrogens is enhanced, then substantial breaking of C–H may occur before the other bonds begin to be affected. For most simple alkyl halides it was proper to envision a balanced transition state, in which there was a synchronous change in all the bonds. Such a model was consistent with the **Zaitsev Rule**.

When the leaving group X carries a positive charge, as do the 4º-ammonium compounds discussed here, the inductive influence of this charge will increase the acidity of both the alpha and the beta-hydrogens. Furthermore, the 4º-ammonium substituent is much larger than a halide or hydroxyl group and may perturb the conformations available to substituted beta-carbons. It seems that a combination of these factors acts to favor base attack at the least substituted (least hindered and most acidic) set of beta-hydrogens. The favored anti orientation of the leaving group and beta-hydrogen, noted for dehydrohalogenation, is found for many Hofmann eliminations; but syn-elimination is also common, possibly because the attraction of opposite charges orients the hydroxide base near the 4º-ammonium leaving group.

Three additional examples of the Hofmann elimination are shown in the following diagram. 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.



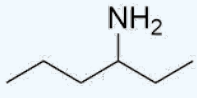
Example #2 illustrates an important aspect of the Hofmann elimination. If the nitrogen atom is part of a ring, then a single application of this elimination procedure does not remove the nitrogen as a separate 3º-amine product. In order to sever the nitrogen function from the molecule, a second Hofmann 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 sever the nitrogen from the remaining molecular framework.

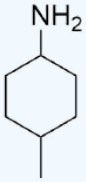
Example #3 is noteworthy because the less stable trans-cyclooctene is the chief product, accompanied by the cis-isomer. An anti-E2-transition state would necessarily give the cis-cycloalkene, so the trans-isomer must be generated by a syn-elimination. The cis-cyclooctene produced in this reaction could 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

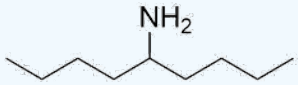
right. Some eclipsed bonds occur in all these conformers, and transannular hydrogen crowding is unavoidable. Since the trimethylammonium substituent is large (about the size of tert-butyl) it will probably assume an equatorial-like orientation to avoid steric crowding. An anti-E2 transition state is likely to require an axial-like orientation of this bulky group, making this an unfavorable path.

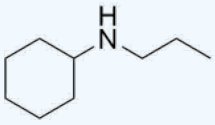
Exercise

17. Draw the product for a Hoffman elimination for each of the following molecules.

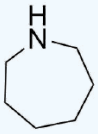
(a) 

(b) 

(c) 

(d) 

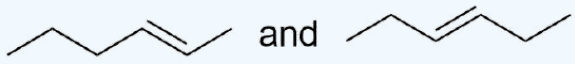
18. Draw the product of a Hoffman elimination for the following molecule.

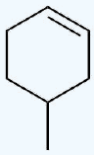


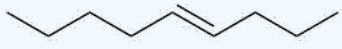
Solutions

Answer

17.

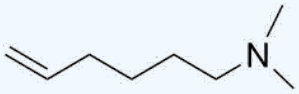
(a) 

(b) 

(c) 

(d)

18.



Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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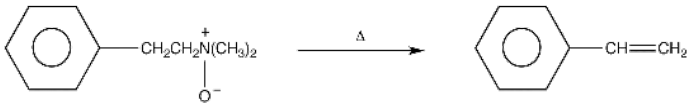
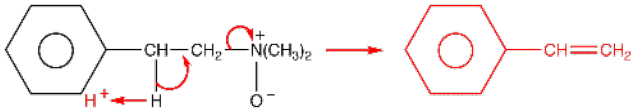
22.9: Oxidation of Amines - The Cope Elimination

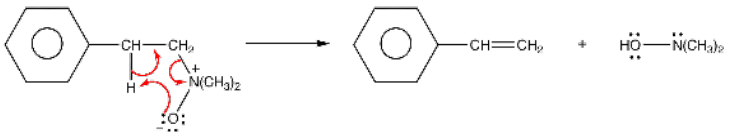
When a tertiary amine oxide bearing one or more beta hydrogens is heated, it is converted to an alkene. The reaction is known as *Cope elimination* or *Cope reaction*, not to be confused with Cope Rearrangement. For example:



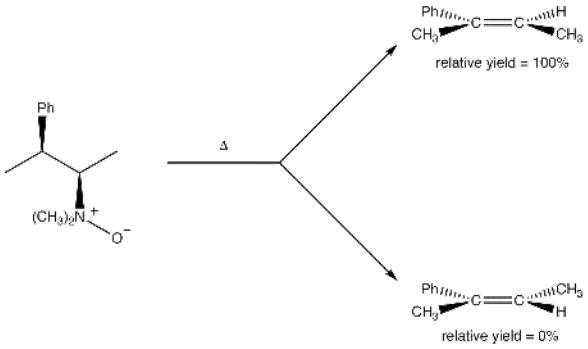
The net reaction is 1,2-elimination, hence the name Cope elimination.



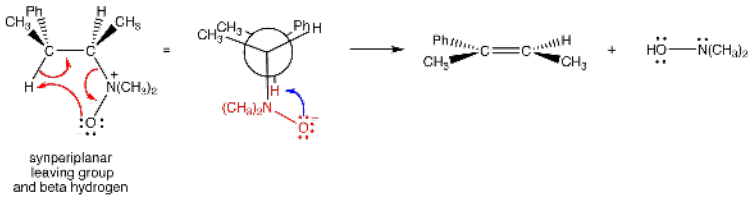
mechanism: Cope elimination is an intramolecular E2 reaction. It is also a pericyclic reaction.

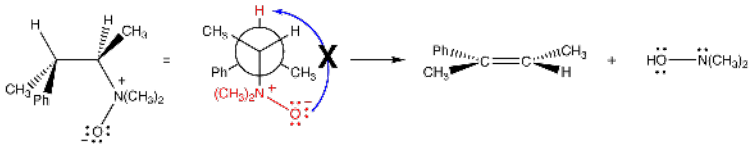


Intermolecular E2 reactions occur preferentially from the conformation of the substrate in which the leaving group and the beta hydrogen abstracted by the base are antiperiplanar, which is not possible in intramolecular E2 reactions in which the base is built into the leaving group because the basic atom is too far away from the beta hydrogen anti to the leaving group. Intramolecular E2 reactions occur preferentially from the conformation of the substrate in which the leaving group and the beta hydrogen abstracted by the base are synperiplanar. The basic atom and the beta hydrogen abstracted by it are closest to each other in this conformation. For example:

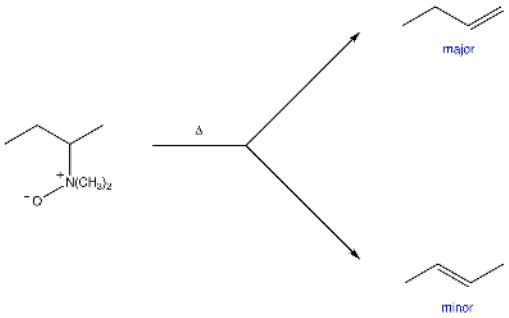


mechanism:





Cope elimination is regioselective. Unlike intermolecular E2 reactions, it does not follow Zaitsev's rule; the major product is always the least stable alkene, i.e., the alkene with the least highly substituted double bond. For example:



This trend is most likely due to the fact that the less highly substituted β-carbon bears more hydrogen atoms than the more highly substituted one; at a given moment, in a sample of the substrate, there are more molecules in which a hydrogen atom on the less highly substituted beta carbon is *synperiplanar* to the leaving group than there are in which a hydrogen atom on the more highly substituted beta carbon is.

Contributors and Attributions

- Gamini Gunawardena from the OChemPal site (Utah Valley University)

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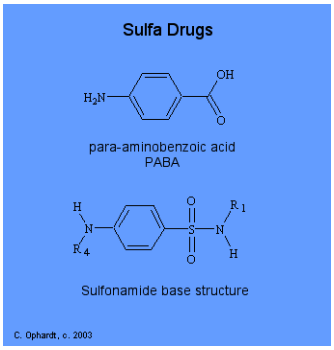
22.10: Sulfa Drugs - a closer look

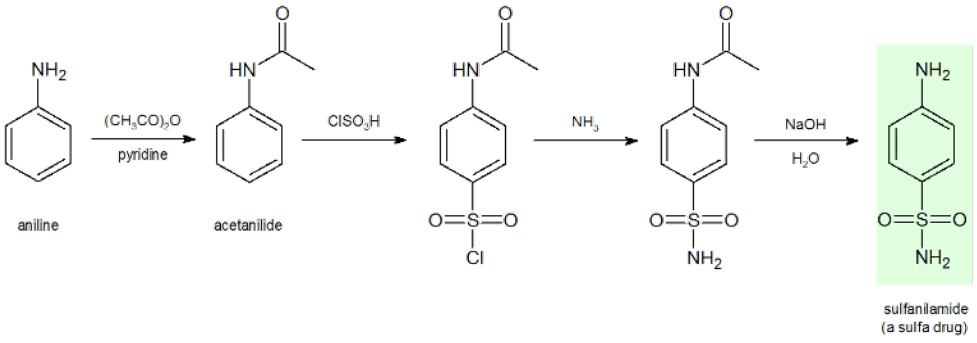
Sulfa Drug Synthesis

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.

Their use introduced and substantiated the concept of metabolic antagonism. Sulfonamides, as antimetabolites, compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides illustrates the principle of selective toxicity where some difference between mammal cells and bacterial cells is exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid. Sulfonamides or sulfa drugs have the following general structures as shown below.



Sulfanilamide which was the first compound used of this type has H's at R1 and R4. To date about 15,000 sulfonamide derivatives, analogues, and related compounds have been synthesized. This has lead to the discovery of many useful drugs which are effective for diuretics, antimalerial and leprosy agents, and antithyroid agents. The basic structure of sulfonamide cannot be modified if it is to be an effective competitive "mimic" for p-aminobenzoic acid. Essential structural features are the benzene ring with two substituents para to each other; an amino group in the fourth position; and the singly substituted 1-sulfonamido group.

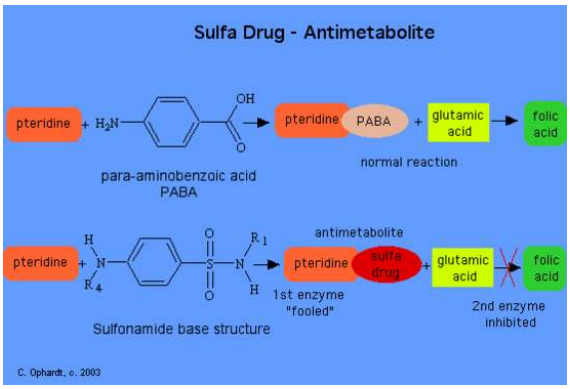


Mechanism for Action

Normally folic acid is synthesized in two steps in bacteria by the top reaction on the left. If A sulfa drug is used, the first enzyme is not to specific and can use the sulfonamide in the first reaction. This reaction produces the product containing pteridine and the sulfa drug. The next and final step is the reaction PABA + with glutamic acid to make folic acid. If the sulfa drug has been substituted for the PABA, then the final enzyme is inhibited and no folic acid is produced.

Recent studies indicate that substituents on the N(1) nitrogen may play the role of competing for a site on the enzyme surface reserved for the glutamate residue in p-aminobenzoic acid-glutamate through one of the following two ways:

1. Direct competition in the linking of PABA-glutamate with the pteridine derivative.
2. Indirect interference with the coupling of glutamate to dihydropteroic acid.



Questions

1. In your own words explain how the sulfa drug works including enzyme inhibition, folic acid, and antimetabolite.

Contributors and Attributions

Charles Ophardt (Professor Emeritus, Elmhurst College); Virtual Chembook

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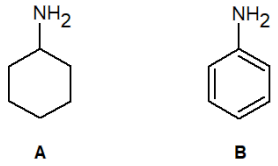
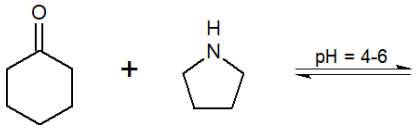
22.11: Additional Exercises

General Review

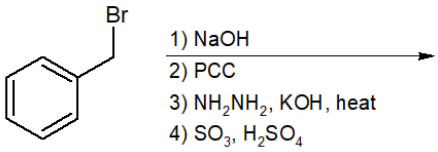
20-1 Predict which amine is more basic and provide a reason for your answer.



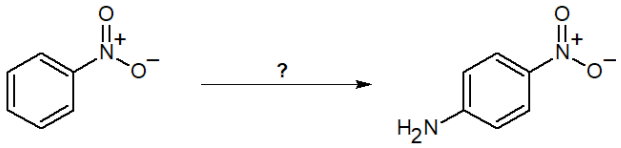
20-2 Give the product of the following reaction.



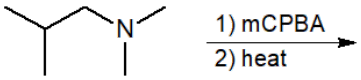
20-3 Predict the final product of the following reaction chain and give its IUPAC name.



20-4 Propose a route of synthesis from nitrobenzene to the given product. Assume the given molecule is the major product, and for the purposes of this problem, ignore its isomers.



20-5 Choose the correct answer that describes the product of the following Cope elimination reaction.



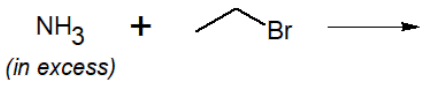
a) N,N,2-trimethylpropan-1-iminium

b) N,N,2-trimethylpropan-1-amine

c) 2-methylprop-1-ene and N-hydroxy-N-methylmethanamine

d) N-hydroxy-N,2-dimethylpropan-1-amine

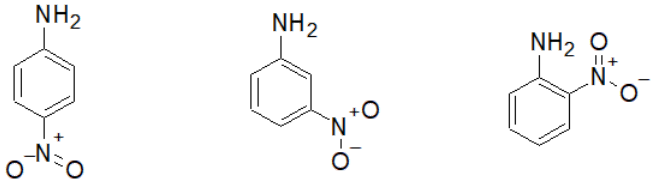
20-6 Explain why the following reaction might not be the best way to synthesize ethanamine.



Basicity and Effects of Amines

20-7 Draw all possible resonance structures for aniline and cyclohexanamine.

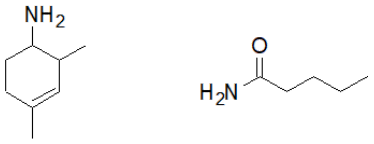
20-8 Identify which of the following nitroaniline isomers is the most basic and give a reason for your answer.



p-nitroaniline **m-nitroaniline** **o-nitroaniline**

20-9 For the following compounds, identify which substituents are pi-acceptors of the electrons from the amine group (if applicable) and if they are, draw their resonance structure to show the movement of electrons.

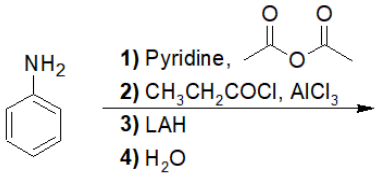
a) **b)**



c) **d)**

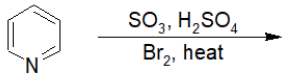
Aromatic Substitution of Arylamines and Pyridin

20-10 Explain why the following arylamine needs to be turned into an amide before a Friedel-Crafts acylation and then predict the final product of the reaction.

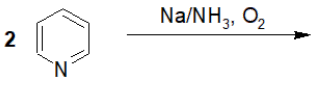


20-11 Predict the products of the following reactions.

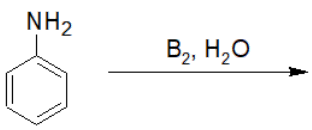
a)



b)

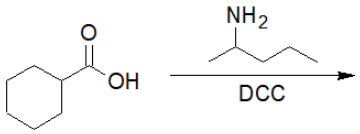


20-12 Predict the product of the following reaction and provide the correct IUPAC nomenclature.

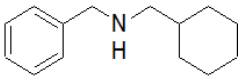


Alkylation and Acylation of Amines

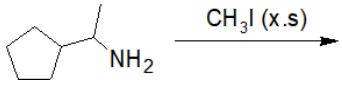
20-13 Predict the product of the following acylation reaction.



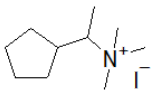
20-14 Suggest a route of synthesis for the following compound, starting with benzoyl chloride.



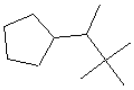
20-15 Choose the correct product of the following reaction.



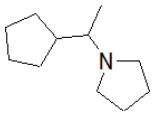
a)



b)

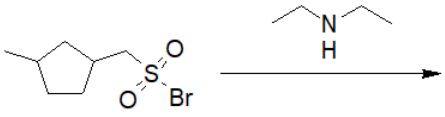


c)

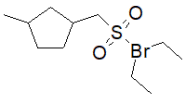


Formation of Sulfonamides

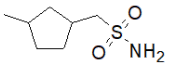
20-16 Choose the correct structure of the product of the following reaction.



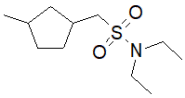
a)



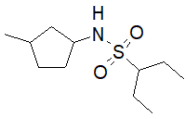
b)



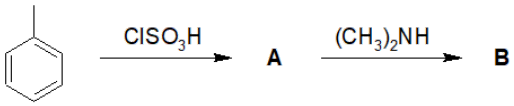
c)



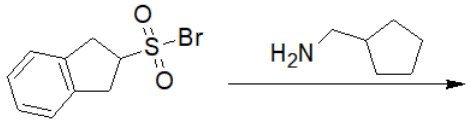
d)



20-17 Provide the structure of the intermediate compound and final product of the following reaction.

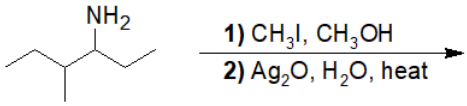


20-18 Predict the product of the following reaction.

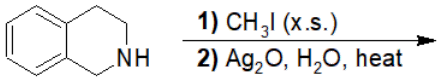


Amines as Leaving Groups: The Hofmann Elimination

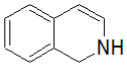
20-19 Predict the major alkene product of the following Hofmann elimination reaction and give the proper IUPAC nomenclature.



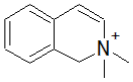
20-20 Choose the correct product of the following reaction.



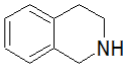
a)



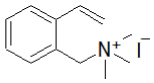
b)



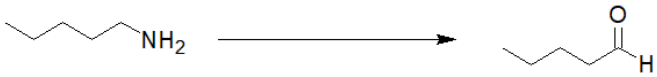
c)



d)

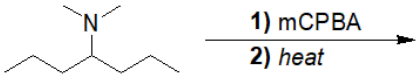


20-21 Propose a route of synthesis from pentan-1-amine to pentanal (include a Hofmann elimination reaction).

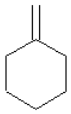


Oxidation of Amines: The Cope Elimination

20-22 Predict the structure and give the proper IUPAC nomenclature of the product of the following reaction.

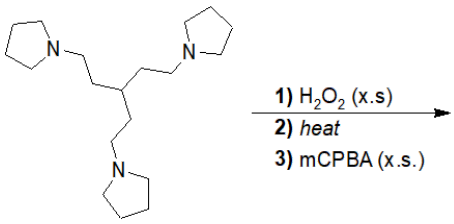


20-23 Propose a route of synthesis for the following compound, starting with cyclohexanecarboxylic acid and include a Cope elimination reaction.



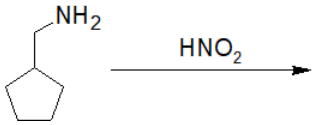
methylidenecyclohexane

20-24 Predict the structure of the product of the following reaction.



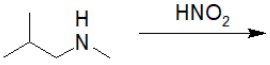
Reactions of Amines with Nitrous Acid

20-25 Predict the product of the following reaction and provide the correct IUPAC nomenclature.

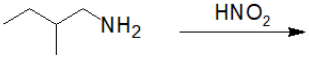


20-26 Predict the products of the following reactions.

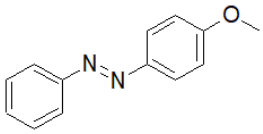
a)



b)



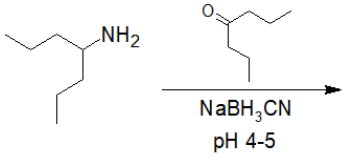
20-27 Suggest a route of synthesis for the following product, starting with aniline.



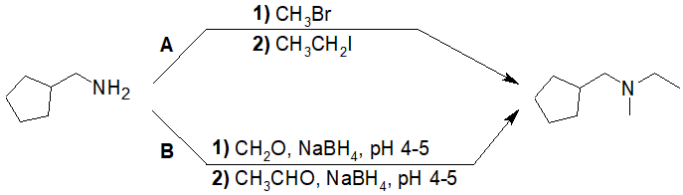
(*E*)-1-(4-methoxyphenyl)-2-phenyldiazene

Synthesis of Amines by Reductive Amination and Acylation-Reduction

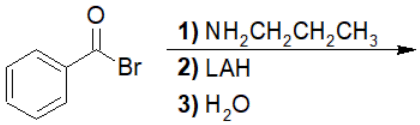
20-28 Predict the product of the following reaction and provide its IUPAC nomenclature.



20-29 Identify which route of synthesis is the better way to make N-(cyclopentylmethyl)- -N-methylethanamine and then show the intermediate molecules for the correct path.



20-30 Choose the correct IUPAC nomenclature of the product of the following reaction.



a) N-propylbenzamide

b) phenyl(propylamino)methanol

c) N-benzylpropan-1-amine

d) benzamide

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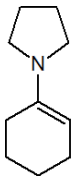
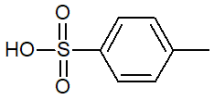
22.12: Solutions to Additional Exercises

20-1 Amine A is the more basic of the two amines. Since its lone pair of electrons cannot resonance into the ring like that of amine B, it is more basic. Amine B can delocalize its electrons, making it a weaker base but a stronger acid.

20-2

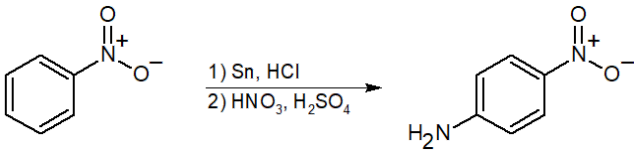


20-3



4-methylbenzene-1-sulfonic acid

20-4



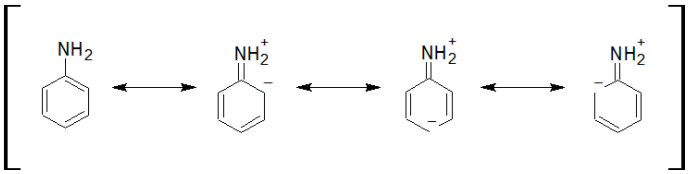
20-5 Answer: C

20-6 This reaction is not the best way to synthesize ethanamine because of the high ratio of mixed products obtained. Because the reaction occurs so fast, we are unable to stop the reaction at only the primary alkylation; the amine will continue on to make many secondary and tertiary amines in addition to our desired product.

Basicity and Effects of Amines

20-7:

Cyclohexanamine has no resonance structure that can contribute to delocalizing its lone pair of electrons.



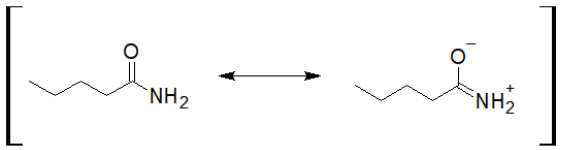
20-8:

Unlike on the para- and ortho-nitroaniline isomers, m-nitroaniline's nitro and amine groups cannot form any resonance structures to delocalize their pi-electrons with each other, making m-nitroaniline the most basic.

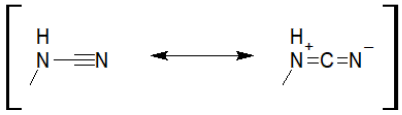
20-9:

a) and d) have no pi-acceptors directly attached to the amine.

b)



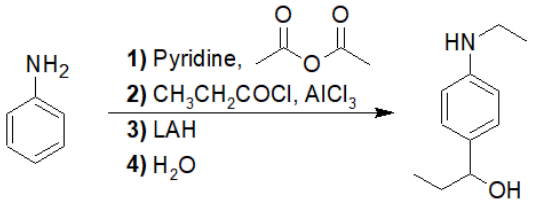
c)



Aromatic Substitution of Arylamines and Pyridine

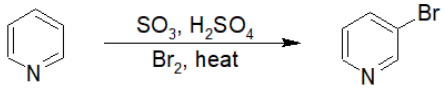
20-10:

If a protecting group is not placed on the amino group of aniline, it will form a complex with AlCl3 during the acylation step of the reaction and prevent the reaction from occurring. By placing a protecting group on the amine, we still maintain an activated ring that can give us ortho- or para- substituted products, but won't interfere with the reaction itself.

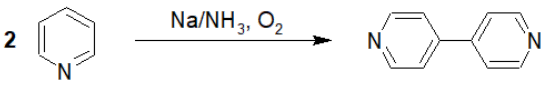


20-11:

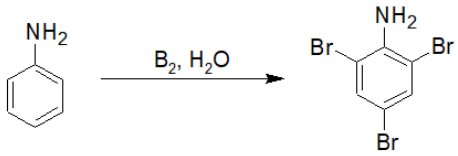
a)



b)



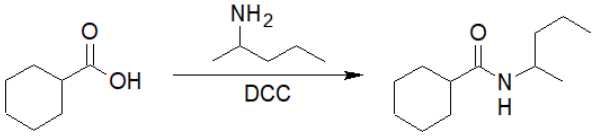
20-12:



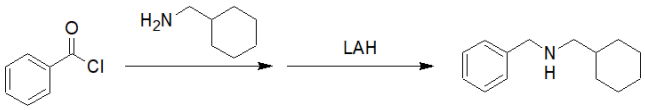
2,4,6-tribromoaniline

Alkylation and Acylation of Amines

20-13:

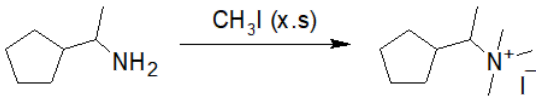


20-14:



20-15:

Answer: A

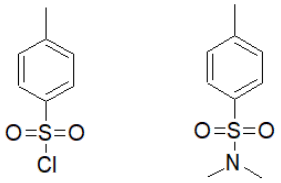


Formation of Sulfonamides

20-16:

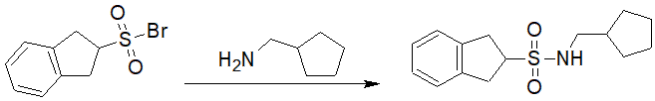
Answer: C

20-17:



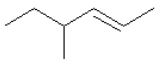
A **B**

20-18:



Amines as Leaving Groups: The Hofmann Elimination

20-19:



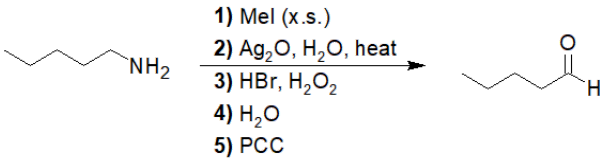
(2*E*)-4-methylhex-2-ene

20-20:

Answer: D

20-21:

Possible route of synthesis:



Oxidation of Amines: The Cope Elimination

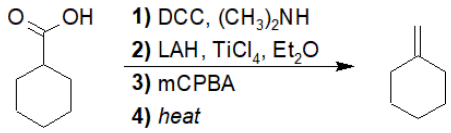
20-22:

https://chem.libretexts.org/@go/page/183161

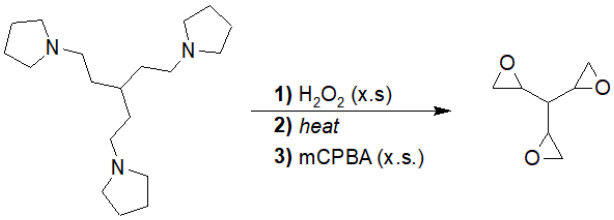
(3*E*/*Z*)-hept-3-ene

20-23:

Possible route of synthesis:

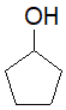


20-24:



Reactions of Amines with Nitrous Acid

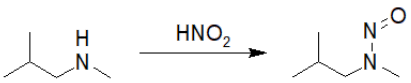
20-25:



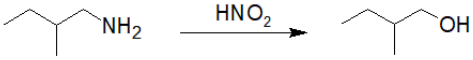
cyclopentanol

20-26:

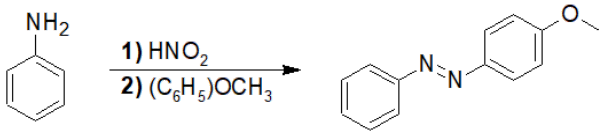
a)



b)

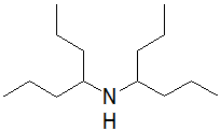


20-27:



Synthesis of Amines by Reductive Amination and Acylation-Reduction

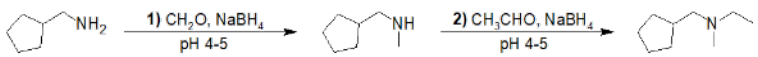
20-28:



***N*-(heptan-4-yl)heptan-4-amine**

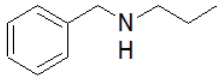
20-29:

Answer: B



20-30:

Answer: C



***N*-benzylpropan-1-amine**

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CHAPTER OVERVIEW

23: Carbohydrates

Topic hierarchy

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23.2: Classification of Carbohydrates
23.3: Fischer Projections
23.4: D and L Sugars
23.5: Configuration of Aldoses
23.6: Cyclic Structures of Monosaccharides
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23.1: 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.

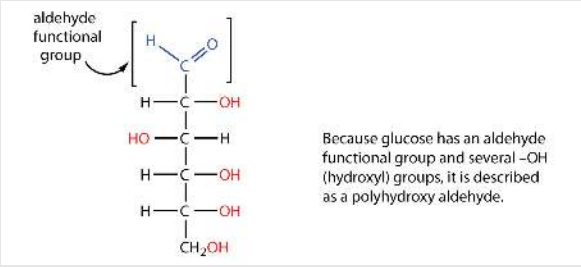
Key Terms

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

- carbohydrate

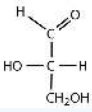
Introduction

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 $C_6 \cdot 6H_2O$.



Example 1

Which compounds would be classified as carbohydrates?

a. 

b.

c.

d.

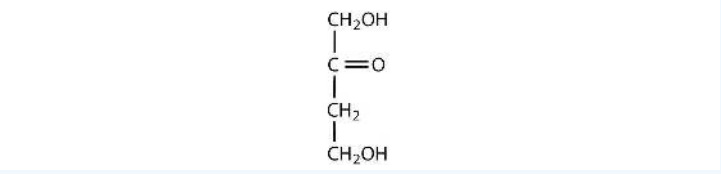
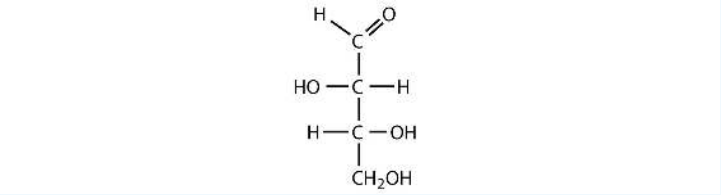
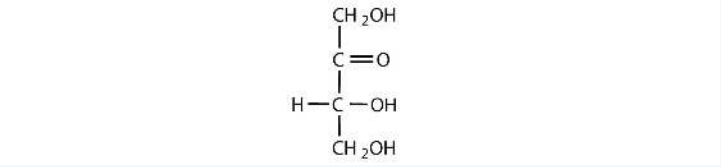
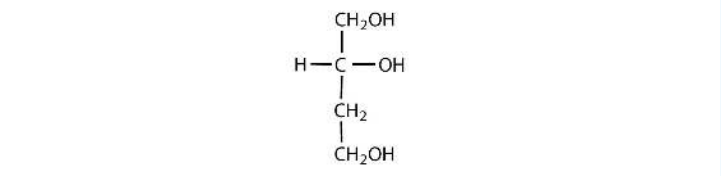
Solution

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. 
2. 
3. 
4. 

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:

$$6CO_2 + 6H_2O + 2870\ \text{kJ} \rightarrow C_6H_{12}O_6 + 6O_2 \quad (1)$$

(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

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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23.2: 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

Carbohydrates are the most abundant class of organic compounds found in living organisms. They originate as products of **photosynthesis**, an endothermic reductive condensation of carbon dioxide requiring light energy and the pigment chlorophyll.

$$nCO_2 + nH_2O + Energy \rightarrow C_nH_{2n}O_n + nO_2 \tag{23.2.1}$$

As noted here, the formulas of many carbohydrates can be written as carbon hydrates, $C_n(H_2O)_n$, hence their name. The carbohydrates are a major source of metabolic energy, both for plants and for animals that depend on plants for food. Aside from the sugars and starches that meet this vital nutritional role, carbohydrates also serve as a structural material (cellulose), a component of the energy transport compound ATP/ADP, recognition sites on cell surfaces, and one of three essential components of DNA and RNA.

Carbohydrates are called **saccharides** or, if they are relatively small, sugars. Several classifications of carbohydrates have proven useful, and are outlined in the following table.

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.

Reactivity	**Reducing** sugars oxidized by Tollens' reagent (or Benedict's or Fehling's reagents). **Non-reducing** sugars not oxidized by Tollens' or other reagents.

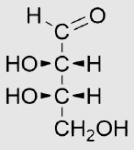
Exercises

Questions

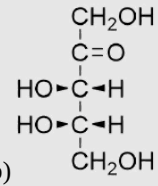
Q25.1.1

Classify each of the following sugars.

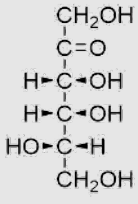
(a)

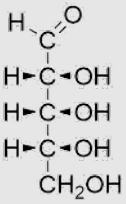


(b)



(c)



(d) 

Solutions

S25.1.1

(a) Aldoterose

(b) Ketopentose

(c) Ketohexose

(d) Aldopentose

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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23.3: Fischer Projections

Objectives

After completing this section, you should be able to

1. draw the Fischer projection of a monosaccharide, given its wedge-and-broken-line structure or a molecular model.
2. draw the wedge-and-broken-line 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-broken-line structure.

Key Terms

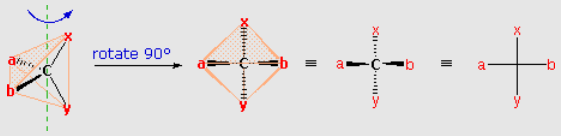
Make certain that you can define, and use in context, the key term below.

- Fischer projection

Study Notes

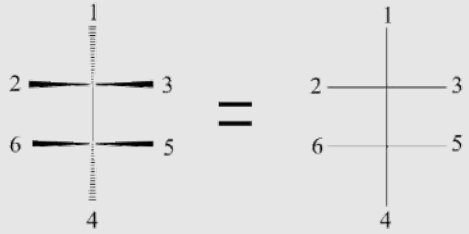
When studying this section, use your molecular model set to assist you in visualizing the structures of the compounds that are discussed. It is important that you be able to determine whether two apparently different Fischer projections represent two different structures or one single structure. Often the simplest way to check is to construct a molecular model corresponding to each projection formula, and then compare the two models.

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 hatched line 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. In a Fischer projection drawing, 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). Since this is not the usual way in which we have viewed such structures, the following diagram shows how a stereogenic carbon positioned in the common two-bonds-in-a-plane orientation (x–C–y define the reference plane) is rotated into the Fischer projection orientation (the far right formula). When writing Fischer projection formulas it is important to remember these conventions. Since the vertical bonds extend away from the viewer and the horizontal bonds toward the viewer, a Fischer structure may only be turned by 180º within the plane, thus maintaining this relationship. **The structure must not be flipped over or rotated by 90º**.



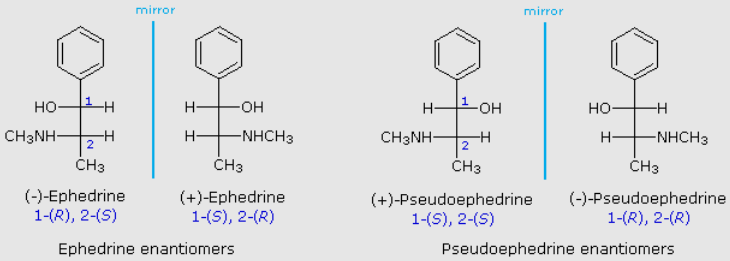
In the above diagram, if x = CO_2H, y = CH_3, a = H & b = OH, the resulting formula describes (*R*)-(–)-lactic acid. The mirror-image formula, where x = CO_2H, y = CH_3, a = OH & b = H, would, of course, represent (*S*)-(+)-lactic acid.

The Fischer Projection consists of both horizontal and vertical lines, where the horizontal lines represent the atoms that are pointed toward the viewer while the vertical line represents atoms that are pointed away from the viewer. The point of intersection between the horizontal and vertical lines represents the central carbon.

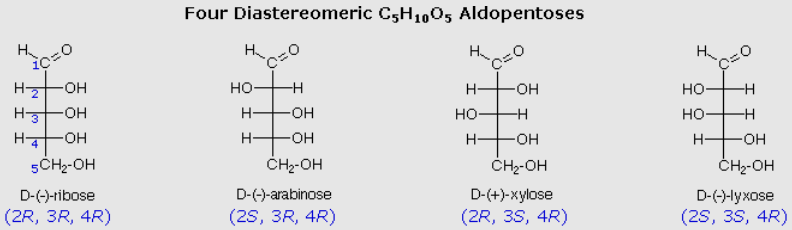


https://chem.libretexts.org/@go/page/183165

Using the Fischer projection notation, the stereoisomers of 2-methylamino-1-phenylpropanol are drawn in the following manner. Note that it is customary to set the longest carbon chain as the vertical bond assembly.



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. 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**. Fischer formulas for these isomers, which Fischer designated as the "D"-family, are shown in the diagram. Each of these compounds has an enantiomer, which is a member of the "L"-family so, as expected, there are eight stereoisomers in all. 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.



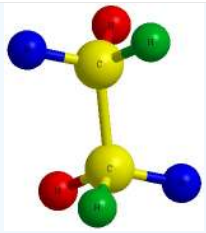
The aldopentose structures drawn above are all diastereomers. A more selective term, **epimer**, is used to designate diastereomers that differ in configuration at only one chiral center. Thus, ribose and arabinose are epimers at C-2, and arabinose and lyxose are epimers at C-3. However, arabinose and xylose are not epimers, since their configurations differ at both C-2 and C-3.

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.

Example 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.



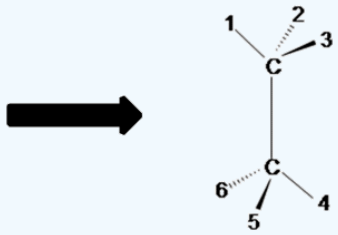


Figure B

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.

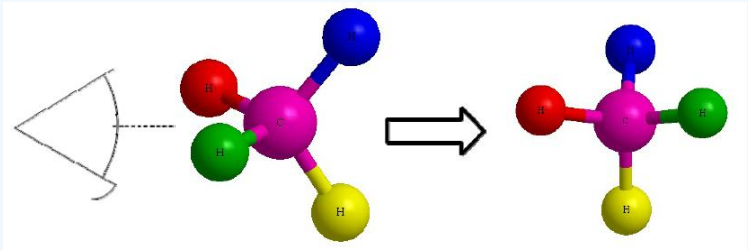
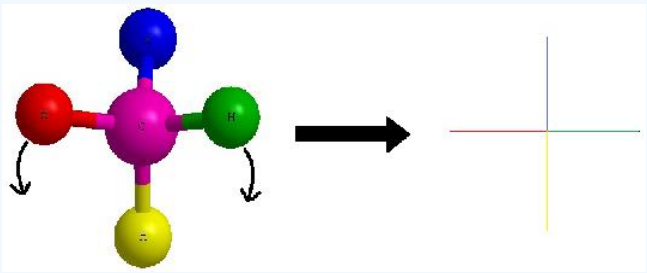


Figure D

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.

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23.4: D and L Sugars

Objectives

After completing this section, you should be able to

1. identify a specific enantioner 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.

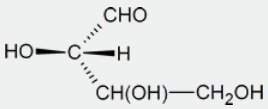
- D sugar
- L sugar

Study Notes

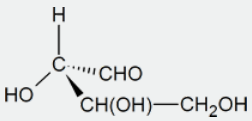
If you find that you have forgotten the meanings of terms such as dextrorotatory and polarimeter, refer back to Section 5.3 in which the fundamentals of optical activity were introduced.

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?

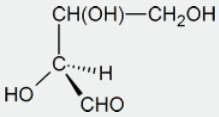
One approach is to focus on the carbon atom of interest and sketch a three-dimensional representation of the configuration around that atom, remembering the convention used in Fischer projections: vertical lines represent bonds going into the page, and horizontal lines represent bonds coming out of the 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.



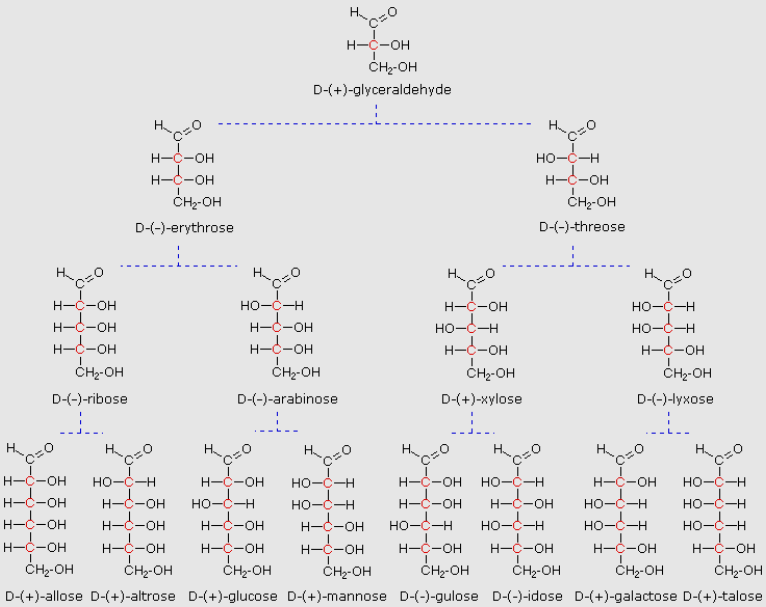
The Cahn-Ingold-Prelog order of priority for the three remaining groups is OH > CHO > $CH(OH)CH_2OH$; thus, we see that we could trace out a counterclockwise path going from the highest-priority group to the second- and third-highest, and we conclude that the central carbon atom has an *S* configuration.

The Configuration of Glucose

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. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula. Click on this link for a review.

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 (+)-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. The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Fischer as the D / L designator site. 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 (the mirror image) then represented the L-family. Fischer's initial assignment of the D-configuration had a 50:50 chance of being right, but all his subsequent conclusions concerning the relative configurations of various aldoses were soundly based. 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.

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). 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.



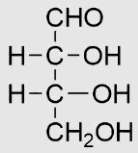
Exercises

Questions

Q25.3.1

Assign R and S for each chiral center and determine whether each sugar is a D or L sugar.

(a)



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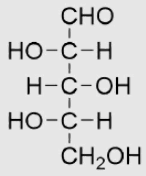

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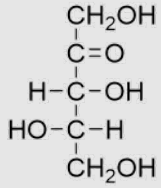

Solutions

S25.3.1

(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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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry

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23.5: Configuration of Aldoses

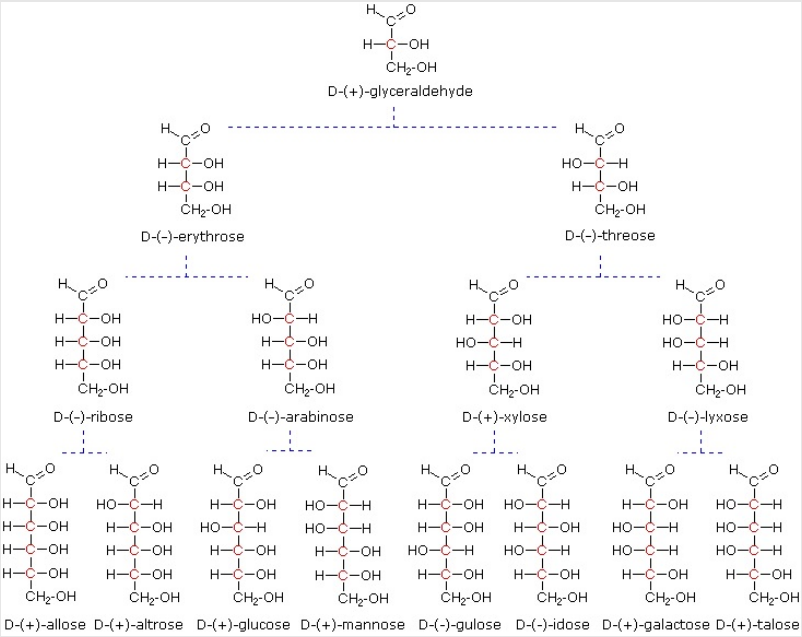
Objectives

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. One of the first tasks faced by Fischer was to devise a method of representing the configuration of each chiral center in an unambiguous manner. To this end, he invented a simple technique for drawing chains of chiral centers, that we now call the Fischer projection formula.

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 (+)-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.



The last chiral center in an aldose chain (farthest from the aldehyde group) was chosen by Fischer as the D / L designator site. 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 (the mirror image) then represented the L-family. Fischer's initial assignment of the D-configuration had a 50:50 chance of being right, but all his subsequent conclusions concerning the relative configurations of various aldoses were soundly based. In 1951 x-ray fluorescence studies of (+)-tartaric acid, carried out in the Netherlands by Johannes Martin Bijvoet (pronounced "buy foot"), proved that Fischer's choice was correct.

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). 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.

Exercises

Questions

Q25.4.1

Draw the following sugars.

(a) D-Xylose

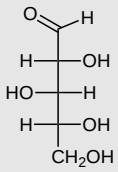
(b) D-Galactose

(c) D-Allose

Solutions

S25.4.1

(a)



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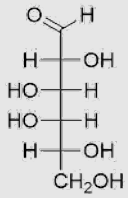
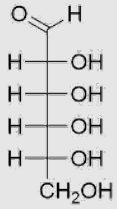


(c)



Contributors and Attributions

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23.6: Cyclic Structures of Monosaccharides

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

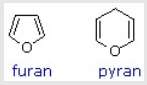
Make certain that you can define, and use in context, the key terms below.

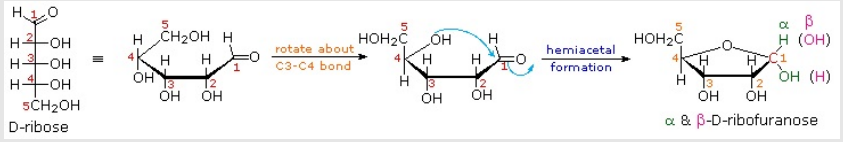
- alpha anomer
- anomer
- anomeric centre
- beta anomer
- furanose
- mutarotation
- pyranose

Study Notes

If necessary, before you attempt to study this section, review the formation of hemiacetals discussed in Section 19.10.

As noted above, the preferred structural form of many monosaccharides may be that of a cyclic hemiacetal. 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 on the right. Ribose, an important aldopentose, commonly adopts a furanose structure, as shown in the following illustration. 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 anomeric carbon atom (colored red here) is placed on the right. The upper bond to this carbon is defined as beta, the lower bond then is alpha.





The cyclic pyranose forms of various monosaccharides are often drawn in a flat projection known as a Haworth formula, after the British chemist, Norman Haworth. As with the furanose ring, the anomeric carbon is placed on the right with the ring oxygen to the back of the edgewise view. In the D-family, the alpha and beta bonds have the same orientation defined for the furanose ring (beta is up & alpha is down). These Haworth formulas are convenient for displaying stereochemical relationships, but do not represent the true shape of the molecules. We know that these molecules are actually puckered in a fashion we call a chair conformation. Examples of four typical pyranose structures are shown below, both as Haworth projections and as the more representative chair conformers. The anomeric carbons are colored red.

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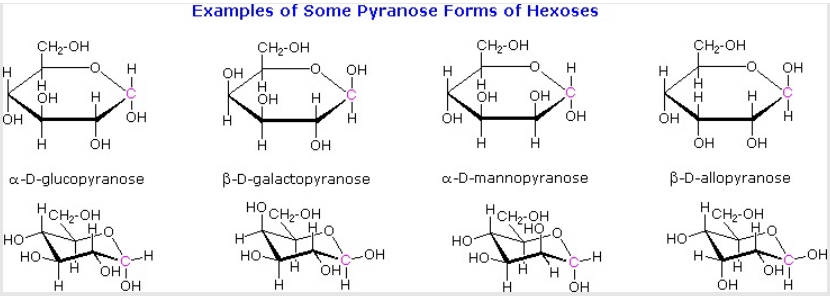
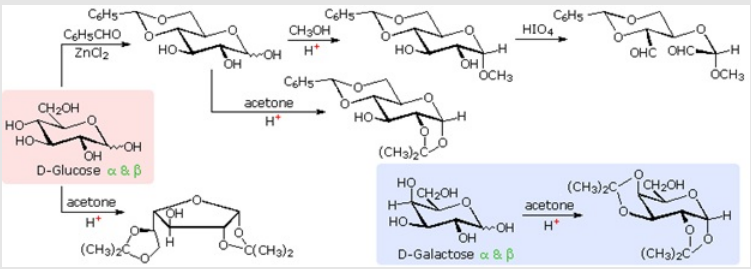




The size of the cyclic hemiacetal ring adopted by a given sugar is not constant, but may vary with substituents and other structural features. Aldolhexoses usually form pyranose rings and their pentose homologs tend to prefer the furanose form, but there are many counter examples. The formation of acetal derivatives illustrates how subtle changes may alter this selectivity. A pyranose structure for D-glucose is drawn in the rose-shaded box on the left. Acetal derivatives have been prepared by acid-catalyzed reactions with benzaldehyde and acetone. As a rule, benzaldehyde forms six-membered cyclic acetals, whereas acetone prefers to form five-membered acetals. The top equation shows the formation and some reactions of the 4,6-O-benzylidene acetal, a commonly employed protective group. A methyl glycoside derivative of this compound (see below) leaves the C-2 and C-3 hydroxyl groups exposed to reactions such as the periodic acid cleavage, shown as the last step. The formation of an isopropylidene acetal at C-1 and C-2, center structure, leaves the C-3 hydroxyl as the only unprotected function. Selective oxidation to a ketone is then possible. Finally, direct di-O-isopropylidene derivatization of glucose by reaction with excess acetone results in a change to a furanose structure in which the C-3 hydroxyl is again unprotected. However, the same reaction with D-galactose, shown in the blue-shaded box, produces a pyranose product in which the C-6 hydroxyl is unprotected. Both derivatives do not react with Tollens' reagent. This difference in behavior is attributed to the cis-orientation of the C-3 and C-4 hydroxyl groups in galactose, which permits formation of a less strained five-membered cyclic acetal, compared with the trans-C-3 and C-4 hydroxyl groups in glucose. Derivatizations of this kind permit selective reactions to be conducted at different locations in these highly functionalized molecules.

Anomers of Simple Sugars: Mutarotation of Glucose

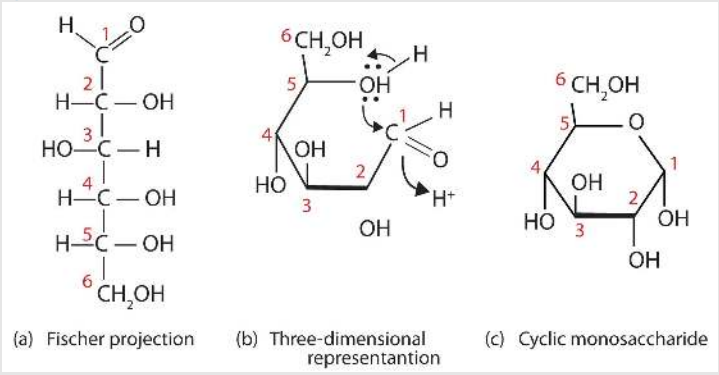


Figure 1: Cyclization of D-Glucose. D-Glucose can be represented with a Fischer projection (a) or three dimensionally (b). By reacting the OH group on the fifth carbon atom with the aldehyde group, the cyclic monosaccharide (c) is produced.

When a straight-chain monosaccharide, such as any of the structures shown in Figure 1, forms a cyclic structure, the carbonyl oxygen atom may be pushed either up or down, giving rise to two stereoisomers, as shown in Figure 2. The structure shown on the left side of Figure 2, with the OH group on the first carbon atom projected downward, represent what is called the

alpha (α) form. The structures on the right side, with 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; they differ in structure around the anomeric carbon—that is, the carbon atom that was the carbonyl carbon atom in the straight-chain form.

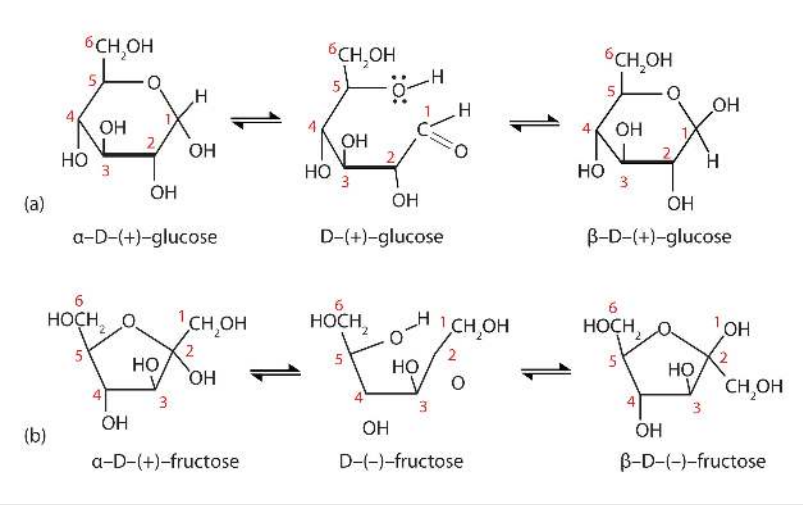


Figure 2: Monosaccharides. In an aqueous solution, monosaccharides exist as an equilibrium mixture of three forms. The interconversion between the forms is known as *mutarotation*, which is shown for D-glucose (a) and D-fructose (b).

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 (part (a) of Figure 2). 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 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 (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°.

Even though only a small percentage of the molecules are in the open-chain aldehyde form at any time, the solution will nevertheless exhibit the characteristic reactions of an aldehyde. As the small amount of free aldehyde is used up in a reaction, there is a shift in the equilibrium to yield more aldehyde. Thus, *all* the molecules may eventually react, even though very little free aldehyde is present at a time.

Commonly, (e.g., in Figures 1 and 2) the cyclic forms of sugars are depicted using a convention first suggested by Walter N. Haworth, an English chemist. The molecules are drawn as planar hexagons with a darkened edge 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 the plane of the ring in a Haworth projection, and any group written to the left in a Fischer projection appears above the plane in a Haworth projection.

The difference between the α and the β forms of sugars may seem trivial, but such structural differences are often crucial in biochemical reactions. This explains why we can get energy from the starch in potatoes and other plants but not from cellulose, even though both starch and cellulose are polysaccharides composed of glucose molecules linked together.

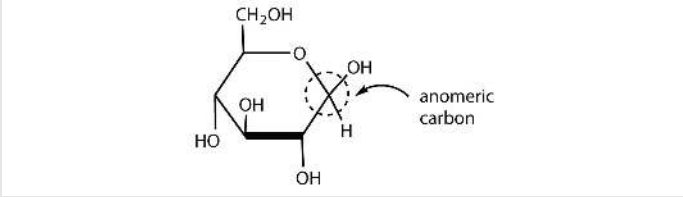
Summary

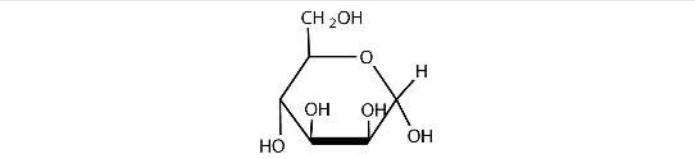
Monosaccharides that contain five or more carbons atoms form cyclic structures in aqueous solution. Two cyclic stereoisomers can form from each straight-chain monosaccharide; these are known as anomers. In an aqueous solution, an equilibrium mixture forms between the two anomers and the straight-chain structure of a monosaccharide in a process known as mutarotation.

Exercises

1. Draw the cyclic structure for β-D-glucose. Identify the anomeric carbon.
2. 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.

Answers

1. 

2. 

Contributors and Attributions

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23.7: 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

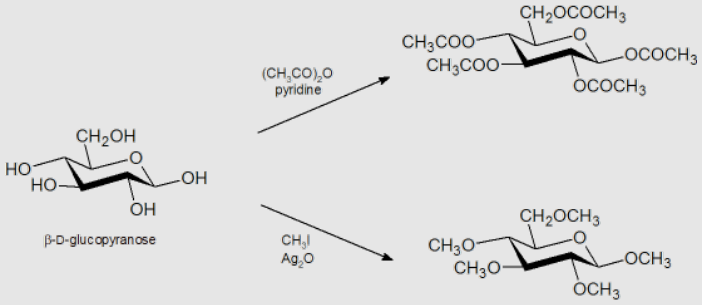
While several reactions are covered in this section, keep in mind that you have encountered them in previous sections. The active functional groups on monosaccharides are essentially carbonyls and hydroxyls. Although they now are a part of much larger molecules, their chemistry should be familiar.

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

Ester and Ether Formation

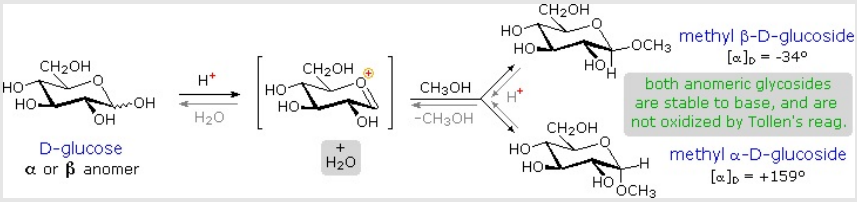
The -OH groups on a monosaccharide can be readily converted to esters and ethers. Esterfication can be done with an acid chloride (Section 21.4) or acid anhydride (Section 21.5), while treatment with an alkyl halide by a Williamson ether synthesis (Section 18.2) leads to the ether.

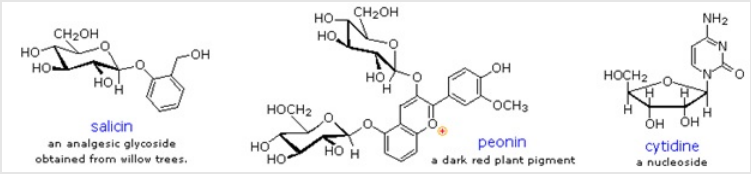


Glycoside Formation

Acetal derivatives formed when a monosaccharide reacts with an alcohol in the presence of an acid catalyst are called glycosides. This reaction is illustrated for glucose and methanol in the diagram below. In naming of glycosides, the "ose" suffix of the sugar name is replaced by "oside", and the alcohol group name is placed first. As is generally true for most acetals, glycoside formation involves the loss of an equivalent of water. The diether product is stable to base and alkaline oxidants such as Tollen's reagent. Since acid-catalyzed aldolization is reversible, glycosides may be hydrolyzed back to their alcohol and sugar components by aqueous acid.

The anomeric methyl glucosides are formed in an equilibrium ratio of 66% alpha to 34% beta. From the structures in the previous diagram, we see that pyranose rings prefer chair conformations in which the largest number of substituents are equatorial. In the case of glucose, the substituents on the beta-anomer are all equatorial, whereas the C-1 substituent in the alpha-anomer changes to axial. Since substituents on cyclohexane rings prefer an equatorial location over axial (methoxycyclohexane is 75% equatorial), the preference for alpha-glycopyranoside formation is unexpected, and is referred to as the anomeric effect.





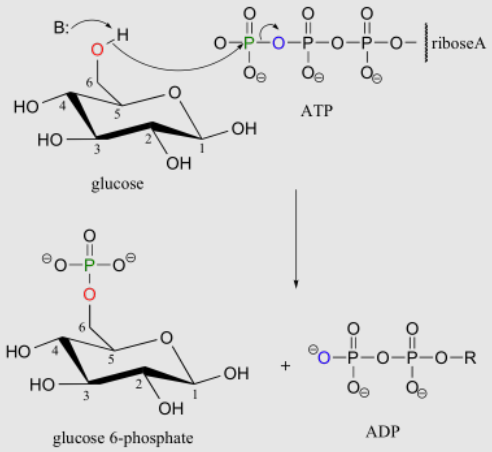
Glycosides abound in biological systems. By attaching a sugar moiety to a lipid or benzenoid structure, the solubility and other properties of the compound may be changed substantially. Because of the important modifying influence of such derivatization, numerous enzyme systems, known as glycosidases, have evolved for the attachment and removal of sugars from alcohols, phenols and amines. Chemists refer to the sugar component of natural glycosides as the glycon and the alcohol component as the aglycon.

Two examples of naturally occurring glycosides and one example of an amino derivative are displayed above. 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. Finally, amino derivatives of ribose, such as cytidine play important roles in biological phosphorylating agents, coenzymes and information transport and storage materials.

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 (look again, for example, at the glucose kinase reaction that we first saw in section 10.1D).



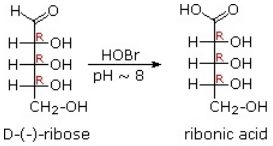
Oxidation

As noted above, sugars may be classified as **reducing** or **non-reducing** based on their reactivity with **Tollens'**, **Benedict's** or **Fehling's** reagents. If a sugar is oxidized by these reagents it is called reducing, 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.

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 hypobromite must be used for this conversion (equation 1). 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 (this could also be accomplished by reducing the aldehyde to CH_2OH, as noted below). Such an operation will disclose any latent

symmetry in the remaining molecule. Thus, ribose, xylose, allose and galactose yield achiral aldaric acids which are, of course, not optically active. The ribose oxidation is shown in equation 2 below.

1.



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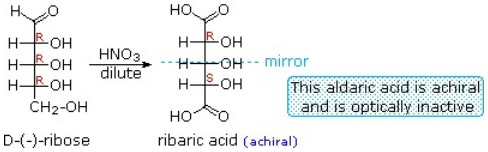

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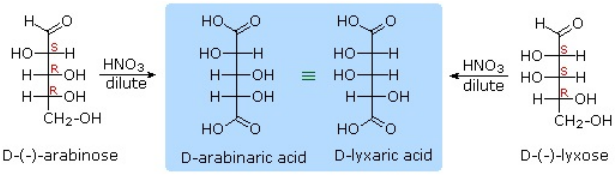


Other aldose sugars may give identical chiral aldaric acid products, implying a unique configurational relationship. The examples of arabinose and lyxose shown in equation 3 above illustrate this result. Remember, a Fischer projection formula may be rotated by 180º in the plane of projection without changing its configuration.

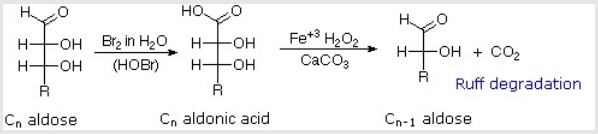
Reduction

Sodium borohydride reduction of an aldose makes the ends of the resulting **alditol** chain identical, $HOCH_2(CHOH)_nCH_2OH$, thereby accomplishing the same configurational change produced by oxidation to an aldaric acid. Thus, allitol and galactitol from reduction of allose and galactose are achiral, and altrose and talose are reduced to the same chiral alditol. A summary of these redox reactions, and derivative nomenclature is given in the following table.

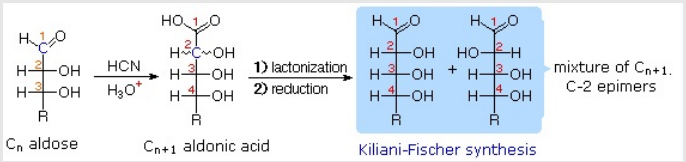
Table: Derivatives of $HOCH_2(CHOH)_nCHO$

$HOBr$ Oxidation	⟶	$HOCH_2(CHOH)_nCO_2H$ an Aldonic Acid
HNO_3 Oxidation	⟶	$H_2OC(CHOH)_nCO_2H$ an Aldaric Acid
$NaBH_4$ Reduction	⟶	$HOCH_2(CHOH)_nCH_2OH$ an Alditol

Chain Shortening and Lengthening



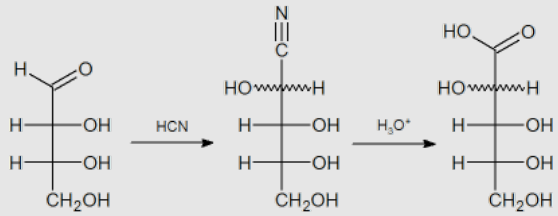
1. Ruff Degradation



2. Kiliani-Fischer Synthesis

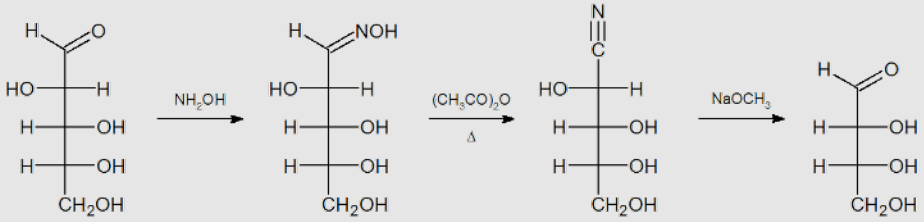
These two procedures permit an aldose of a given size to be related to homologous smaller and larger aldoses. The importance of these relationships may be seen in the array of aldose structures presented earlier, where the structural connections are given by the dashed blue lines. Thus Ruff degradation of the pentose arabinose gives the tetrose erythrose. Working in the opposite direction, a Kiliani-Fischer synthesis applied to arabinose gives a mixture of glucose and mannose. An alternative chain shortening procedure known as the Wohl degradation is essentially the reverse of the Kiliani-Fischer synthesis.

Note that in the Kiliani-Fischer synthesis the first step is to generate a cyanohydrin intermediate, which is then has its nitrile group hydrolyzed to the carboxylic acid. From there the cyclic ester (lactone) is formed and reduced to the final products (epimers).



Wohl Degradation

The ability to shorten (degrade) an aldose chain by one carbon was an important tool in the structure elucidation of carbohydrates. This was commonly accomplished by the Ruff procedure. An interesting alternative technique, known as the **Wohl degradation** has also been used. The following equation illustrates the application of this procedure to the aldopentose, arabinose. Based on your knowledge of carbonyl chemistry, and considering that the Wohl degradation is in essence the reverse of the Kiliani-Fischer synthesis.



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23.8: Disaccharides and Glycosidic Bonds

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

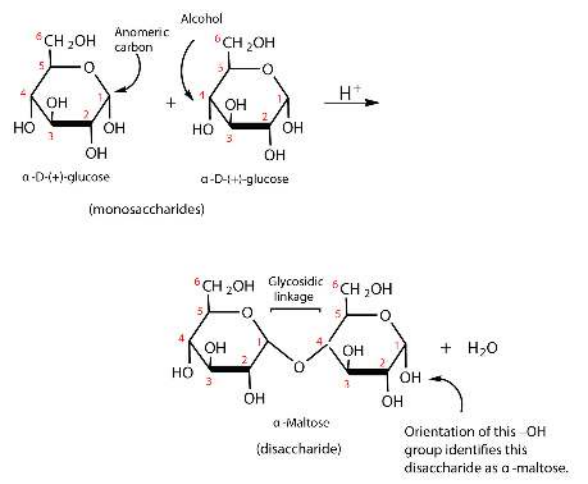
Make certain that you can define, and use in context, the key terms below.

- 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. 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. We'll consider each sugar in more detail.

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.

$$\text{maltose} \xrightarrow{\text{H}^+ \text{ or maltase}} 2\ \text{D-glucose} \tag{23.8.1}$$

Maltose is a reducing sugar. Thus, its two glucose molecules must be linked in such a way as to leave one anomeric carbon that can open to form an aldehyde group. The glucose units in maltose are joined 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 (that is, an α-1,4-glycosidic linkage; see Figure 1). 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 glucose can be in either the α or the β position, as shown in Figure 1.

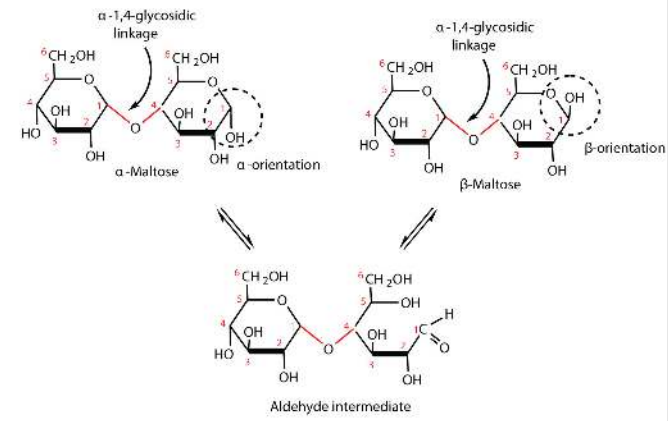
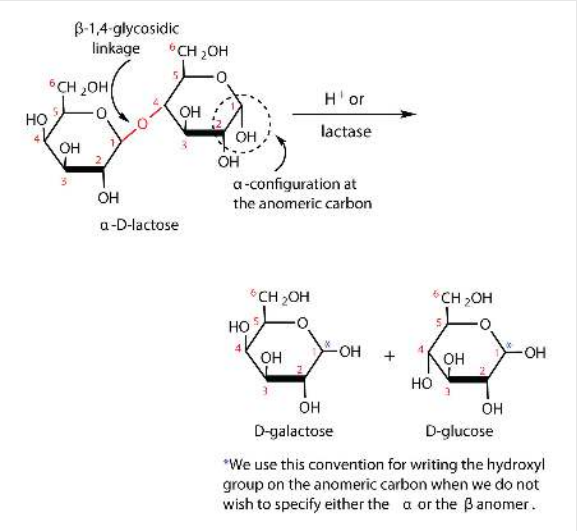


Figure 1 An Equilibrium Mixture of Maltose Isomers

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.

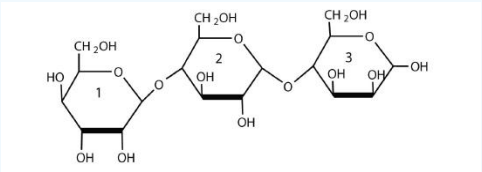
Lactose is a reducing sugar composed of one molecule of D-galactose and one molecule of D-glucose joined by a β-1,4-glycosidic bond (the bond from the anomeric carbon of the first monosaccharide unit being directed upward). The two monosaccharides are obtained from lactose by acid hydrolysis or the catalytic 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

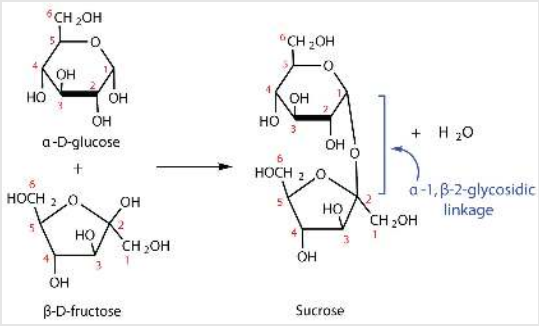
at drugstores and grocery stores. These are taken orally with dairy foods—or may be added to them directly—to assist in their digestion.

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 “uncyclizes” to form an open-chain structure. 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.

Concept Review Exercise

1. What monosaccharides are obtained by the hydrolysis of each disaccharide?

    a. sucrose
    b. maltose
    c. lactose

Answer

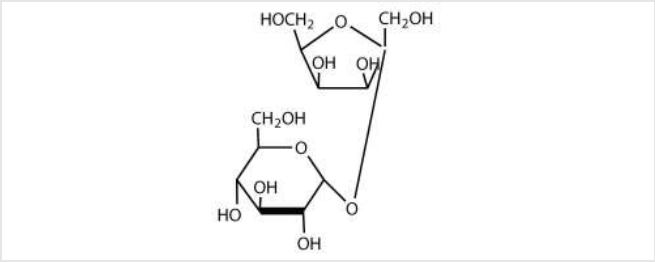
1. a. D-glucose and D-fructose
    b. two molecules of D-glucose
    c. D-glucose and D-galactose

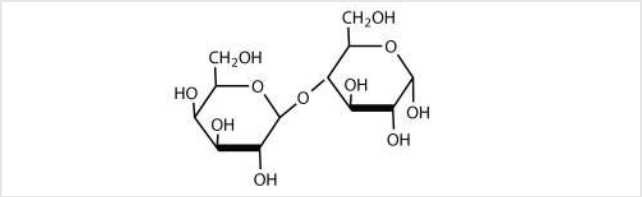
Exercises

1. Identify each sugar by its common chemical name.

    a. milk sugar
    b. table sugar

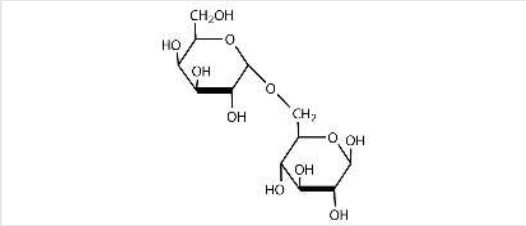
2. For each disaccharide, indicate whether the glycosidic linkage is α or β.

    a. 

    b. 

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

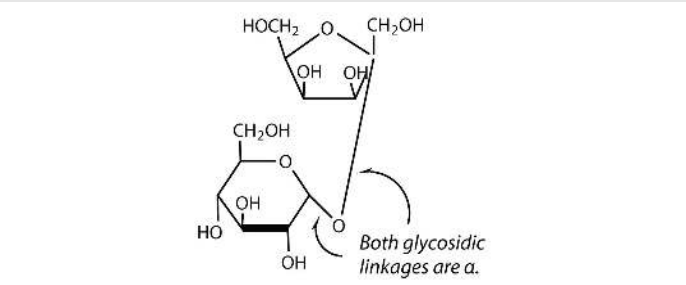
4. Melibiose is a disaccharide that occurs in some plant juices. Its structure is as follows:

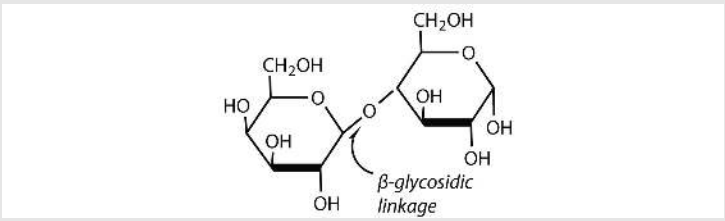


    a. What monosaccharide units are incorporated into melibiose?
    b. What type of linkage (α or β) joins the two monosaccharide units of melibiose?
    c. Melibiose has a free anomeric carbon and is thus a reducing sugar. Circle the anomeric carbon and indicate whether the OH group is α or β

Answers

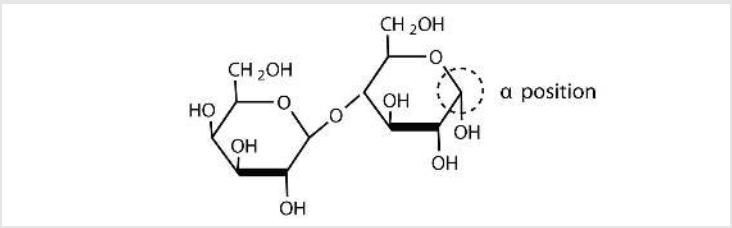
1. a. lactose
   b. sucrose

2. a. 

2. b. 

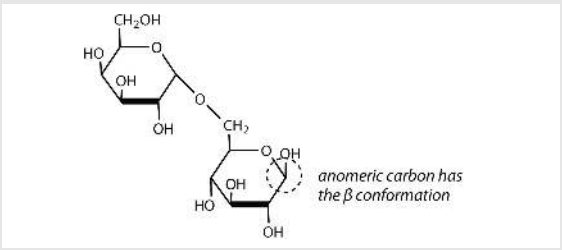
3. a. nonreducing

3. b. reducing



4. a. galactose and glucose

4. b.α-glycosidic linkage

4. c. 

Contributors and Attributions

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23.9: Polysaccharides

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

Learning Objectives

- To compare and contrast the structures and uses of starch, glycogen, and cellulose.

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.

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 **23.9.1**). 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 **23.9.1**). 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.

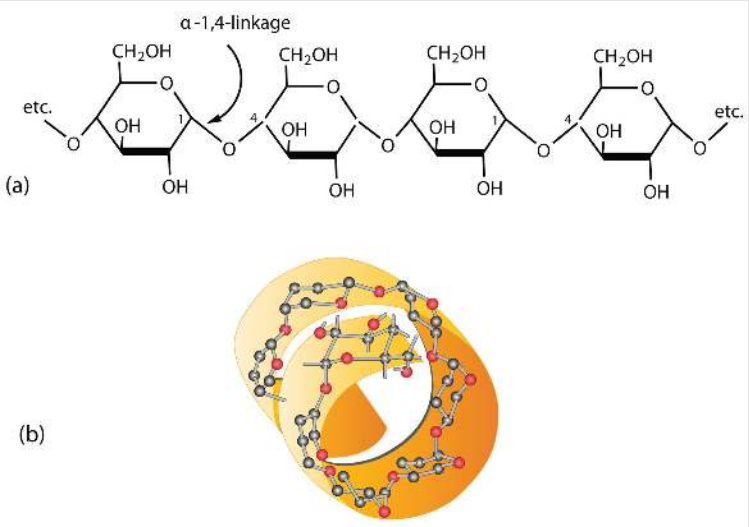

Figure **23.9.1**: Amylose. (a) Amylose is a linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. (b) Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.

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 **23.9.2**). 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.

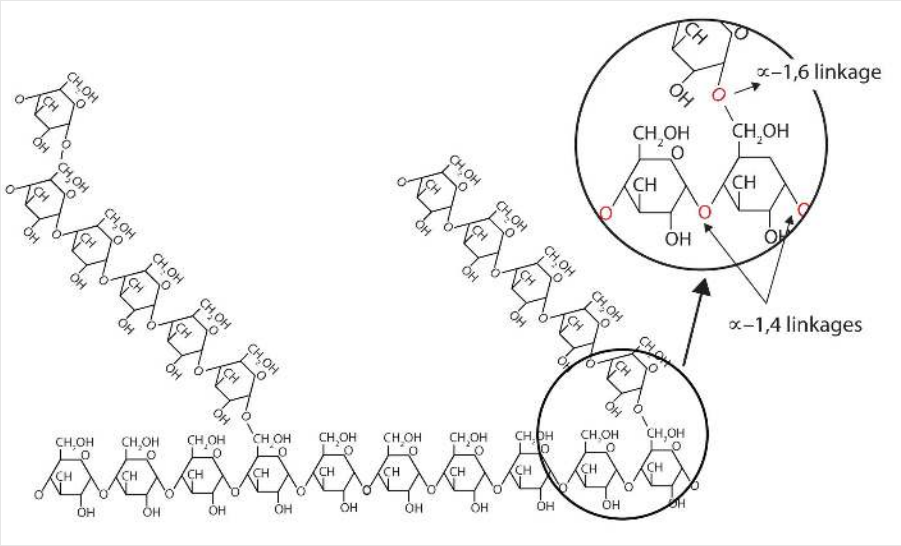

Figure **23.9.2**: Representation of the Branching in Amylopectin and Glycogen. Both amylopectin and glycogen contain branch points that are linked through α-1,6-linkages. These branch points occur more often in glycogen.

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 noncellulose 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 **23.9.3**). 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 **23.9.3**). 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.

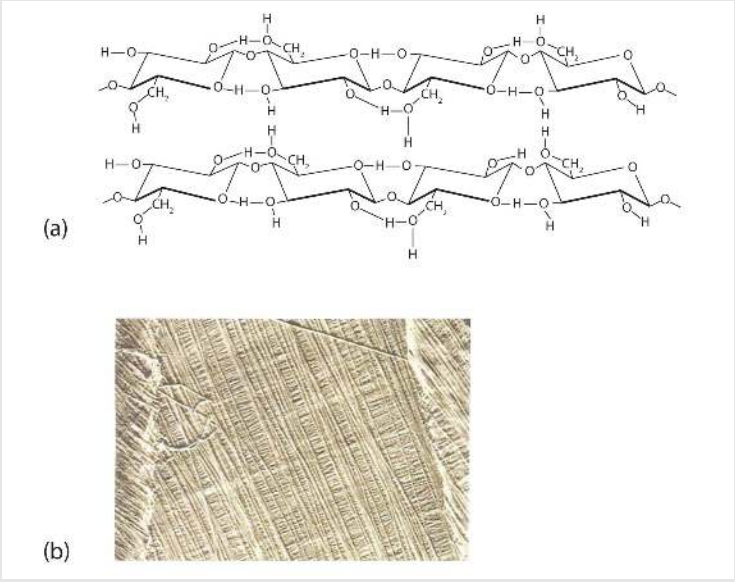

Figure **23.9.3**: Cellulose. (a) There is extensive hydrogen bonding in the structure of cellulose. (b) In this electron micrograph of the cell wall of an alga, the wall consists of successive layers of cellulose fibers in parallel arrangement.

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.

Career Focus: Certified Diabetes Educator

Certified diabetes educators come from a variety of health professions, such as nursing and dietetics, and specialize in the education and treatment of patients with diabetes. A diabetes educator will work with patients to manage their diabetes. This involves teaching the patient to monitor blood sugar levels, make good food choices, develop and maintain an exercise program, and take medication, if required.

A certified diabetes educator at Naval Medical Center Portsmouth (left) and a registered dietician at the medical center (center), provide nutritional information to a diabetes patient and her mother at the Diabetes Boot Camp.

Diabetes educators also work with hospital or nursing home staff to improve the care of diabetic patients. Educators must be willing to spend time attending meetings and reading the current literature to maintain their knowledge of diabetes medications, nutrition, and blood monitoring devices so that they can pass this information to their patients.

Summary

Starch is a storage form of energy in plants. It contains two polymers composed of glucose units: amylose (linear) and amylopectin (branched). Glycogen is a storage form of energy in animals. It is a branched polymer composed of glucose units. It is more highly branched than amylopectin. Cellulose is a structural polymer of glucose units found in plants. It is a linear polymer with the glucose units linked through β-1,4-glycosidic bonds.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Anonymous by request
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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23.10: Other Important Carbohydrates

Objectives

After completing this section, you should be able to identify deoxy and amino sugars, given their structures.

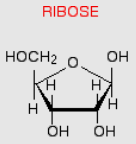
Key Terms

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

- amino sugar
- deoxy sugar

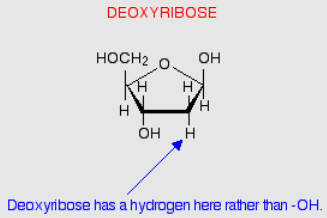
The sugars in the backbone of DNA

The backbone of DNA is based on a repeated pattern of a sugar group and a phosphate group. The full name of DNA, deoxyribonucleic acid, gives you the name of the sugar present - deoxyribose. Deoxyribose is a modified form of another sugar called ribose. I'm going to give you the structure of that first, because you will need it later anyway. Ribose is the sugar in the backbone of RNA, ribonucleic acid.

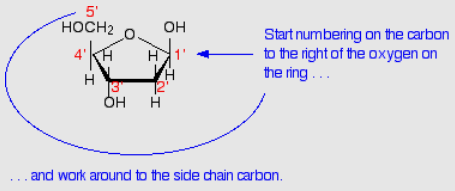


This diagram misses out the carbon atoms in the ring for clarity. Each of the four corners where there isn't an atom shown has a carbon atom. The heavier lines are coming out of the screen or paper towards you. In other words, you are looking at the molecule from a bit above the plane of the ring.

So that's ribose. Deoxyribose, as the name might suggest, is ribose which has lost an oxygen atom - **"de-oxy"**.



The only other thing you need to know about deoxyribose (or ribose, for that matter) is how the carbon atoms in the ring are numbered. The carbon atom to the right of the oxygen as we have drawn the ring is given the number 1, and then you work around to the carbon on the CH_2OH side group which is number 5.



You will notice that each of the numbers has a small dash by it - 3' or 5', for example. If you just had ribose or deoxyribose on its own, that wouldn't be necessary, but in DNA and RNA these sugars are attached to other ring compounds. The carbons in the sugars are given the little dashes so that they can be distinguished from any numbers given to atoms in the other rings. You read 3' or 5' as "3-prime" or "5-prime".

Amino sugar

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.

Structure of the chitin molecule, showing two of the *N*-acetylglucosamine units that repeat to form long chains in β-(1→4)-linkage.

Chitin is is a polymer of *N*-acetylglucosamine 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.

Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- Jim Clark (Chemguide.co.uk)
- Wikipedia

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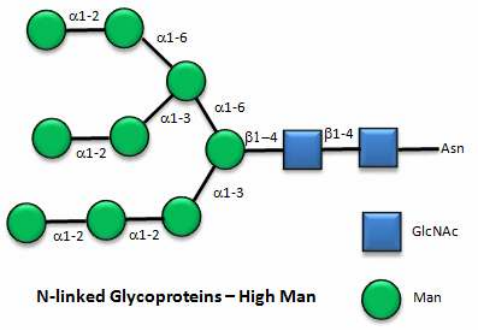
23.11: Cell Surface Carbohydrates and Influenza Viruses

Objectives

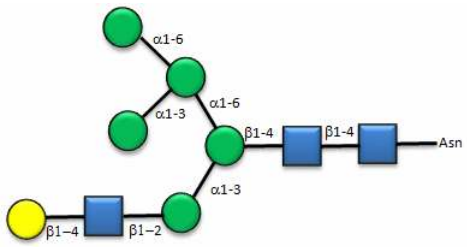
You may omit Section 25.11.

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. A special kind of glycoprotein, a proteoglycan, actually has more carbohydrate mass than protein. 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, there 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, allowing for their import into the cell.

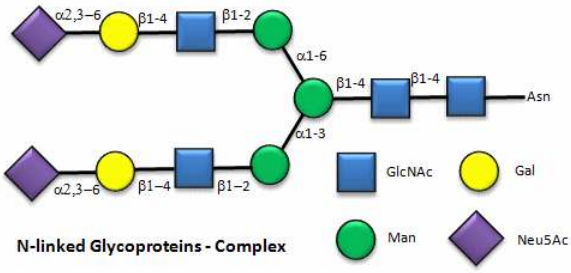
Here are some "cartoon" examples of carbohydrates covalently linked to the amino acid asparagine (Asn) on a glycoprotein.



N-linked Glycoproteins – High Man



N-linked Glycoproteins – Mixed (Hybrid)

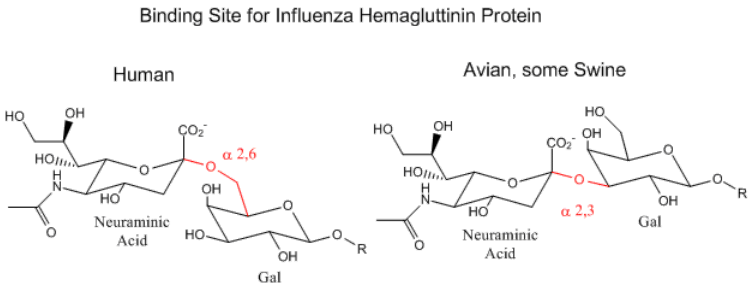


N-linked Glycoproteins - Complex

Here are some examples of biomolecular interactions promoted by IMFs involving carbohydrates.

Influenza Virus binding to Cell Surface Glycoproteins with Neu5Ac - A protein on the surface of influenza virus, hemagluttinin, bind to sialic acid (Sia), which is covalently attached to many cell membrane glycoproteins on host cells. 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, the major

form in human respiratory tract. The swine influenza HA bind to Sia (alpha 2,6) Gal and some Sia (alpha 2,3)both of which found in swine.



- Jmol model of viral hemagluttinin bound to antiviral drugs and sialic (neuraminic acid) from Proteopedia

Leukocyte: Cell Wall binding - During inflammation, circulating leukocytes (a type of white blood cell) tether and roll on the walls of blood vessels where they become active. E-, L- and P-selectin proteins are the primary proteins responsible for the tethering and rolling of these leukocytes. P-selectin binds, in part, to a tetrasaccharide, sialyl-Lewisx (SLEX) on the cell surface.. The interaction between P-selectin and the cell mediates the initial binding/rolling of the leukocyte on the vessel wall.

- Jmol model of P-selectin binding to tetrasaccharide

Contributors and Attributions

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CHAPTER OVERVIEW

24: Amino Acids, Peptides, and Proteins

24.1: Introduction
24.2: Structure and Stereochemistry of the Amino Acids
24.3: Isoelectric Points and Electrophoresis
24.4: Synthesis of Amino Acids
24.5: Peptides and Proteins
24.6: Amino Acid Analysis of Peptides
24.7: Peptide Sequencing: The Edman Degradation
24.8: Peptide Synthesis
24.9: Automated Peptide Synthesis: The Merrifield Solid-Phase Technique
24.10: Levels of Protein Structure
24.11: Enzymes and Coenzymes
24.12: How do enzymes work?

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24.1: 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

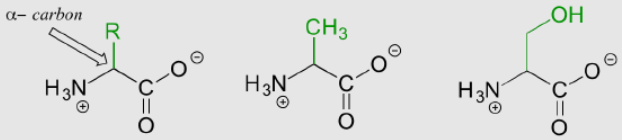
Make certain that you can define, and use in context, the key terms below.

- 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—N bond present in amides (see Section 21.7). We shall review the nature of such bonds in Section 26.4.

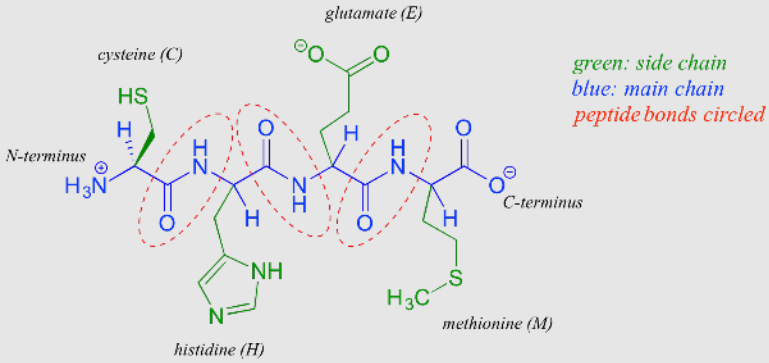
Proteins are polymers of **amino acids**, linked by amide groups known as **peptide bond**s. An amino acid can be thought of as having two components: a 'backbone', or 'main chain', composed of an ammonium group, an 'alpha-carbon', and a carboxylate, and a variable 'side chain' (in green below) bonded 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.



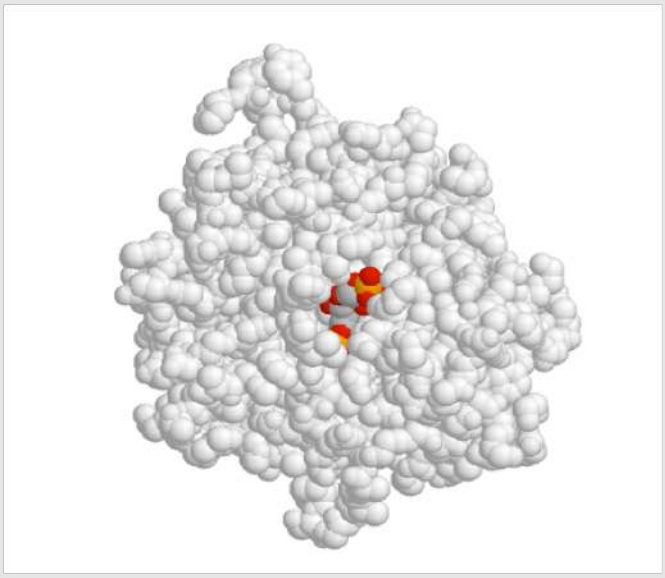
CHEM peptide

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 ⇒

Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)

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24.2: Structure and Stereochemistry of the 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 condensation reaction by the amino group of an amino acid with 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)

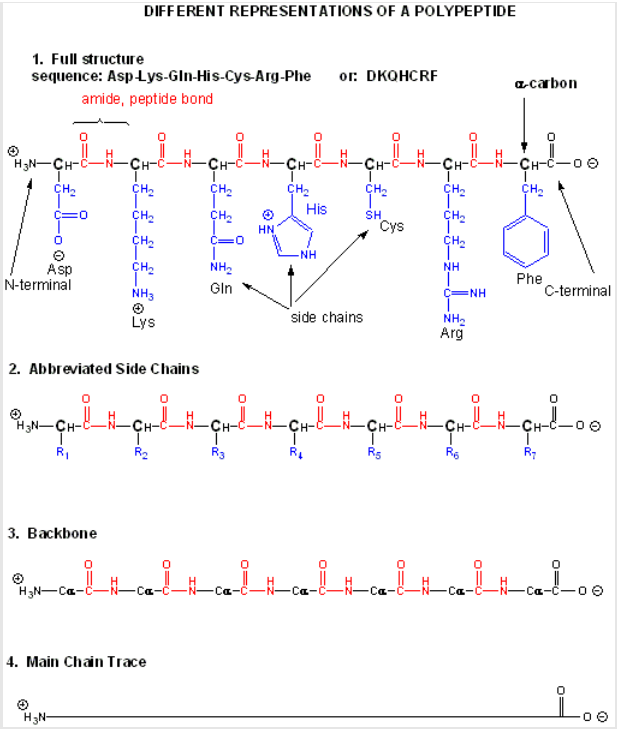
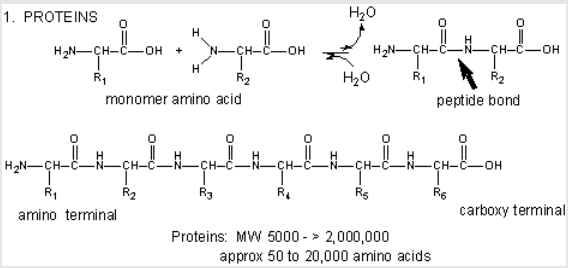


Figure: Amino Acids React to Form Proteins

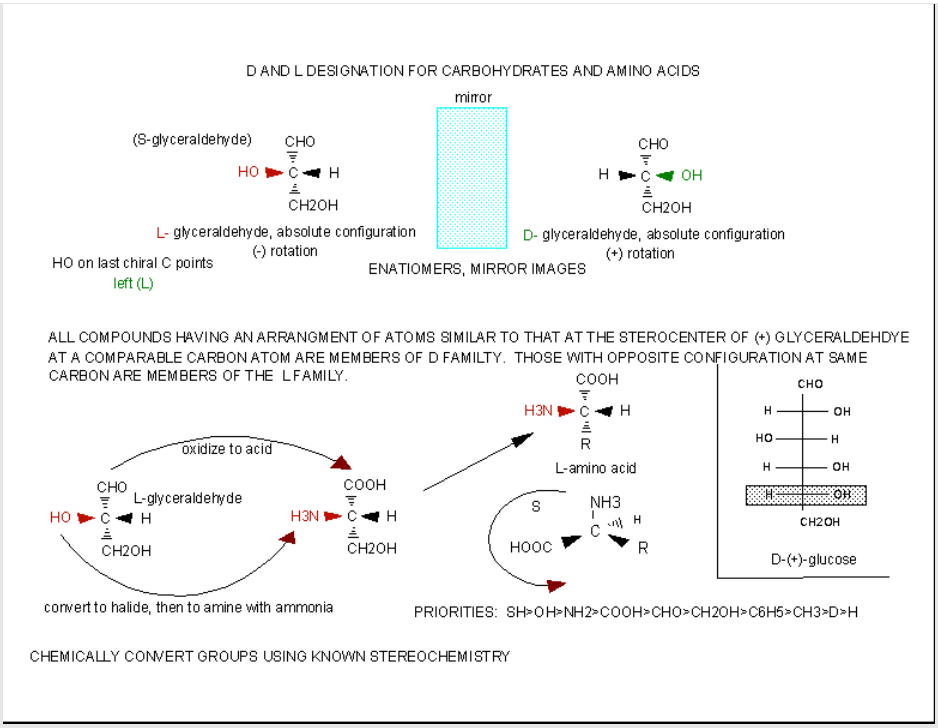


(Note: above picture represents the amino acid in an unlikely protonation state with the weak acid protonated and the weak base deprotonated for simplicity in showing removal of water on peptide bond formation and the hydrolysis reaction.) Proteins are polymers of twenty naturally occurring amino acids. 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.

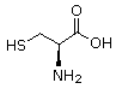
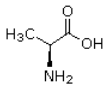
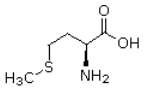
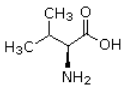
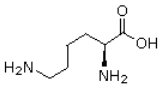
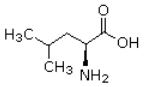
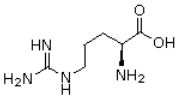
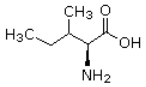
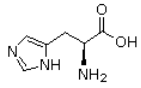
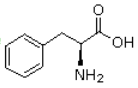
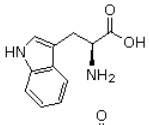
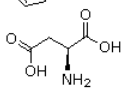
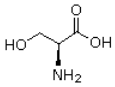
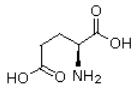
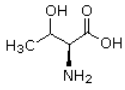
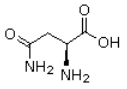
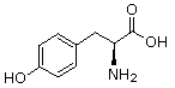
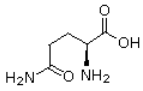
"In addition, however, chemists often need to define a configuration unambiguously in the absence of any reference compound, and for this purpose the alternative (R,S) system is ideal, as it uses priority rules to specify configurations. These rules sometimes lead to absurd results when they are applied 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.

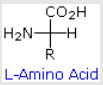
It follows that it is not just conservatism or failure to understand the (R,S) system that causes biochemists to continue with D and L: it is just that the DL system fulfils their needs much better. As mentioned, chemists also use D and L when they are appropriate to their needs. The explanation given 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 α-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 α-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

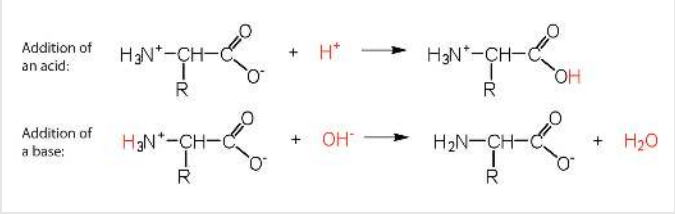
Zwitterion

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.

$$CH_3CH(NH_2)CO_2H \rightleftharpoons CH_3CH(NH_3)^{(+)}CO_2^{(-)}$$

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.

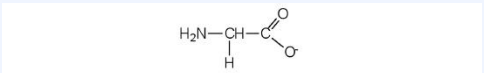


Example 26.1

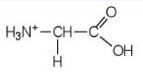
a. Draw the structure for the anion formed when glycine (at neutral pH) reacts with a base.
b. Draw the structure for the cation formed when glycine (at neutral pH) reacts with an acid.

Solution

a. The base removes H^+ from the protonated amine group.

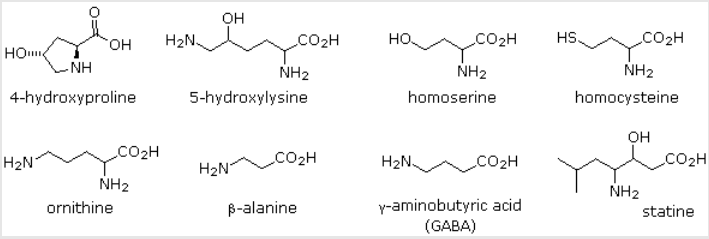


b. The acid adds H^+ to the carboxylate group.



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.



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.

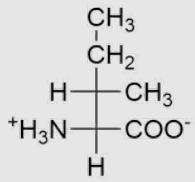
Solutions

S26.1.1

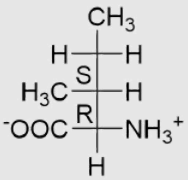
The sulfur atom in the side chain causes the side chain to have higher priority than the other substituents.

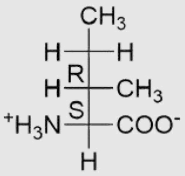
S26.1.2

(a)



(b)





Contributors and Attributions

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- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
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24.3: Isoelectric Points and Electrophoresis

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).

$$pK_a = pH + \log_{10} \frac{[HA]}{A^-]} \tag{24.3.1}$$

The titration curve for alanine in Figure **24.3.2** 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.

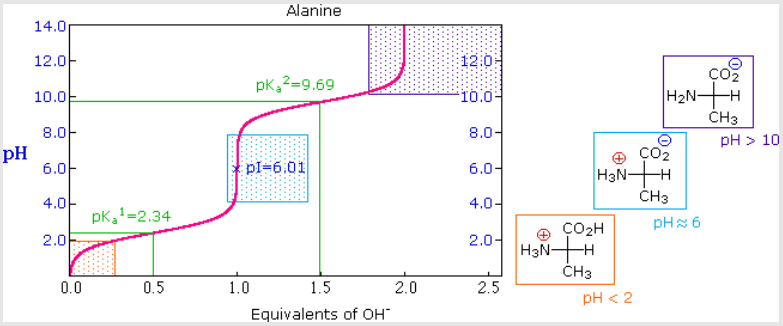


Figure **24.3.1**: Titration curves for many other amino acids may be examined at a useful site provided by The University of Virginia in Charlottesville.

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 **24.3.2**). 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.

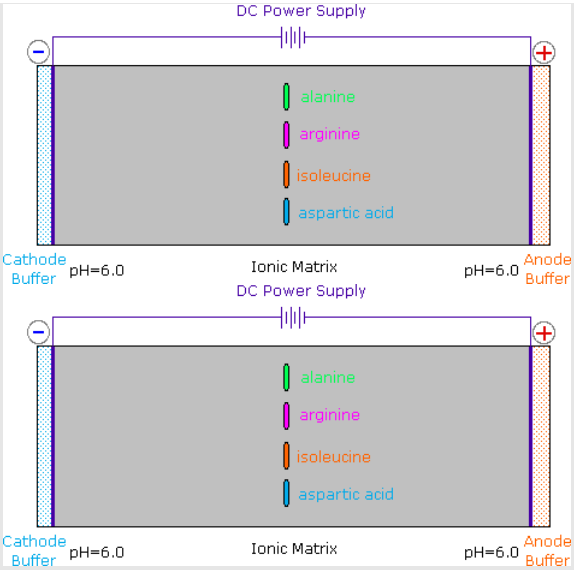
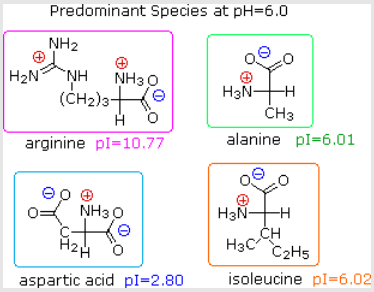


Figure **24.3.2**: In the example shown here, four different amino acids are examined simultaneously in a pH 6.00 buffered medium. To see the result of this experiment, click on the illustration. Note that the colors in the display are only a convenient reference, since these amino acids are colorless.

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 **24.3.1**: 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 **24.3.1**. 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.

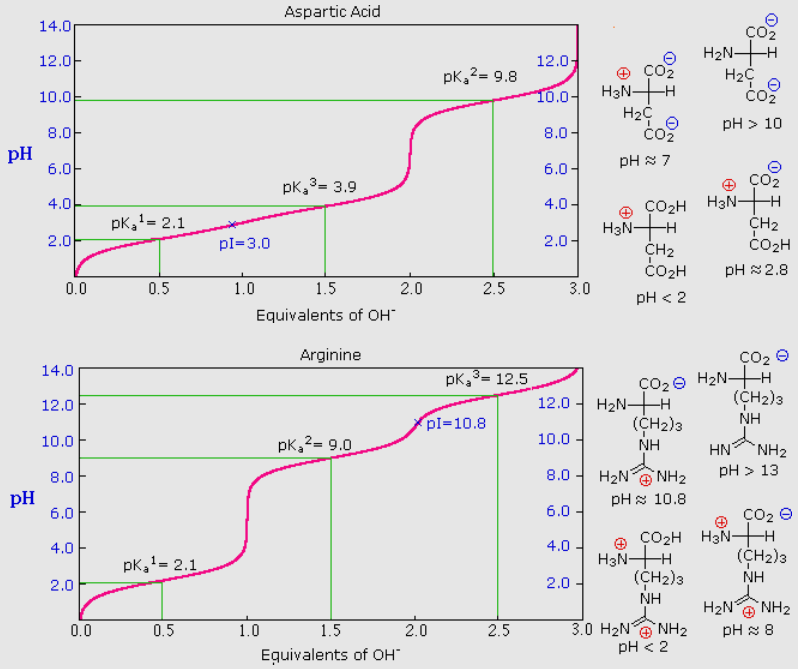


Figure **24.3.3**

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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24.4: 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.

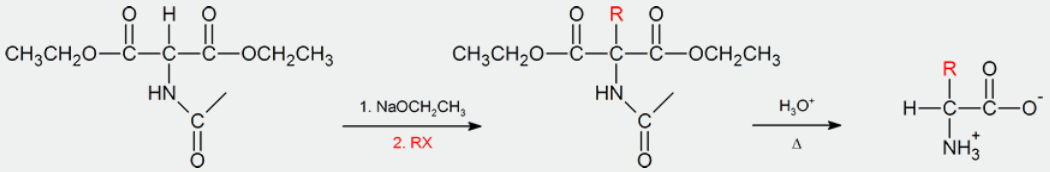
- amidomalonate synthesis
- enantioselective synthesis
- racemic mixture

Study Notes

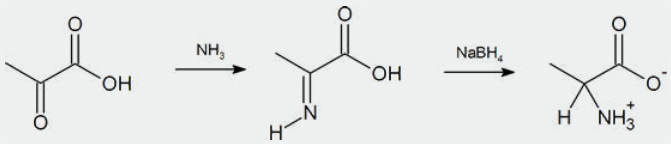
Do not be alarmed by the number of methods to synthesize amino acids described in this section.You have seen many of these reactions in previous sections and should already be familiar with the approaches discussed here.

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 α-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,

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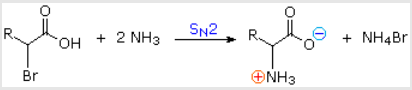
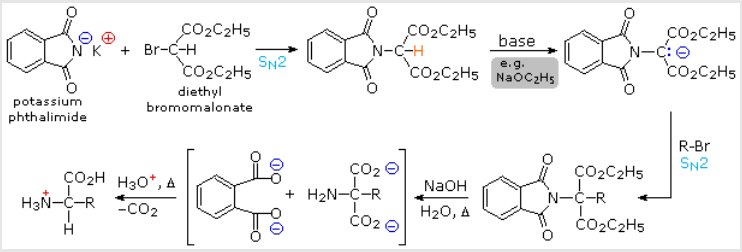
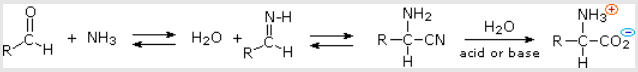
it is more effective for making amino acids, thanks to the reduced nucleophilicity of the nitrogen atom in the product. Nevertheless, more complex procedures that give good yields of pure compounds are often chosen for amino acid synthesis.



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).

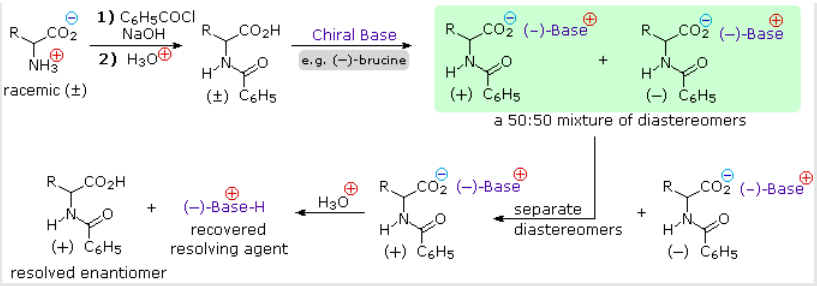


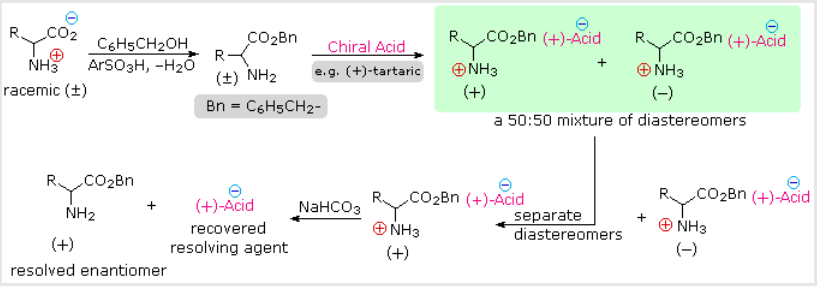
3) An elegant procedure, known as the **Strecker synthesis**, assembles an alpha-amino acid from ammonia (the amine precursor), cyanide (the carboxyl precursor), and an aldehyde. This reaction (shown below) is essentially an imino analog of cyanohydrin formation. The alpha-amino nitrile formed in this 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.





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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24.5: 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—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.

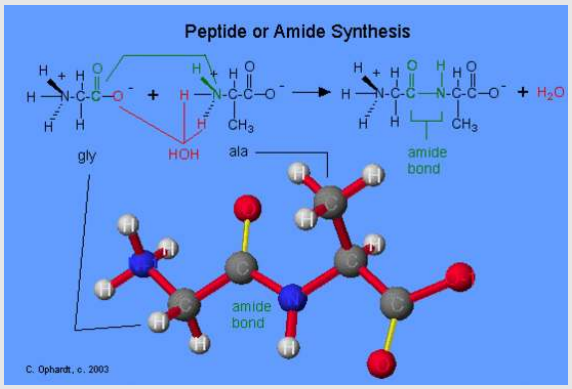
- C-terminal amino acid
- N-terminal amino acid
- peptides
- residues

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.

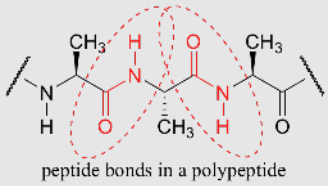
Exercise \PageIndex1

Write the reactions for:

a. ala + gly ---> Answer graphic
b. phe + ser ----> Answer graphic

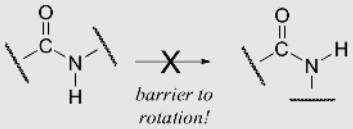
Resonance contributors for the peptide bonds

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.

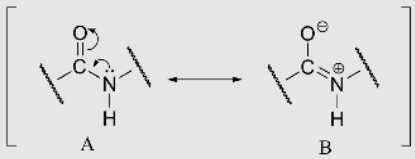


peptide bonds in a polypeptide

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.



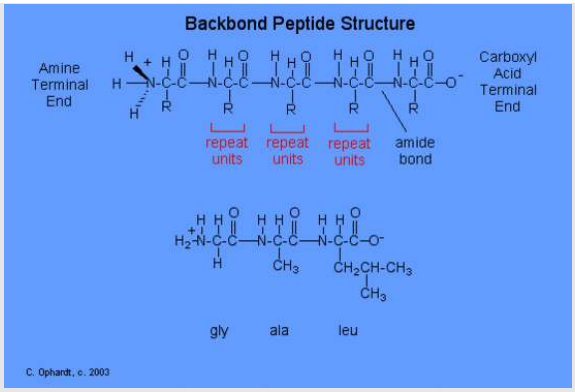
Although B is a minor contributor due to the separation of charges, it is still very relevant in terms of peptide and protein structure – our proteins would simply not fold up properly if there was free rotation about the peptide C-N bond.

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 \PageIndex2

Write the tripeptide structure for val-ser-cys. First write the "backbone" and then add the specific side chains.

Solution

 Answer graphic

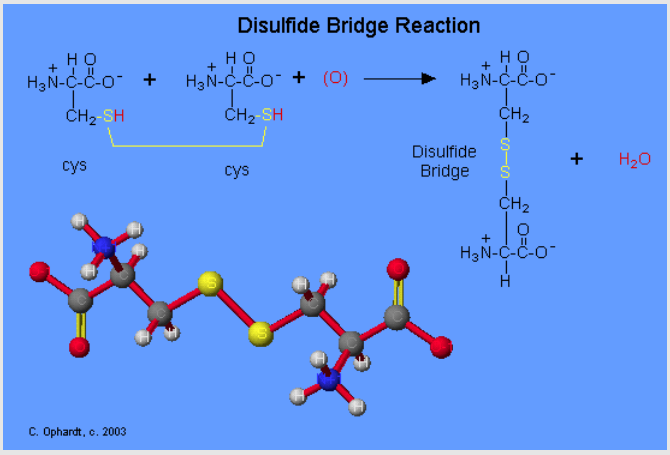
QUES. Write the structure for the tripeptide:

2 a) glu-cys-gly ---> Answer graphic

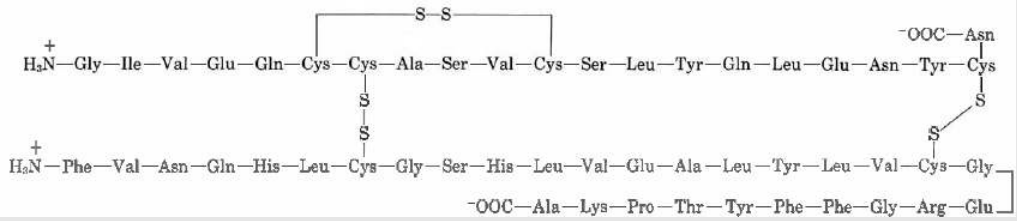
2 b) phe-tyr-asn ---> Answer graphic

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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- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)

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24.6: 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 analyzed, 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.

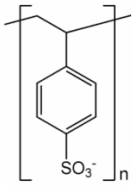


Fig 26.5.1: A Cation Rasin like Dowex 50 is a polymeric bead bearing aryl sulfonic acid groups

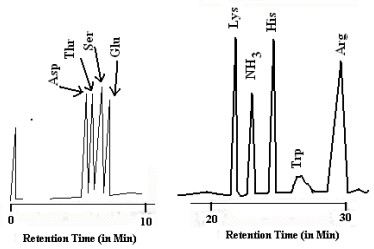
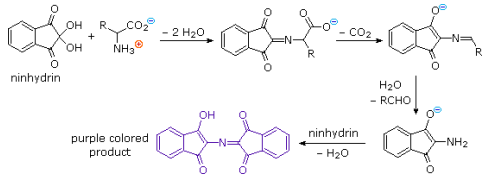


Fig 26.5.2: Some typical chromatograms from an amino acid analyzer

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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24.7: Peptide Sequencing: 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

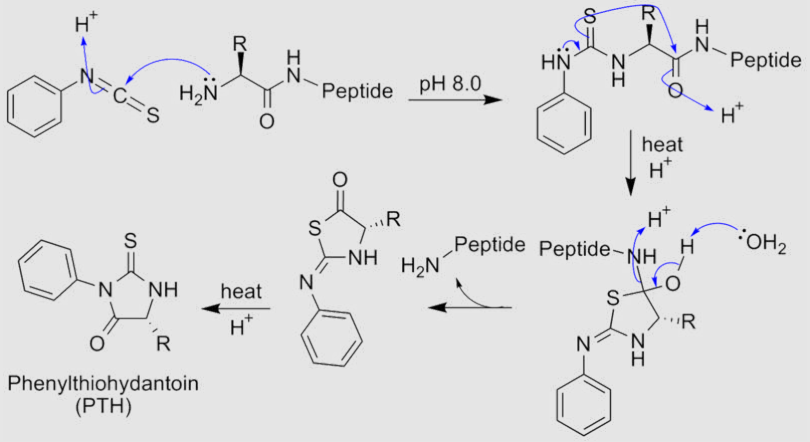
Study Notes

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.

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24.8: 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).

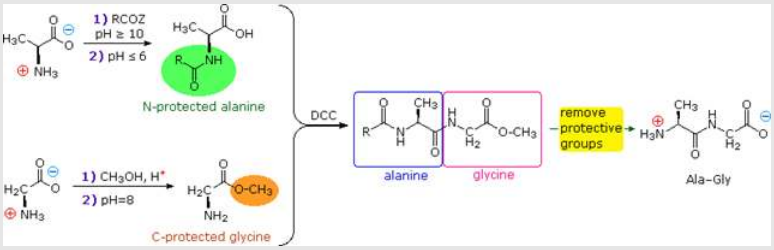
From the perspective of an organic chemist, peptide synthesis requires selective acylation of a free amine. To accomplish the desired amide bond formation, we must first deactivate all extraneous amine functions so they do not compete for the acylation reagent. Then we must selectively activate the designated 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.

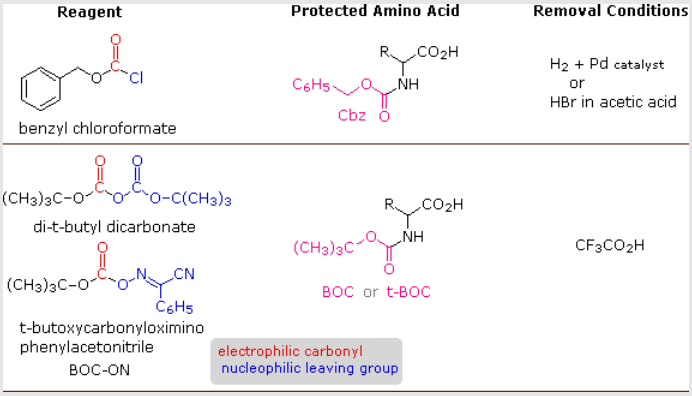


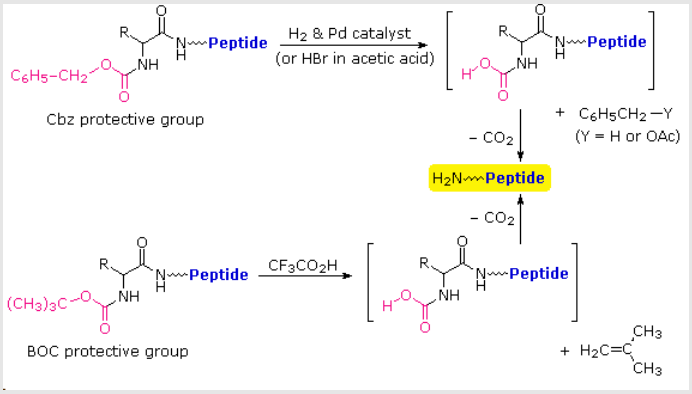
An important issue remains to be addressed. Since the N-protective group is an amide, removal of this function might require conditions that would also cleave the just formed peptide bond. Furthermore, the harsh conditions often required for amide hydrolysis might cause extensive racemization of the 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.





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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24.9: Automated Peptide Synthesis: 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)

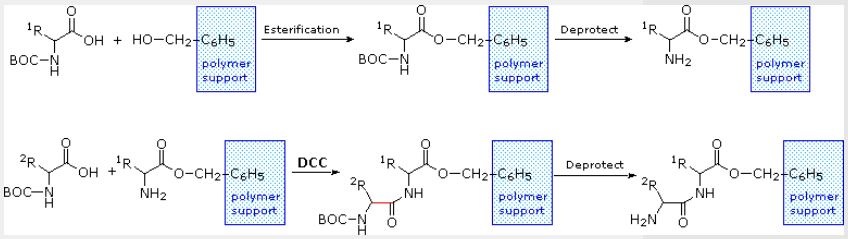
Study Notes

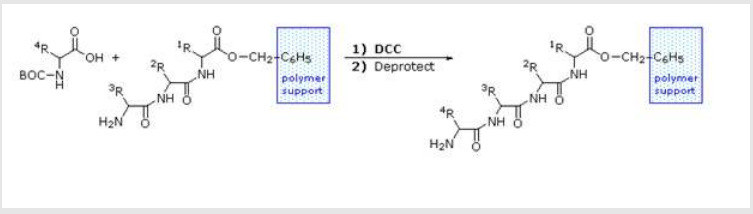
The solid-phase used in this method is a polymer support. You will not be examined on the details of the Merrifield solid-phase method; however, you should be prepared to write a couple of paragraphs describing this important process.

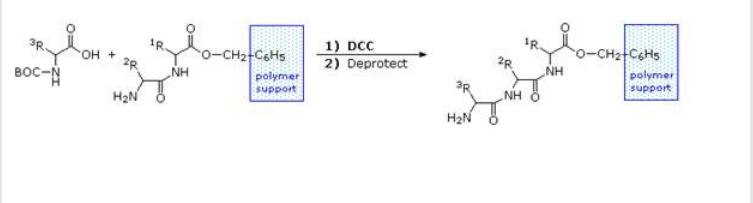
For his work on the synthesis of peptides, Bruce Merrifield was awarded the 1984 Nobel Prize in chemistry.

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







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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.

Contributors and Attributions

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24.10: Levels of 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.

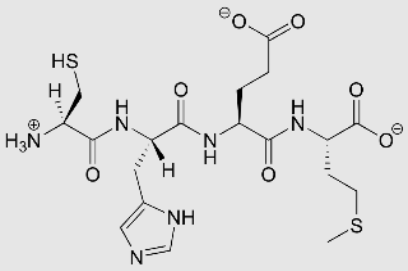
- α helix
- β pleated sheet
- primary structure
- quaternary structure
- secondary structure
- tertiary structure

Study Notes

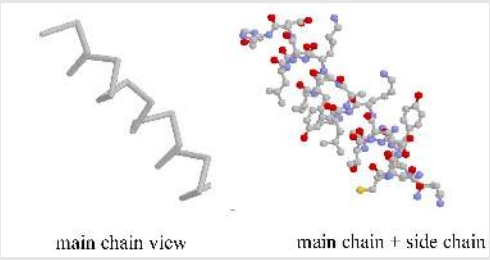
Note that in a diagram of the α-helical structure of a protein, the C-terminal of the protein is at the bottom of the diagram and the N-terminal is at the top. In an α helix, such as the one shown in Figure 26.9.1, the bulky R groups are all found on the outside of the helix, where they have the most room.

The four levels of protein structure

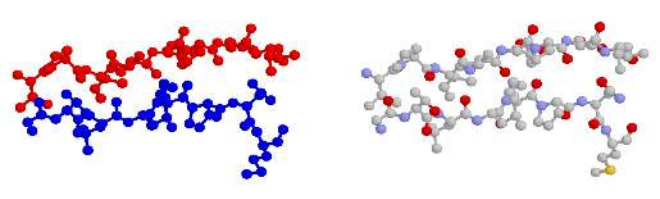
Protein structure can be discussed at four distinct levels. A protein's **primary structure** is two-dimensional - simply the sequence of amino acids in the peptide chain. Below is a Lewis structure of a short segment of a protein with the sequence CHEM (cysteine - histidine - glutamate - methionine)



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.

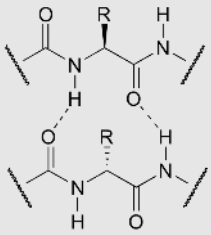


In a beta-sheet (or beta-strand) structure, two sections of protein chain are aligned side-by-side in an extended conformation. The figure below shows two different views of the same beta-sheet: in the left-side view, the two regions of protein chain are differentiated by color.



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.

α-Helices

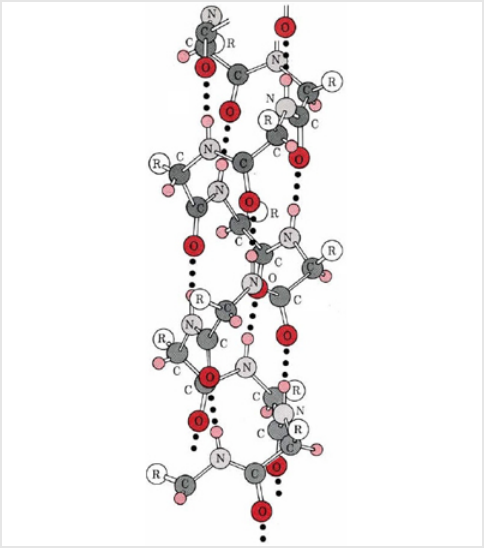
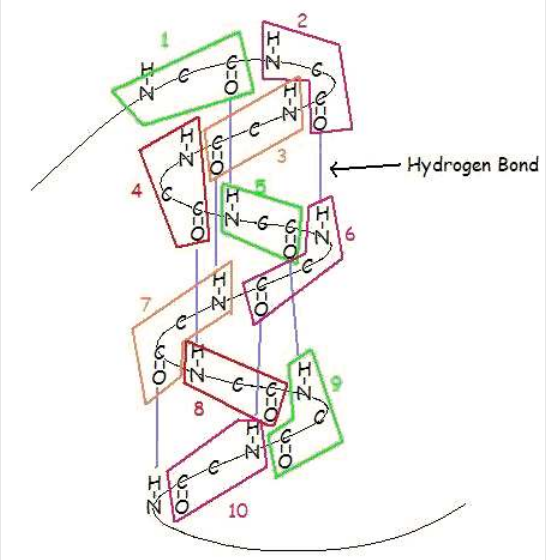


Figure: *Ball-and-stick model of the α helix. Hydrogen bonds are shown as dotted bonds. Note that R groups extend almost perpendicular from the axis.*

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.

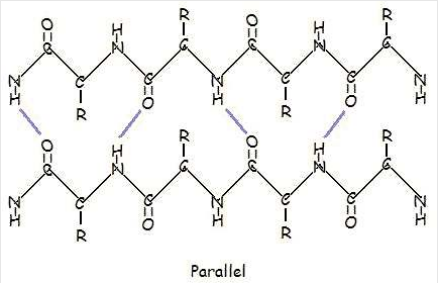
The structural integrity of an α-helix is in part dependent on correct steric configuration. Amino acids whose R-groups are too large (tryptophan, tyrosine) or too small (glycine) destabilize α-helices. Proline also destabilizes α-helices because of its irregular geometry; its R-group bonds back to the 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.

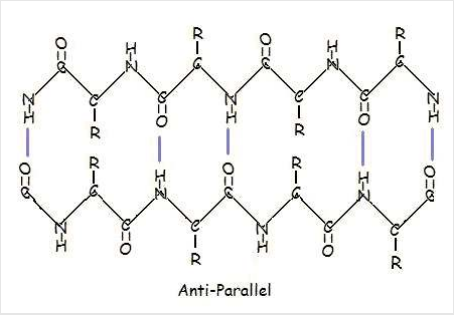


BETA-PLEATED SHEETS

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:



Or in anti-parallel arrangement:



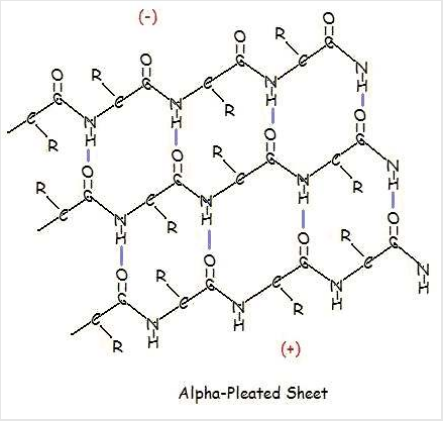
Parallel and anti-parallel arrangement is the direct consequence of the directionality of the polypeptide chain. In anti-parallel arrangement, the C-terminus end of one segment is on the same side as the N-terminus end of the other segment. In parallel arrangement, the C-terminus end and the N-terminus 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.

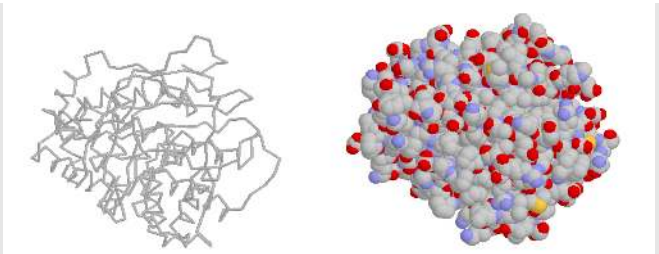
Commonly, an anti-parallel beta-pleated sheet forms when a polypeptide chain sharply reverses direction. This can occur in the presence of two consecutive proline residues, which create an angled kink in the polypeptide chain and bend it back upon itself. This is not necessary for distant segments of 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.

α-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.



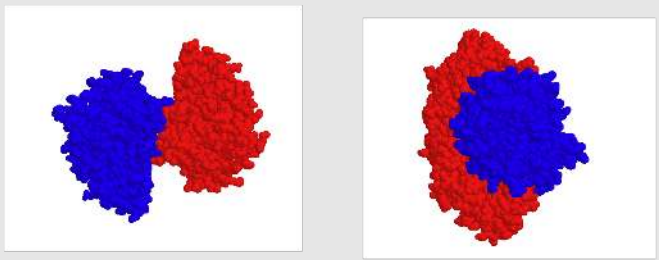
A protein's **tertiary structure** is the shape in which the entire protein chain folds together in three-dimensional space, and it is this level of structure that provides protein scientists with the most information about a protein's specific function.



folded protein chain (main chain view)

folded protein chain ('space-filling' view)

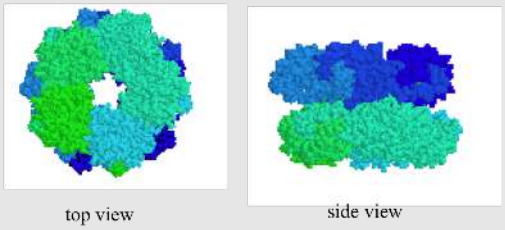
While a protein's secondary and tertiary structure is defined by how the protein chain folds together, **quaternary structure** is defined by how two or more folded protein chains come together to form a 'superstructure'. Many proteins consist of only one protein chain, or **subunit**, and thus have 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):

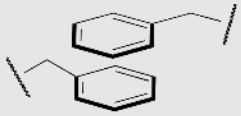


top view

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.

Contributors and Attributions

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- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- Organic Chemistry With a Biological Emphasis by Tim Soderberg (University of Minnesota, Morris)
- 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.

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24.11: 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 **24.11.1**.

Table **24.11.1**: ***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.
i	reactions in which a compound is converted to its isomer	Isomerases may catalyze the conversion of an aldose to a

Class	Type of Reaction Catalyzed	Examples
somerases		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 24.11.1). 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 24.11.2):

$$S + E \rightleftharpoons E\text{–}S \tag{24.11.1}$$

$$E\text{–}S \rightarrow P + E \tag{24.11.2}$$

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 **24.11.1**).

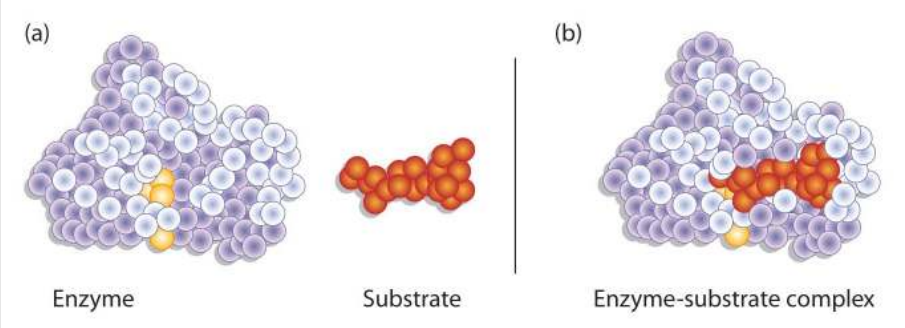


Figure* 24.11.1*: *Substrate Binding to the Active Site of an Enzyme. The enzyme dihydrofolate reductase is shown with one of its substrates: $NADP^+$ (a) unbound and (b) bound. The $NADP^+$ (shown in red) binds to a pocket that is complementary to it in shape and ionic properties.*

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 **24.11.2**). This model portrayed the enzyme as conformationally rigid and able to bond only to substrates that exactly fit the active site.

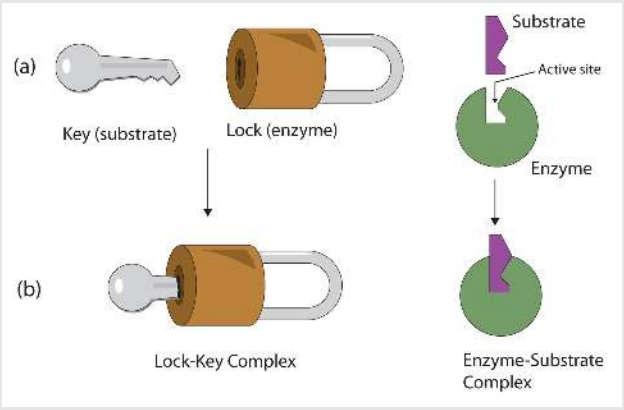


Figure **24.11.2**: The Lock-and-Key Model of Enzyme Action. (a) Because the substrate and the active site of the enzyme have complementary structures and bonding groups, they fit together as a key fits a lock. (b) The catalytic reaction occurs while the two are bonded together in the enzyme-substrate 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 **24.11.3**. After catalysis, the enzyme resumes its original structure.

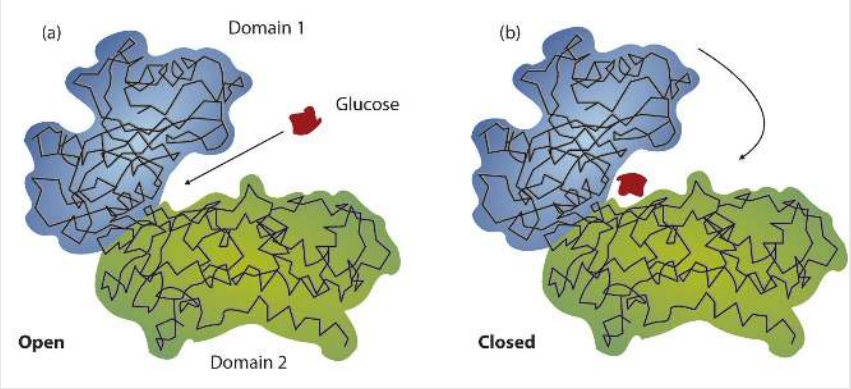


Figure **24.11.3**: The Induced-Fit Model of Enzyme Action. (a) The enzyme hexokinase without its substrate (glucose, shown in red) is bound to the active site. (b) The enzyme conformation changes dramatically when the substrate binds to it, resulting in additional interactions between hexokinase and 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 24.11.1

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 24.11.1

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 **24.11.2**: 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 **24.11.2**), which include vitamins A, D, E, and K, and the *water-soluble vitamins*, which are the B complex vitamins and vitamin C (Table **24.11.3**). 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 **24.11.3**: ***Water-Soluble Vitamins and Physiological Functions***

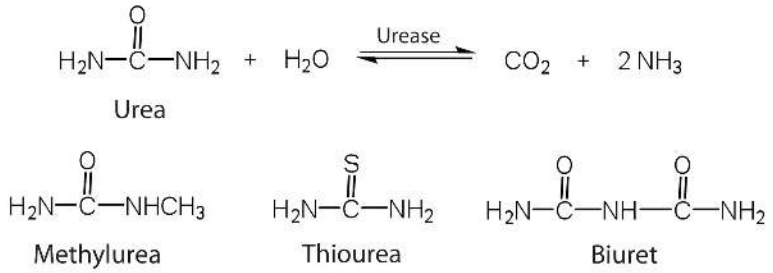
Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
vitamin B_1 (thiamine)	thiamine pyrophosphate	decarboxylation reactions	beri-beri
vitamin B_2 (riboflavin)	flavin mononucleotide or flavin adenine dinucleotide	oxidation-reduction reactions involving two hydrogen atoms	—
vit	nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate	oxidation-reduction reactions involving the hydride ion (H^-)	pellagra

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
amin B_3 (niacin)			
vitamin B_6 (pyridoxine)	pyridoxal phosphate	variety of reactions including the transfer of amino groups	—
vitamin B_1	methylcobalamin or deoxyadenoxylcobalamin	intramolecular rearrangement reactions	pernicious anemia

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
B_{12} (cyanocobalamin)			
biotin	biotin	carboxylation reactions	—
folic acid	tetrahydrofolate	carrier of one-carbon units such as the formyl group	anemia
pantothenic	coenzyme A	carrier of acyl groups	—

Vitamin	Coenzyme	Coenzyme Function	Deficiency Disease
Acid			
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. COO^-
   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. ionic bonding (salt bridge)
   b. ionic bonding (salt bridge)
   c. hydrogen bonding
   d. dispersion forces

2. a. disulfide bridge
b. H-bond because we can infer this amino group is part of an amide since it is not ionized
c. London dispersion
d. salt bridge (ionic bonding)

3. a. The amino acid has a positively charged side chain capable of forming salt bridges: histidine or arginine or lysine.
   b. The amino acid has a negatively charged side chain capable of forming salt bridges; aspartic acid or glutamic acid.
   c. The amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine or cysteine.
   d. The amino acid has a nonpolar side chain with London dispersion forces: alanine or valine or phenylalanine or leucine or isoleucine or methionine or tryptophan or proline or glycine.

4. a. The amino acid can form a disulfide bridge: cysteine OR the amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine

b. The amino acid has a polar side chain capable of engaging in hydrogen bonding: serine or threonine or tyrosine or asparagine or glutamine or cysteine.

c. The amino acid has a nonpolar side chain with London dispersion forces: alanine or valine or phenylalanine or leucine or isoleucine or methionine or tryptophan or proline or glycine.

d. The amino acid has a positively charged side chain capable of forming salt bridges: histidine or arginine or lysine.

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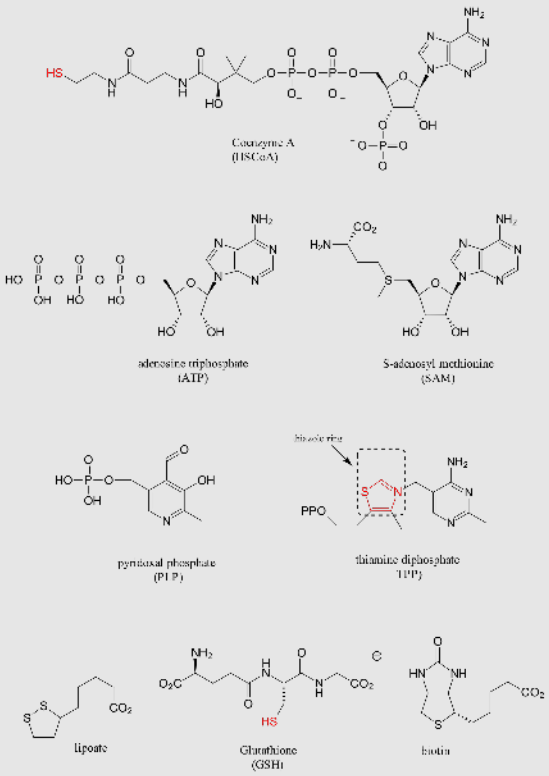
24.12: How do enzymes work?

Objectives

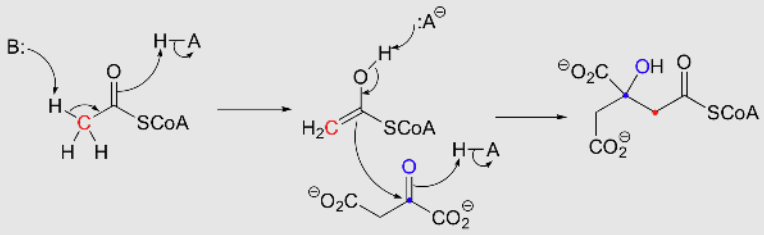
After completing this section, you should be able to

1. describe and explain the general function of an enzyme like citrate synthase in a reaction.
2. identify the structures of ten common coenzymes.

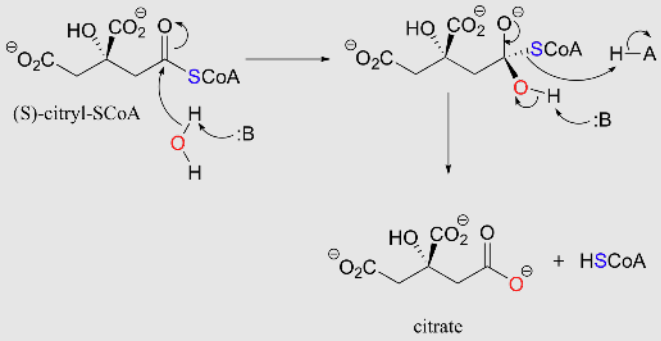


Oxaloacetate to Citrate Catalyzed by Citrate Synthase

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

25: Lipids

25.1: Introduction
25.2: Waxes, Fats, and Oils
25.3: Saponification of Fats and Oils; Soaps and Detergents
25.4: Phospholipids
25.5: Prostaglandins and other Eicosanoids
25.6: Terpenes and Terpenoids
25.7: Steroids
25.8: Biosynthesis of Steroids

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25.1: Introduction

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 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. The diagram below presents one scheme for classifying the various kinds of lipids.

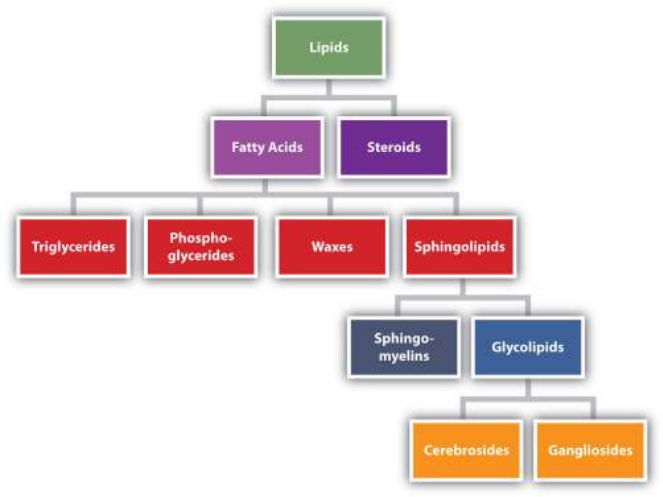

Figure: *Lipid Organization Based on Structural Relationships*

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25.2: 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. The systematic names for these compounds are shown in the tables below.

Saturated Fatty Acids

Table 27.1 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 27.2 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.

Waxes are esters of fatty acids with long chain monohydric alcohols (one hydroxyl group). Natural waxes are often mixtures of such esters, and may also contain hydrocarbons. The formulas for three well known waxes are given below, with the carboxylic acid moiety colored red and the alcohol colored blue.

Spermaceti		**Beeswax**		**Carnuba wax**
$CH_3(CH_2)_{14}CO_2$-$(CH_2)_{15}CH_3$		$CH_3(CH_2)_{24}CO_2$-$(CH_2)_{29}CH_3$		$CH_3(CH_2)_{30}CO_2$-$(CH_2)_{33}CH_3$

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. Carnuba wax is valued for its toughness and water resistance.

Triglycerides are esters of fatty acids and a trifunctional alcohol - glycerol (IUPAC name is 1,2,3-propantriol). The properties of fats and oils follow the same general principles as already described for the fatty acids. The important properties to be considered are: melting points and degree of unsaturation from component fatty acids. Since glycerol has three alcohol functional groups, three fatty acids must react to make three ester functional groups. The three fatty acids may or may not be identical. In fact, three different fatty acids may be present. The synthesis of a triglyceride is another application of the ester synthesis reaction. To write the structure of the triglyceride you must know the structure of glycerol and be given or look up the structure of the fatty acid in the table.

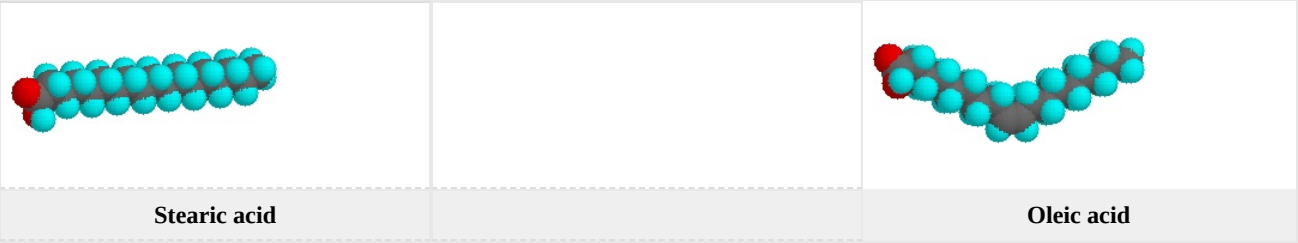
The common fats and oils including fatty acid content are listed below.

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	-

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

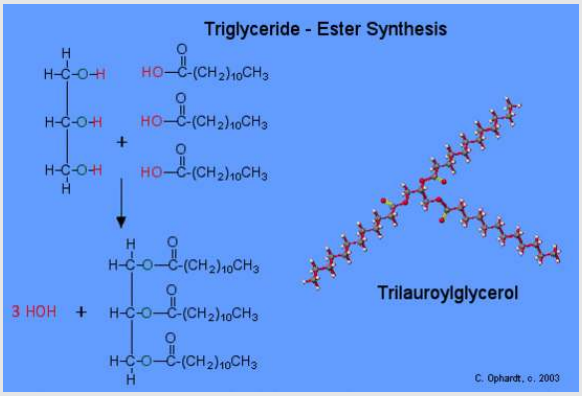
Unsaturated Fatty Acids		
Formula	Common Name	Melting Point
$CH_3(CH_2)_5CH{=}CH(CH_2)_7CO_2H$	palmitoleic acid	0 °C
$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	oleic acid	13 °C
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linoleic acid	-5 °C
$CH_3CH_2CH{=}CHCH_2CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$	linolenic acid	-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. 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. The trans-double bond isomer of oleic acid, known as elaidic acid, has a linear shape and a melting point of 45 °C (32 °C higher than its cis isomer). The shapes of stearic and oleic acids are displayed in the models below.



Stearic acid **Oleic acid**

Two polyunsaturated fatty acids, linoleic and linolenic, are designated "essential" because their absence in the human diet has been associated with health problems, such as scaley skin, stunted growth and increased dehydration. These acids are also precursors to the prostaglandins, a family of physiologically potent lipids present in minute amounts in most body tissues.

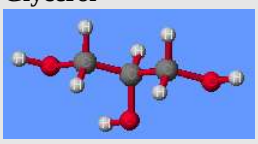


Synthesis of a Triglyceride

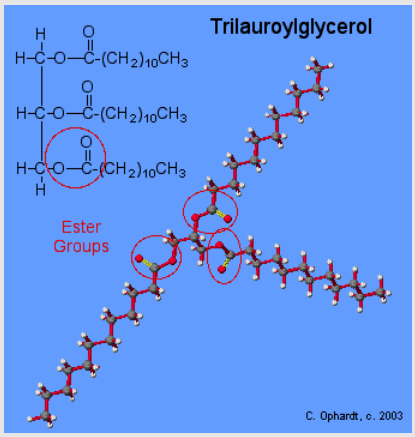
Since glycerol, (IUPAC name is 1,2,3-propantriol), has three alcohol functional groups, three fatty acids must react to make three ester functional groups. The three fatty acids may or may not be identical. In fact, three different fatty acids may be

present. nThe synthesis of a triglyceride is another application of the ester synthesis reaction. To write the structure of the triglyceride you must know the structure of glycerol and be given or look up the structure of the fatty acid in the table - find lauric acid.

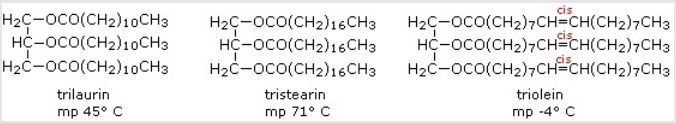
Glycerol



The simplified reaction reveals the process of breaking some bonds and forming the ester and the by product, water. Refer to the graphic on the left for the synthesis of **trilauroylglycerol**. First, the -OH (red) bond on the acid is broken and the -H (red) bond on the alcohol is also broken. Both join to make HOH, a water molecule. Secondly, the oxygen of the alcohol forms a bond (green) to the acid at the carbon with the double bond oxygen. This forms the ester functional group. This process is carried out three times to make three ester groups and three water molecules.



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 º C, whereas olive oil melts near -6 º 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.



Triglycerides having three identical acyl chains, such as tristearin and triolein (above), are called "simple", while those composed of different acyl chains are called "mixed". If the acyl chains at the end hydroxyl groups (1 & 3) of glycerol are different, the center carbon becomes a chiral center and enantiomeric configurations must be recognized.

The hydrogenation of vegetable oils to produce semisolid products has had unintended consequences. Although the hydrogenation imparts desirable features such as spreadability, texture, "mouth feel," and increased shelf life to naturally liquid vegetable oils, it introduces some serious health problems. These occur when the cis-double bonds in the fatty acid chains are not completely saturated in the hydrogenation process. The catalysts used to effect the addition of hydrogen isomerize the remaining double bonds to their trans configuration. These unnatural trans-fats appear to to be associated with increased heart disease, cancer, diabetes and obesity, as well as immune response and reproductive problems.

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25.3: Saponification of Fats and Oils; Soaps and Detergents

Learning Objectives

After completing this section, you should be able to

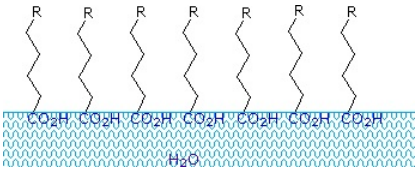
1. a. write an equation to represent the formation of a soap.
   b. identify the structure of the fat required to produce a given soap.
   c. identify the structure of a soap, given the structure of the fat from which it is produced.
2. describe the mechanism by which soaps exert their cleansing action.
3. 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

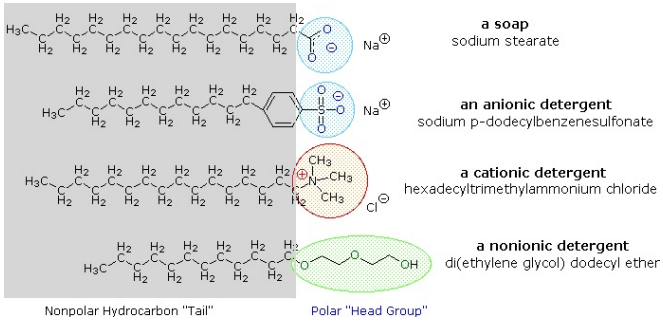
Make certain that you can define, and use in context, the key terms below.

- hydrophilic
- lipophilic (hydrophobic)
- amphiphilic
- micelles

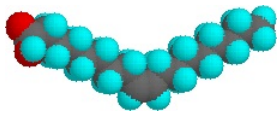
Carboxylic acids and salts having alkyl chains longer than eight carbons exhibit unusual behavior in water due to the presence of both hydrophilic (CO_2) and hydrophobic (alkyl) regions in the same molecule. Such molecules are termed **amphiphilic** (Gk. amphi = both) or **amphipathic**. Fatty acids 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.



Very small amounts of these surfactants dissolve in water to give a random dispersion of solute molecules. However, when the concentration is increased an interesting change occurs. The surfactant molecules reversibly assemble into polymolecular aggregates called micelles. 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. These micelles are often spherical in shape, but may also assume cylindrical and branched forms, as illustrated on the right. Here the polar head group is designated by a blue circle, and the nonpolar tail is a zig-zag black line.

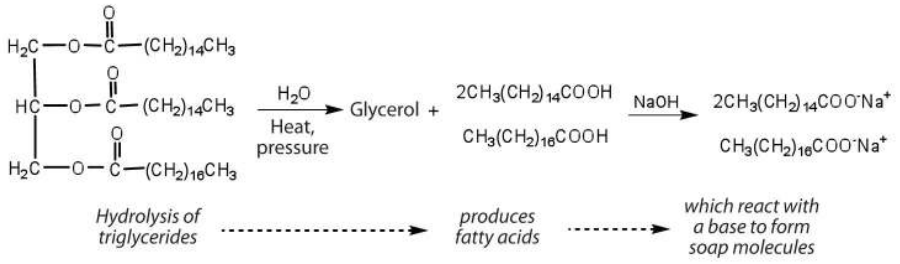


The oldest amphiphilic cleaning agent known to humans is soap. Soap is manufactured by the base-catalyzed hydrolysis (saponification) of animal fat (see below). Before sodium hydroxide was commercially available, a boiling solution of potassium carbonate leached from wood ashes was used. Soft potassium soaps were then converted to the harder sodium soaps by washing with salt solution. 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 is caused by the presence of calcium and magnesium salts in the water supply (hard water). These divalent cations cause aggregation of the micelles, which then deposit as a dirty scum.

These problems have been alleviated by the development of synthetic amphiphiles called detergents (or syndets). By using a much stronger acid for the polar head group, water solutions of the amphiphile 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 amphiphile 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

Chemical Reactions of Fats and Oils

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 [700 lb/in^2 (~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):



Contributors and Attributions

- Dr. Dietmar Kennepohl FCIC (Professor of Chemistry, Athabasca University)
- Prof. Steven Farmer (Sonoma State University)
- William Reusch, Professor Emeritus (Michigan State U.), Virtual Textbook of Organic Chemistry
- *The Basics of General, Organic, and Biological Chemistry* by David W. Ball, John W. Hill, and Rhonda J. Scott.

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25.4: Phospholipids

Learning Objectives

After completing this section, you should be able to

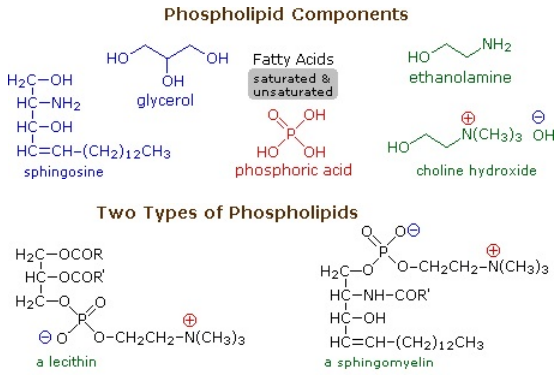
1. draw the general structure of a phosphoglyceride.
2. describe the occurrence and importance of phosphoglycerides in plant and animal tissues.

Key Terms

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

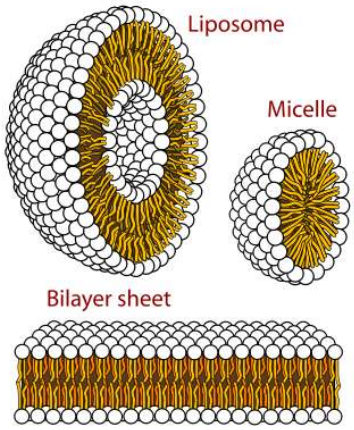
- phosphoglyceride
- phospholipid

Phospholipids are the main constituents of cell membranes. They resemble the triglycerides in being ester or amide derivatives of glycerol or sphingosine with fatty acids and phosphoric acid. The phosphate moiety of the resulting phosphatidic acid is further esterified with ethanolamine, choline or serine in the phospholipid itself. The following diagram shows the structures of some of these components. Clicking on the diagram will change it to display structures for two representative phospholipids. Note that the fatty acid components (R & R') may be saturated or unsaturated.



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. The phospholipid molecules can move about in their half the bilayer, but there is a significant energy barrier preventing migration to the other side of the bilayer.

This bilayer membrane structure is also found in aggregate structures called **liposomes**. Liposomes are microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. They are formed when phospholipids are vigorously mixed with water. Unlike micelles, liposomes have both aqueous interiors and exteriors.



A cell may be considered a very complex liposome. The bilayer membrane that separates the interior of a cell from the surrounding fluids is largely composed of phospholipids, but it incorporates many other components, such as cholesterol, that contribute to its structural integrity. Protein channels that permit the transport of various kinds of chemical species in and out of the cell are also important components of cell membranes.

The interior of a cell contains a variety of structures (organelles) that conduct chemical operations vital to the cells existence. Molecules bonded to the surfaces of cells serve to identify specific cells and facilitate interaction with external chemical entities. The sphingomyelins are also membrane lipids. They are the major component of the myelin sheath surrounding nerve fibers. Multiple Sclerosis is a devastating disease in which the myelin sheath is lost, causing eventual paralysis.

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25.5: 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.

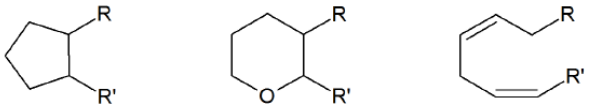
Key Terms

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

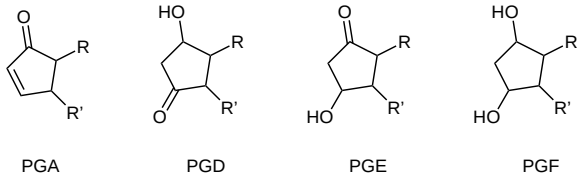
- eicosanoid
- prostaglandin

Eicosanoids

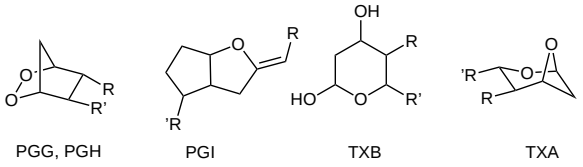
The members of this group of structurally related natural hormones have an extraordinary range of biological effects. They can lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses. Because their genesis in body 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.

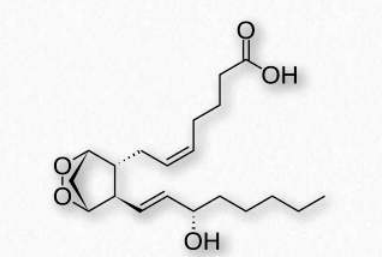


Prostaglandin structures for PGA, PGD, PGE and PGF



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.



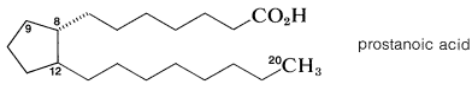
Prostaglandin PGH_2

Prostaglandins

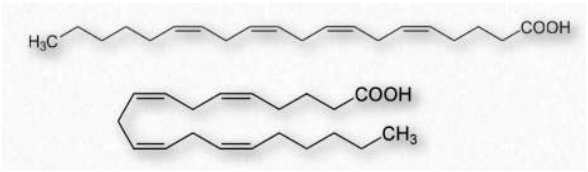
Prostaglandins were first discovered and isolated from human semen in the 1930s by Ulf von Euler of Sweden. Thinking they had come from the prostate gland, he named them prostaglandins. It has since been determined that they exist and are synthesized in virtually every cell of the body. Prostaglandins, 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.

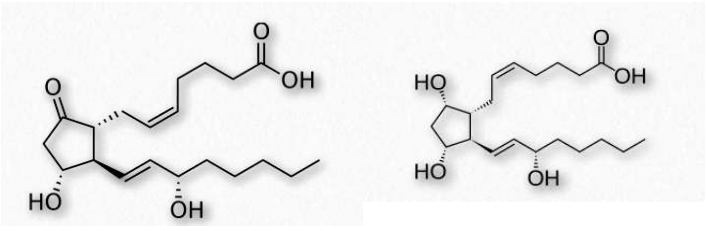


They are biochemically synthesized from the fatty acid, arachidonic acid. The unique shape of the arachidonic acid caused by a series of cis double bonds helps to put it into position to make the five member ring of the prostaglandin.



Arachidonic acid

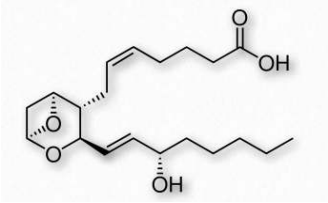
There are a variety of functional groups present in prostaglandin structures. The can have one, two, or three double bonds. On the five member ring there may also be double bonds, a ketone, or alcohol groups. Some typical structures are shown below.



Prostaglandin E2 (left) and Prostaglandin $F_{2\alpha}$ (Right)

Thromboxanes

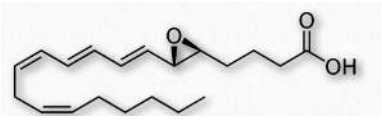
Thromboxanes play roles in clot formation and named for their role in thrombosis. They are potent vasoconstrictors and facilitate platelet aggregation. They are synthesized in platelets, as well. The anti-clotting effects of aspirin have their roots in the inhibition of synthesis of PGH2, which is the precursor of the thromboxanes. The most common thromboxanes are A2 (Figure 2.217) and B2.



Thromboxane $A2_2$

Leukotrienes

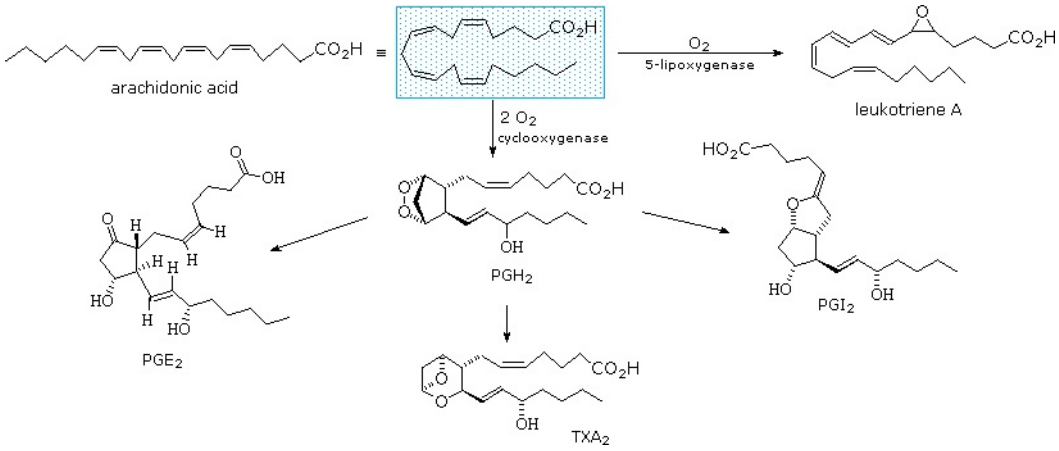
Another group of eicosanoid compounds are the leukotrienes (Figure 2.219). Like prostaglandins, leukotrienes are made from arachidonic acid. The enzyme catalyzing their formation is a dioxygenase known as arachidonate 5-lipoxygenase. Leukotrienes are involved in regulating immune responses. They are 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)

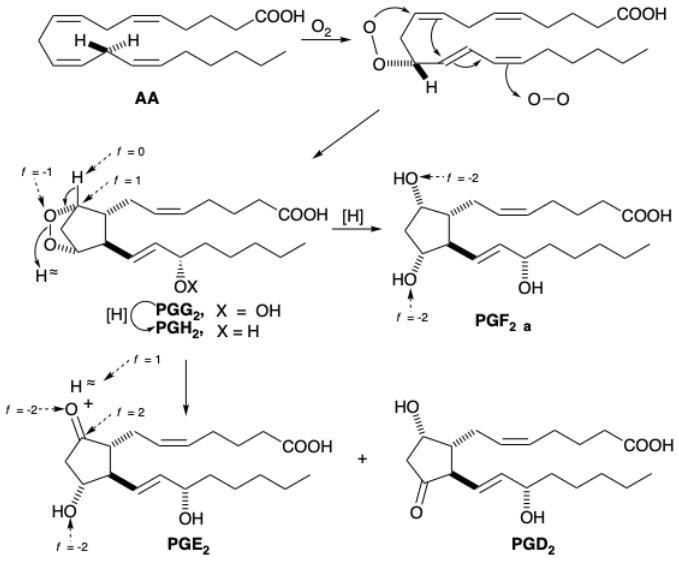
Eicosanoid Biosynthesis

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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- **2.8: Structure and Function - Lipids and Membranes** by Kevin Ahern, Indira Rajagopal, & Taralyn Tan is licensed CC BY-NC-SA 4.0. Original source: http://biochem.science.oregonstate.edu/content/biochemistry-free-and-easy.

25.6: Terpenes and Terpenoids

Objectives

After completing this section, you should be able to

1. identify a terpene from a given list of organic structures.
2. analyse 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

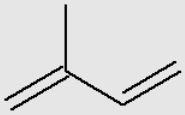
Make certain that you can define, and use in context, the key terms below.

- 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.

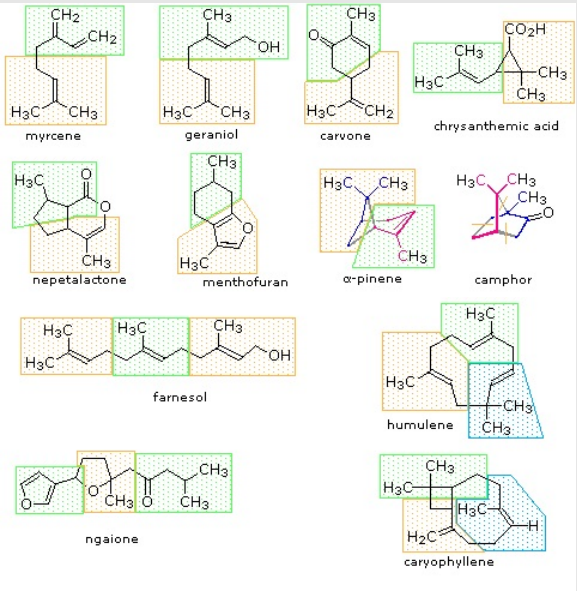


Figure 27.5.1: Monoterpenes and sesquiterpenes

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.

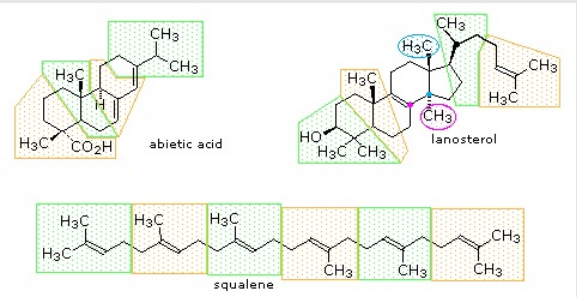
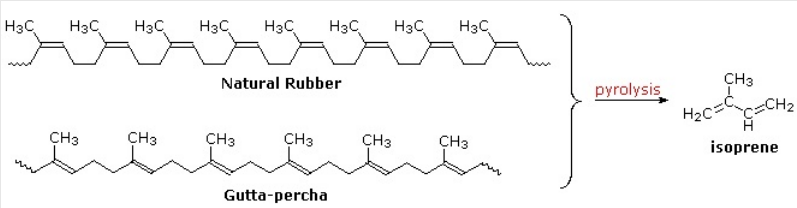


Figure 27.5.2: Triterpenes

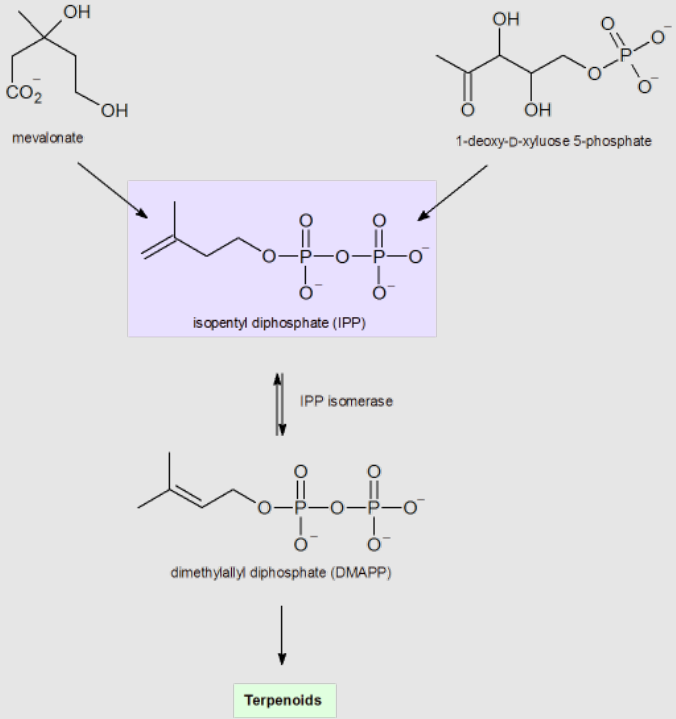
Polymeric isoprenoid hydrocarbons have also been identified. Rubber is undoubtedly the best known and most widely used compound of this kind. It occurs as a colloidal suspension called latex in a number of plants, ranging from the dandelion to the rubber tree (*Hevea brasiliensis*). Rubber is a polyene, 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.

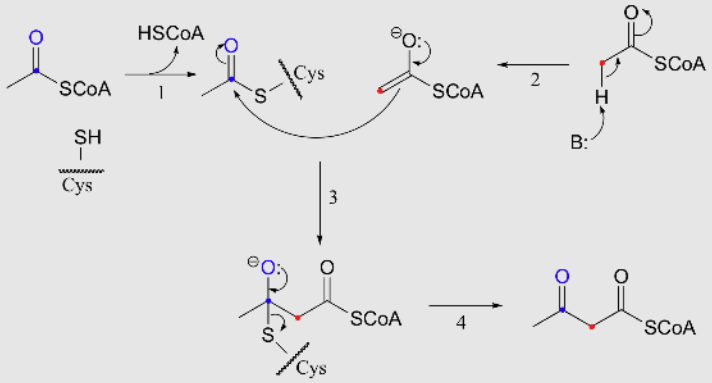


Mevalonate Pathway

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

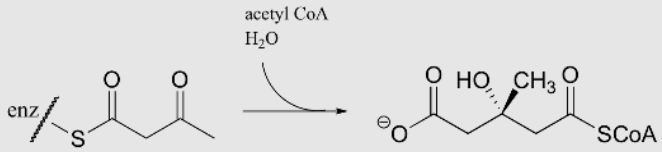
cysteine (Reaction 1). In the Claisen condensation phase of the reaction, the alpha-carbon of a second acetyl CoA is deprotonated, forming an enolate (Reaction 2).



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

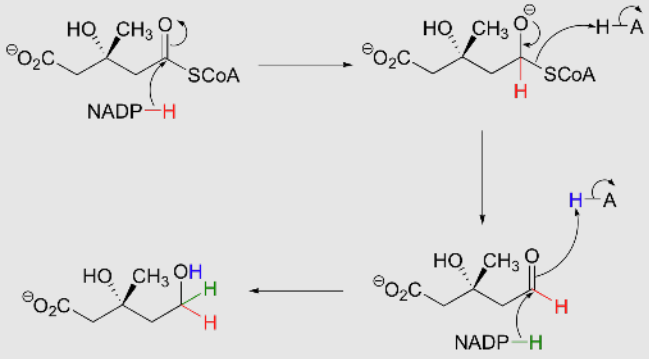
Acetyl CoA then reacts with the acetoacetyl CoA in an aldol-like addition. Subsequent hydrolysis produces (3*S*)-3-hydroxy-3-methylglutaryl CoA (HMG-CoA).



Generating HMG-CoA

Step 3 - Reduction of the Thioester

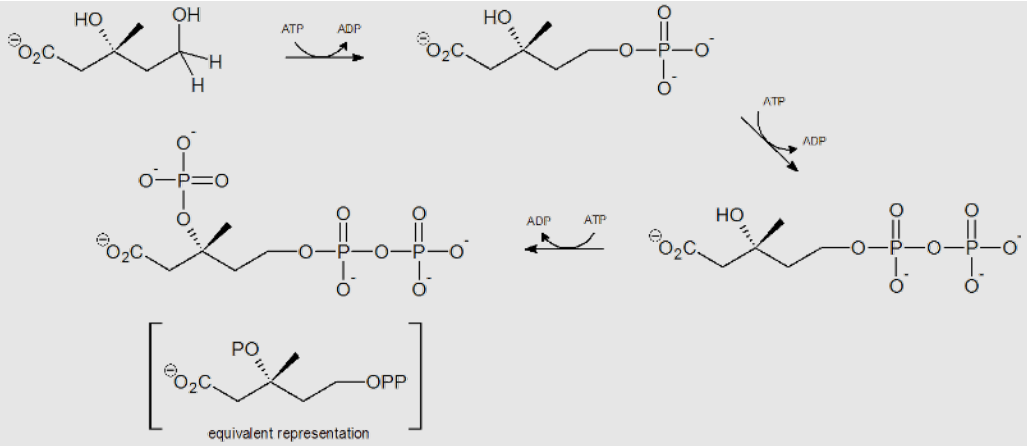
The thioester is reduced first to an aldehyde, then to a primary alcohol by two equivalents of NADPH producing (*R*)-mevalonate. The enzyme catalyzing this reaction is the target of the statin family of cholesterol-lowering drugs.



Generating (*R*)-Mevalonate

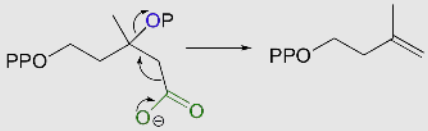
Step 4 - Mevalonate Phosphorylation

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.



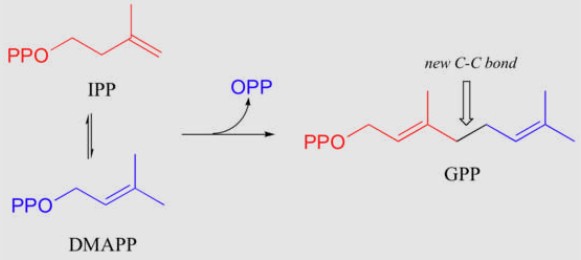
Step 5 - **Decarboxylation**

Finally isopentenyl diphosphate (IPP), the 'building block' for all isoprenoid compounds, is formed from a decarboxylation-elimination reaction.

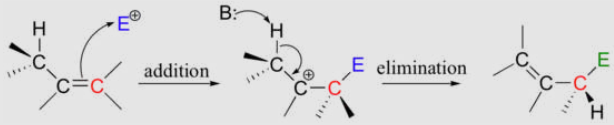


Conversion of IPP to Terpenoids

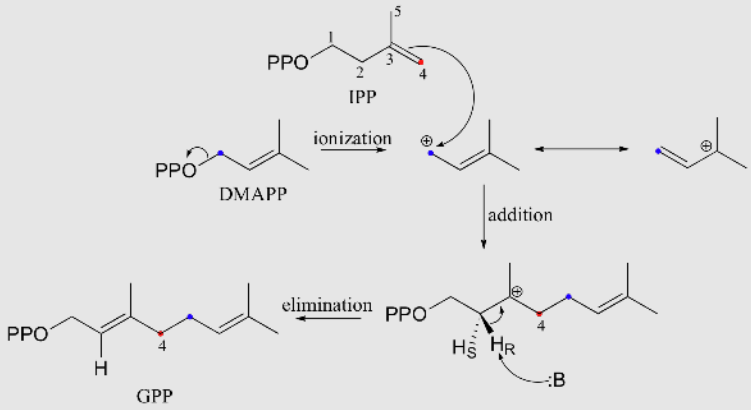
The electrophilic double bond isomerization catalyzed by IPP isomerase is a highly reversible reaction, with an equilibrium IPP:DMAPP ratio of about 6:1. In the next step of isoprenoid biosynthesis, the two five-carbon isomers condense to form a 10-carbon isoprenoid product called geranyl diphosphate (GPP).



This is a nice example of an electrophilic addition/elimination mechanism:

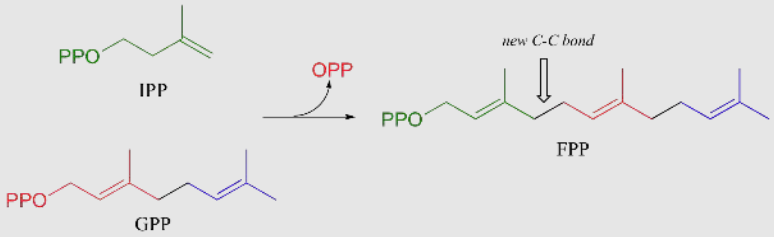


The first step is ionization of the electrophile - in other words, the leaving group departs and a carbocation intermediate is formed. In this case, the pyrophosphate group on DMAPP is the leaving group, and the electrophilic species is the resulting allylic carbocation.

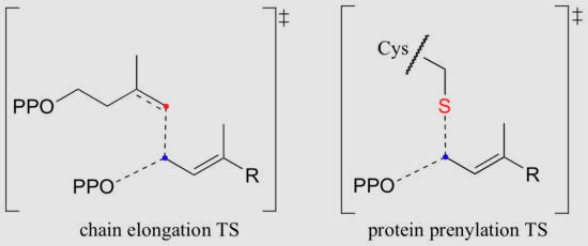


In the condensation (addition) step, the C_3-C_4 double bond in IPP attacks the positively-charged C_1 of DMAPP, resulting in a new carbon-carbon bond and a second carbocation intermediate, this time at a tertiary carbon. In the elimination phase, proton abstraction leads to re-establishment of a double 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).

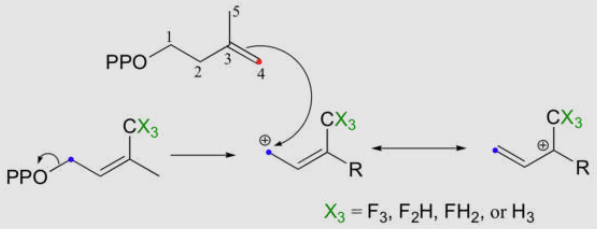


How do we know that these are indeed S_N1-like mechanisms with carbocation intermediates, rather than concerted S_N2-like mechanisms? First of all, recall that the question of whether a substitution is dissociative (S_N1-like) or associative (S_N2-like) is not always clear-cut - it could be somewhere 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.

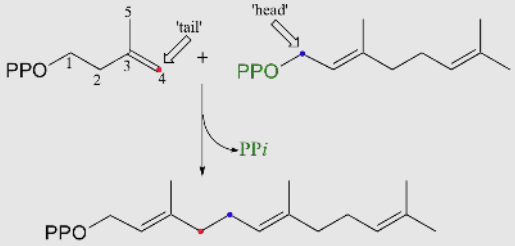
So it makes perfect sense that the chain elongation reaction should more S_N1-like than S_N2-like. Is this in fact the case? We know how to answer this question experimentally - just run the reaction with fluorinated DMAPP or GPP substrates and observe how much the fluorines slow things down.



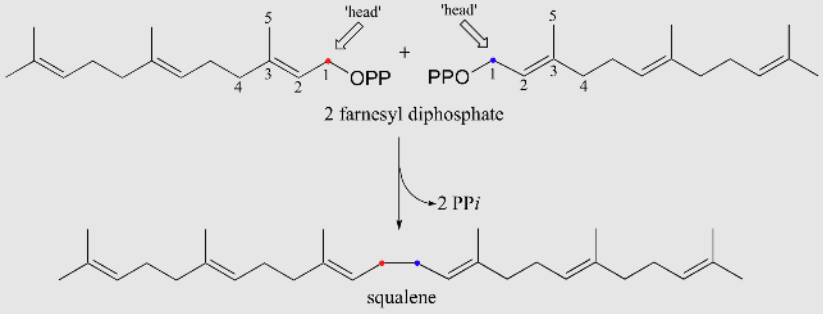
If the reaction is S_N1-like, the electron-withdrawing fluorines should destabilize the allylic carbocation intermediate and thus slow the reaction down considerably. If the mechanism is S_N2-like, the fluorine substitutions should not have a noticeable effect, because a carbocation intermediate would 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.

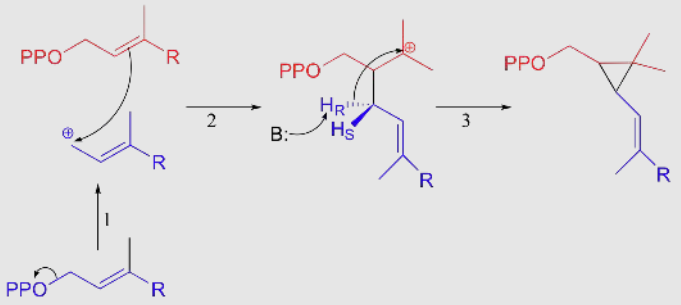
Cholesterol, as we discussed earlier in this chapter, is derived from a 30-carbon isoprenoid molecule called squalene. Squalene, in turn, is derived from the condensation of two molecules of farnesyl diphosphate (FPP), a 15-carbon isoprenoid. You may recall that FPP is the product of the C_4 to C_1, 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.

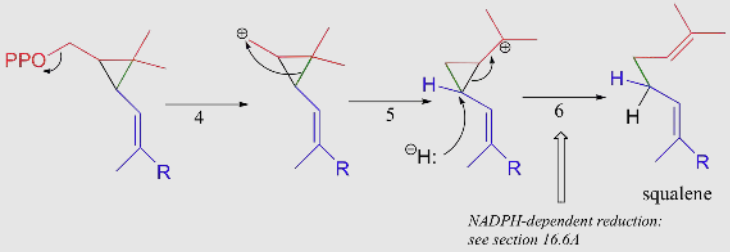


The first two steps are familiar: first, the pyrophosphate on one FPP molecule leaves (step 1), resulting in an allylic carbocation that is attacked by the C_2-C_3 π bond of the second molecule (step 2).

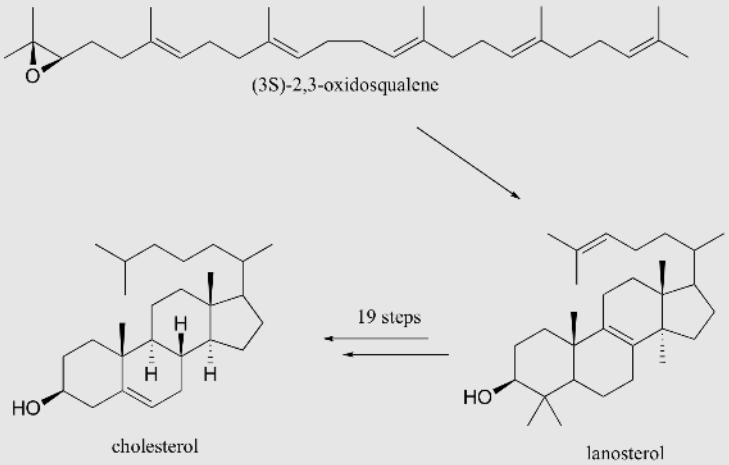


This results in a new carbon-carbon bond between the two FPP molecules, but with incorrect C_1 to C_2 connectivity (remember, the overall reaction is a C_1 to C_1 condensation). In step 3, a proton is abstracted and the electrons from the broken C-H bond bridge across a 2-carbon gap to form a cyclopropyl 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.



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25.7: 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-broken line 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-broken line structure from which to work.

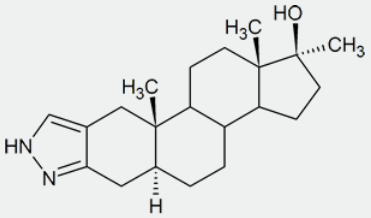
Key Terms

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

- steroid

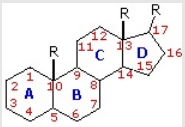
Study Notes

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

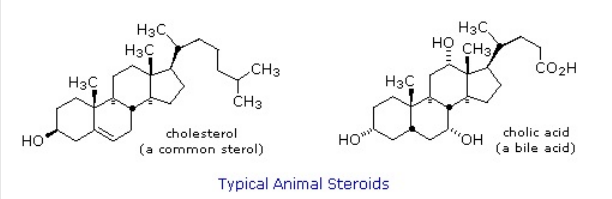
The important class of lipids called **steroids** are actually metabolic derivatives of terpenes, but they are customarily treated as a separate group. Steroids may be recognized by their tetracyclic skeleton, consisting of three fused six-membered and one five-membered ring, as shown in the diagram to the right. 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 if it is not a functional group. 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.

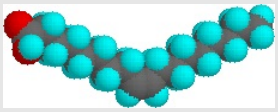


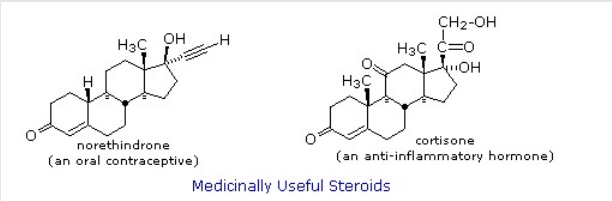
The Steroid
Carbon Skeleton

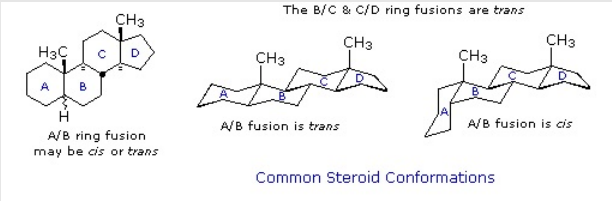
Steroids are widely distributed in animals, where they are associated with a number of physiological processes. Examples of some important steroids are shown in the following diagram. Norethindrone is a synthetic steroid, all the other examples occur naturally. A common strategy in pharmaceutical chemistry is to take a natural compound, having certain desired biological properties together with undesired side effects, and to modify its structure to enhance the desired characteristics and diminish the undesired. This is sometimes accomplished by trial and error.

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. This is shown in the last of the toggled displays, along with the preferred conformations of the rings.



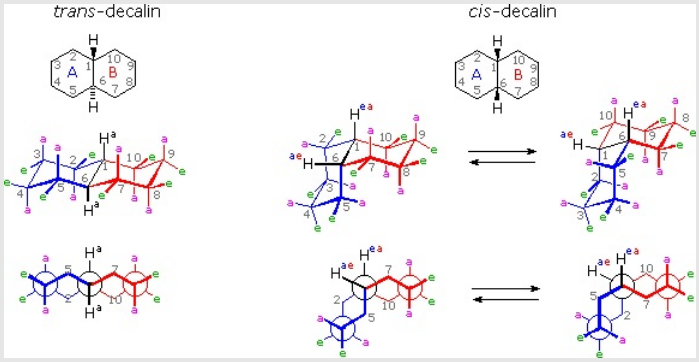


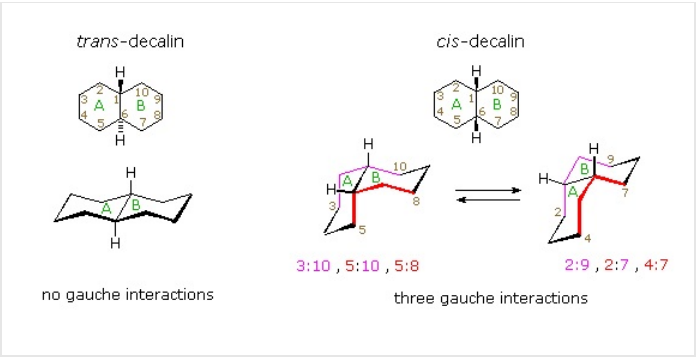




Chemical studies of the steroids were very important to our present understanding of the configurations and conformations of six-membered rings. Substituent groups at different sites on the tetracyclic skeleton will have axial or equatorial orientations that are fixed because of the rigid structure of 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.

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.



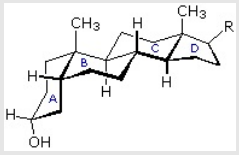


The trans-isomer is the easiest to describe because the fusion of the A & B rings creates a rigid, roughly planar, structure made up of two chair conformations. Each chair is fused to the other by equatorial bonds, leaving the angular hydrogens (Ha) axial to both rings. Note that the bonds directed above 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.

Steroids in which rings A and B are fused cis, such as the example on the right, do not have the sameconformational 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.

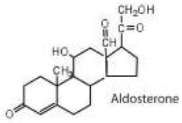
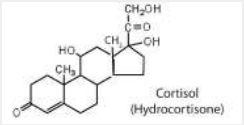
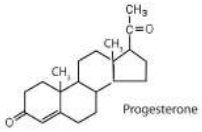
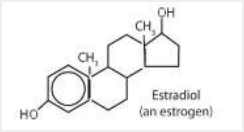
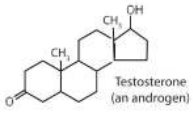


Steroid Hormones

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 17.3), 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 17.3 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.

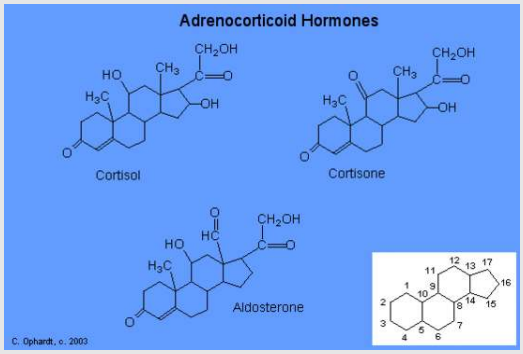
Sex hormones, both natural and synthetic, are sometimes used therapeutically. For example, a woman who has had her ovaries removed may be given female hormones to compensate. Some of the earliest chemical compounds employed in cancer chemotherapy were sex hormones. For example, estrogens are one treatment 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 mineralocrticoid 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.



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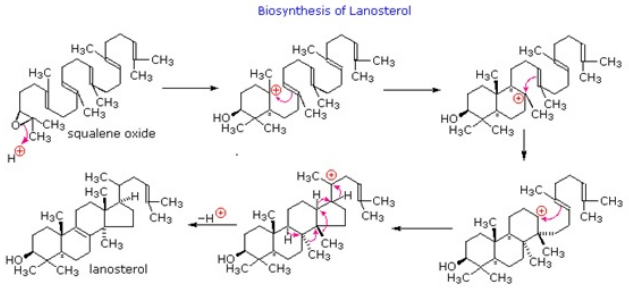
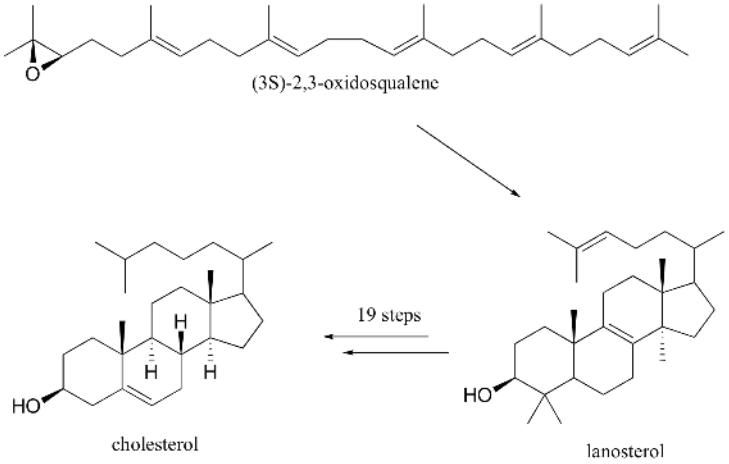
25.8: Biosynthesis of Steroids

On the diagram below, the series of cation-like cyclizations and rearrangements, known as the Stork-Eschenmoser hypothesis, is shown, which were identified in the biosynthesis of the triterpene lanosterol. Lanosterol is a precursor in the biosynthesis of steroids. This takes place by metabolic removal of three methyl groups and degradation of the side chain.

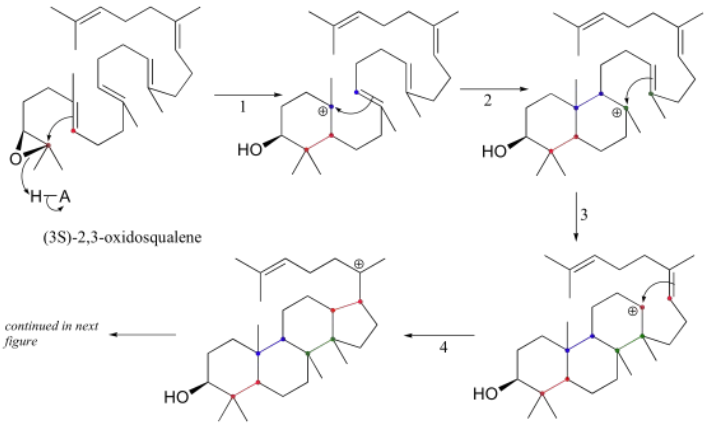


Rearrangements are particularly important in carbocation-intermediate reactions in which isoprenoid molecules cyclize to form complex multi-ring structures. One of the key steps in the biosynthesis of cholesterol is the electrophilic cyclization of oxidosqualene to form a steroid called lanosterol.

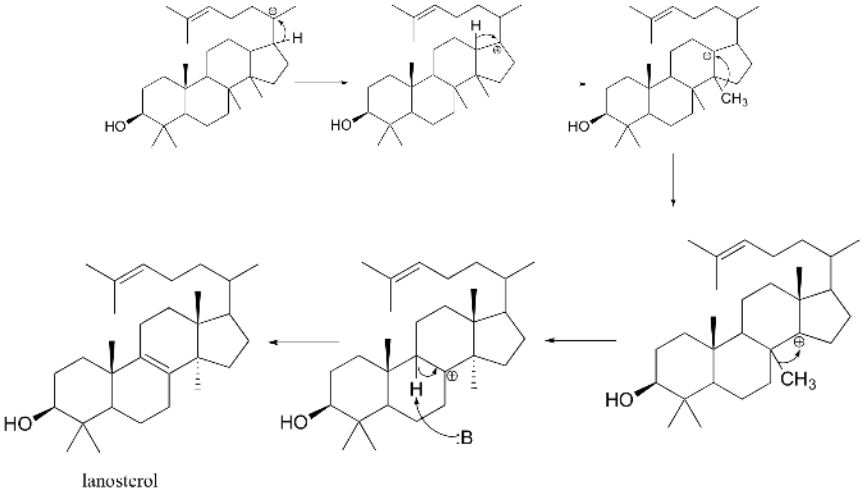


This fascinating reaction has two phases. The first phase, in which the actual cyclization takes place, is a series of electrophilic addition steps. The second phase is a series of hydride and methyl shifts. There is some argument about whether these processes occur in a stepwise fashion (with discreet carbocation intermediates) or in a concerted manner. For the sake of clarity, we will show the reaction proceeding stepwise.

The cyclization phase begins with attack by pi electrons on an epoxide electrophile (step 1 - review epoxide ring-opening reactions in section 8.6B).



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. Next comes the rearrangement phase of the reaction. which is a series of two hydride shifts and two methyl shifts, followed by a proton abstraction which finally quenches the positive charge to form lanosterol.



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CHAPTER OVERVIEW

26: Nucleic Acids

Topic hierarchy

26.1: Nucleotides and Nucleic Acids
26.2: DNA Base Pairs
26.3: DNA Replication
26.4: Transcription of DNA
26.5: Translation of RNA: Protein Biosynthesis
26.6: DNA Sequencing
26.7: Polymerase Chain Reactions

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26.1: Nucleotides and Nucleic Acids

Objectives

After completing this section, you should be able to

1. outline the relationship between nucleic acids, nucleotides and nucleosides.
2. identify, in general terms, the enzymatic hydrolysis products of nucleosides.
3. explain the structural difference between the sugar components of DNA and RNA.
4. identify by name the four heterocyclic amine bases found in deoxyribonucleotides.
5. identify by name the four heterocyclic amine bases found in ribonucleotides.
6. draw the general structure of a nucleotide and a nucleoside.
7. indicate the nitrogen atom by which a given purine or pyrimidine base attaches to the sugar component in nucleotides and nucleosides.
8. 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.

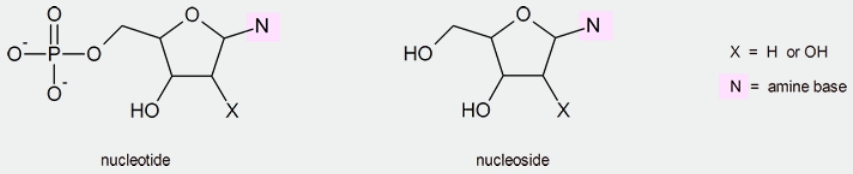
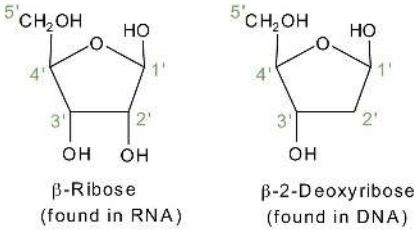


Figure **26.1.2** The Pyrimidine and Purine Nucleotides below.

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 phosphoric acid (H_3PO_4), a pentose sugar (a sugar with five carbon atoms), and a nitrogenous base (a base containing nitrogen atoms).

$$\text{nucleic acids} \xrightarrow[\text{down into}]{\text{can be broken}} \text{nucleotides} \xrightarrow[\text{down into}]{\text{can be broken}} H_3PO_4 + \text{nitrogen base} + \text{pentose sugar} \tag{28.1.1}$$

If the pentose sugar is ribose, the nucleotide is more specifically referred to as a *ribonucleotide*, and the resulting nucleic acid is ribonucleic acid (RNA). If the sugar is 2-deoxyribose, the nucleotide is a *deoxyribonucleotide*, and the nucleic acid is DNA.



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 **26.1.1**).

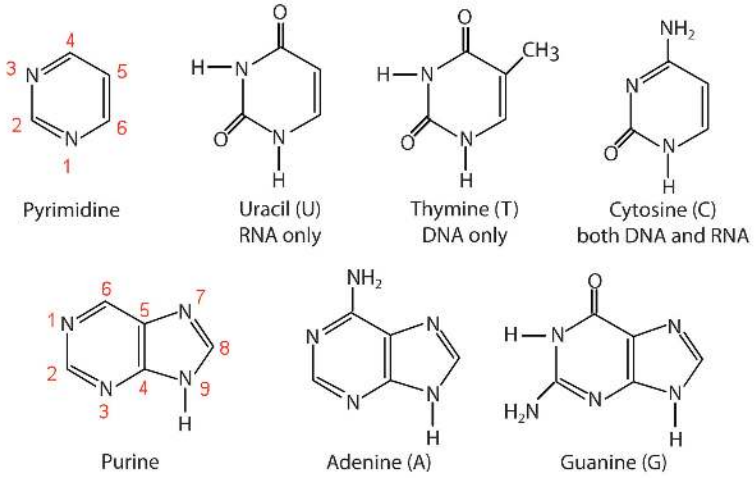


Figure **26.1.1**: The Nitrogenous Bases Found in DNA and RNA

The formation of a bond between C1′ of the pentose sugar and N1 of the pyrimidine base or N9 of the purine base joins the pentose sugar to the nitrogenous base. In the formation of this bond, a molecule of water is removed. Table 28.1.1 summarizes the similarities and differences in the composition of nucleotides in DNA and RNA.

Example 26.1.1

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.

Table **26.1.1**: Composition of Nucleotides in DNA and RNA

Composition	DNA	RNA
purine bases	adenine and guanine	adenine and guanine
pyrimidine bases	cytosine and thymine	cytosine and uracil
pentose sugar	2-deoxyribose	ribose
inorganic acid	phosphoric acid (H_3PO_4)	H_3PO_4

The names and structures of the major ribonucleotides and one of the deoxyribonucleotides are given in Figure **26.1.2**.

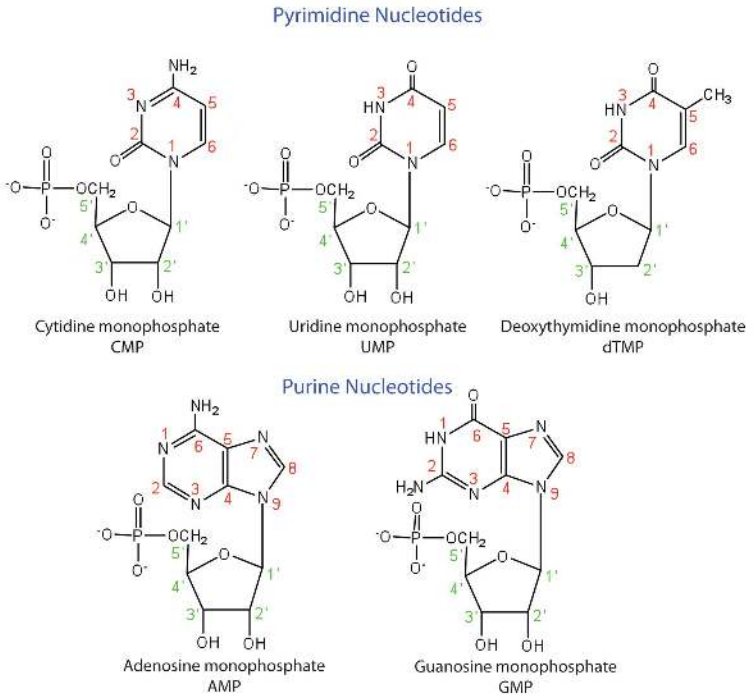


Figure **26.1.2** The Pyrimidine and Purine Nucleotides

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 **26.1.3**, 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.

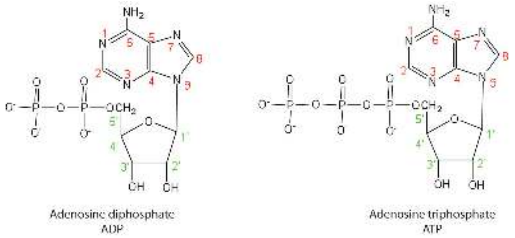


Figure **26.1.3**: Structures of Two Important Adenine-Containing Nucleotides

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 third 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.

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*.

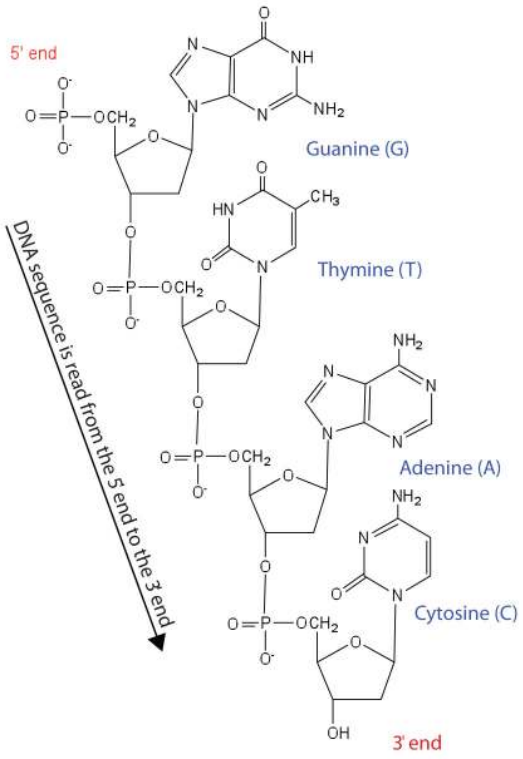


Figure **26.1.4**: Structure of a Segment of DNA. A similar segment of RNA would have OH groups on each C2′, and uracil would replace thymine.

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.

Concept Review Exercises

1. Identify the three molecules needed to form the nucleotides in each nucleic acid.
    a. DNA
    b. RNA
2. Classify each compound as a pentose sugar, a purine, or a pyrimidine.
    a. adenine
    b. guanine
    c. deoxyribose
    d. thymine
    e. ribose
    f. cytosine

Answers

1. 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
2. a. purine
   b. purine
   c. pentose sugar
   d. pyrimidine
   e. pentose sugar
   f. pyrimidine

Key Takeaways

- Nucleotides are composed of phosphoric acid, a pentose sugar (ribose or deoxyribose), and a nitrogen-containing base (adenine, cytosine, guanine, thymine, or uracil).
- Ribonucleotides contain ribose, while deoxyribonucleotides contain deoxyribose.

Exercises

1. What is the sugar unit in each nucleic acid?

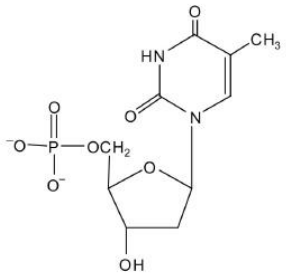
   a. RNA
   b. DNA

2. Identify the major nitrogenous bases in each nucleic acid.

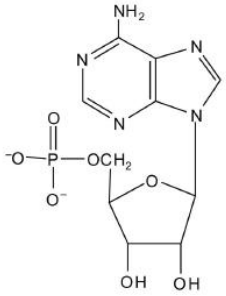
   a. DNA
   b. RNA

3. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

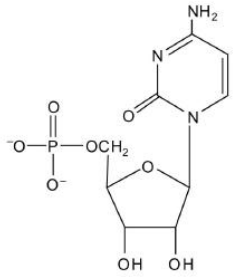
   a.

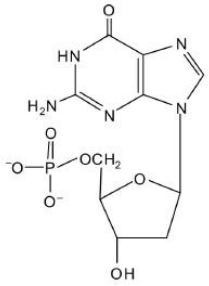


   b.

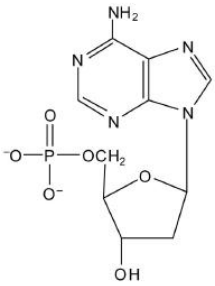


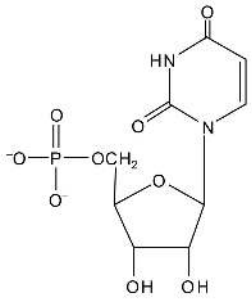
4. For each structure, circle the sugar unit and identify the nucleotide as a ribonucleotide or a deoxyribonucleotide.

a. 

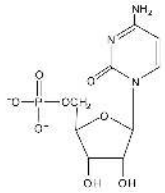
b. 

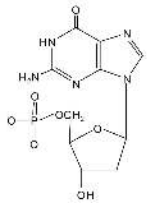
5. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

a. 

b. 

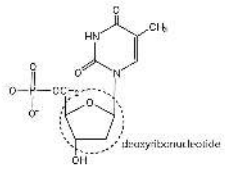
6. For each structure, circle the nitrogenous base and identify it as a purine or pyrimidine.

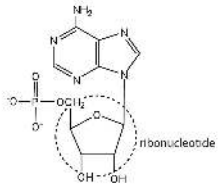
a. 

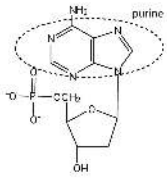
b. 

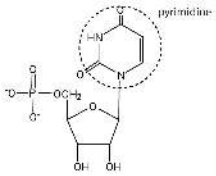
Answers

1. a. ribose
   b. deoxyribose

3. a. 

   b. 

a. 

b. 

Contributors and Attributions

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26.2: DNA Base Pairs

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.

References

Kass-Simon, G., and P. Farnes. Women of Science: Righting the Record. Bloomington, IN: Indiana University Press, 1990.

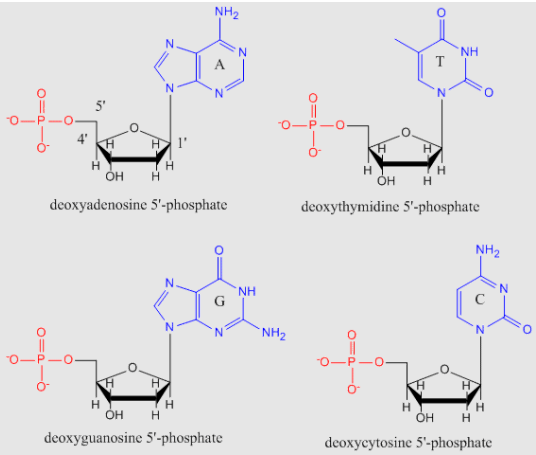
Maddox, B. Rosalind Franklin: The Dark Lady of DNA. New York: HarperCollins, 2002.

Intermolecular Forces in Nucleic Acids

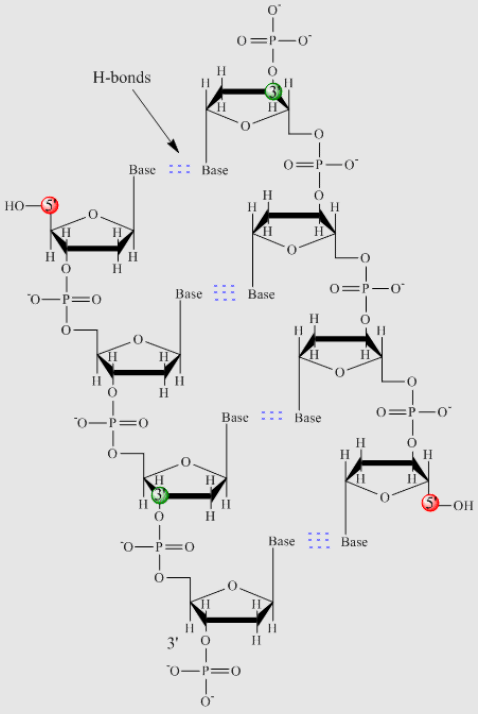
The nucleic acids RNA and DNA are involved in the storage and expression of genetic information in a cell. Both are polymers of monomeric nucleotides. DNA exists in the cell as double-stranded helices while RNA typically is a single-stranded molecule which can fold in 3D space to form complex secondary (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 below), a phosphate group (in red), and a cyclic organic R group (in blue) that is analogous to the side chain of an amino acid.

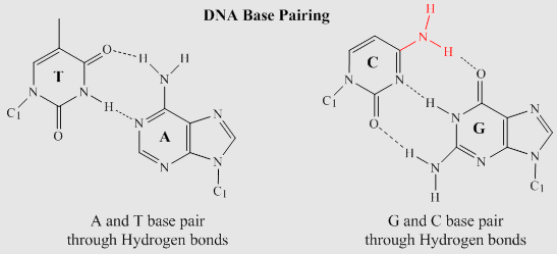


Only four bases are used in DNA (in contrast to the 20 different side chains in proteins) which we will abbreviate, for simplicity, as A, G, C and T. They are bases since they contain amine groups that can accept protons. The polymer consists of a sugar - phosphate - sugar - phosphate backbone, with 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 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.



A and T base pair through Hydrogen bonds

G and C base pair through Hydrogen bonds

Double stranded DNA 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). The following links provide interactive Jmol models of dsDNA made by Angel Herráez, Univ. de Alcalá (Spain) and Eric Martz.

- Jmol model of ds-DNA with base pairs and H-bonds
- Jmol model of DNA strands and helical backbone
- Jmol model of DNA ends and parallelisms

Chromosomes consist of one dsDNA with many different bound proteins. The human genome has about 3 billion base pairs of DNA. Therefore, on average, each single chromosome of a pair has about 150 million base pairs and lots of proteins bound to it. dsDNA is a highly charged molecule, and can be viewed, to a first approximation, as a long rod-like molecule with a large negative charge. It is a polyanion. This very large molecule must somehow be packed into a small nucleus of a tiny cell. In complex (eukaryotic) cells, this packing problem is solved by coiling DNA around a core complex of four different pairs (eight proteins total) of histone proteins (H2A, H2B, H3, and H4) which have net positive charges. The histone core complex with dsDNA wound around approximately 2.5 times is called the nucleosome.

Jmol model of the nucleosome

DNA can adopt two other types of double-helical forms. The one discovered by Watson and Crick and found in most textbooks is called B-DNA. Depending on the actual DNA sequence and the hydration state of the DNA, it can be coaxed to form two other types of double-stranded helices, Z and A DNA. The A form is much more open then the B form.

The 3.2 billion base pairs of DNA in humans contains about 24,000 short stretches (genes) that encode different proteins. These genes are interspersed among DNA that helps determining if the gene is decoded into RNA molecules (see below) and ultimately into proteins. For a particular gene to be activated (or "turned on"), specific proteins must bind to the region of a particular gene. How can binding proteins find specific binding targets among the vast number of base pairs that to a first approximation have a repetitive sugar-phosphate-base repeat? The Jmol below shows how specificity can be achieved. When DNA winds into a double helix through base-pairs between AT and GC, hydrogen bond donors (amide Hs) and acceptors (Os) on the bases that are not used in intrastrand base pairing,are still available in the major and minor grove of the ds-DNA helix (see Jmol below). Unique base pair sequences will display unique patterns of H bond donors and acceptors in the major grove. These donors/acceptors can be recognized by specific DNA binding proteins which on binding can lead to gene activation.

- Jmol model of dsDNA showing unique H bond donors and acceptors in the major grove

Contributors and Attributions

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- Chris P Schaller, Ph.D., (College of Saint Benedict / Saint John's University)
- (Henry Jakubowski)

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26.3: DNA Replication

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.

New cells are continuously forming in the body through the process of cell division. For this to happen, the DNA in a dividing cell must be copied in a process known as replication. The complementary base pairing of the double helix provides a ready model for how genetic replication occurs. If the two chains of the double helix are pulled apart, disrupting the hydrogen bonding between base pairs, each chain can act as a *template*, or pattern, for the synthesis of a new complementary DNA chain.

The nucleus contains all the necessary enzymes, proteins, and nucleotides required for this synthesis. A short segment of DNA is "unzipped," so that the two strands in the segment are separated to serve as templates for new DNA. DNA polymerase, an enzyme, recognizes each base in a template strand and matches it to the complementary base in a free nucleotide. The enzyme then catalyzes the formation of an ester bond between the 5′ phosphate group of the nucleotide and the 3′ OH end of the new, growing DNA chain. In this way, each strand of the original DNA molecule is used to produce a duplicate of its former partner (Figure 28.3.1). Whatever information was encoded in the original DNA double helix is now contained in each replicate helix. When the cell divides, each daughter cell gets one of these replicates and thus all of the information that was originally possessed by the parent cell.

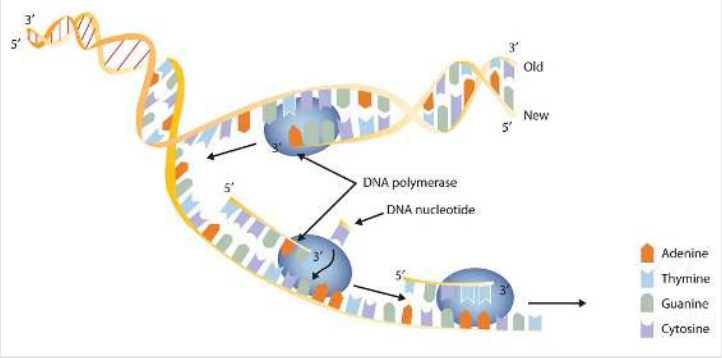

Figure: A Schematic Diagram of DNA Replication. DNA replication occurs by the sequential unzipping of segments of the double helix. Each new nucleotide is brought into position by DNA polymerase and is added to the growing strand by the formation of a phosphate ester bond. Thus, two double helixes form from one, and each consists of one old strand and one new strand, an outcome called *semiconservative replications*. (This representation is simplified; many more proteins are involved in replication.)

Example

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

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?

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.

Contributors and Attributions

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26.4: Transcription of DNA

Objectives

After completing this section, you should be able to

1. describe, very briefly, how RNA is synthesized in the nucleus of the cell by transcription of DNA.
2. identify the important structural differences between DNA and DNA.
3. given the appropriate Kekulé structures, show how uracil can form strong hydrogen bonds to adenine.
4. 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.

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 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.

There are three key differences between replication and transcription: (1) RNA molecules are much shorter than DNA molecules; only a portion of one DNA strand is copied or transcribed to make an RNA molecule. (2) RNA is built from ribonucleotides rather than deoxyribonucleotides. (3) The newly synthesized RNA strand does not remain associated with the DNA sequence it was transcribed from.

The DNA sequence that is transcribed to make RNA is called the *template strand*, while the complementary sequence on the other DNA strand is 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.

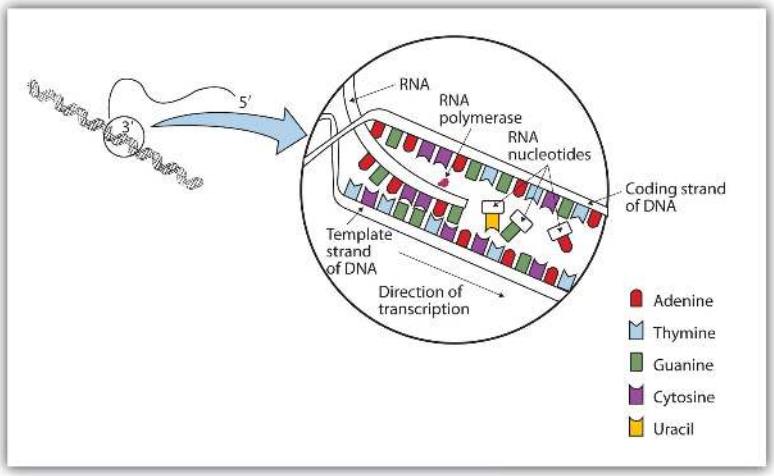

Figure: **A Schematic Diagram of RNA Transcription from a DNA Template**. The representation of RNA polymerase is proportionately much smaller than the actual molecule, which encompasses about 50 nucleotides at a time.

Example

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?

Solution

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

A portion of the template strand of a gene has the sequence 5′-CCAGTGAATTGCCTAT-3′. What is the sequence of nucleotides in the RNA that is formed from this template?

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: 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

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.

Molecules of tRNA, which bring amino acids (one at a time) to the ribosomes for the construction of proteins, differ from one another in the kinds of amino acid each is specifically designed to carry. A set of three nucleotides, known as a codon, on the mRNA determines which kind of tRNA will add its amino acid to the growing chain. 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.

The two-dimensional structure of a tRNA molecule has three distinctive loops, reminiscent of a cloverleaf (Figure 28.4.2). On one loop is a sequence of three nucleotides that varies for each kind of tRNA. This triplet, called the anticodon, is complementary to and pairs with the codon on the mRNA. At the opposite end of the molecule is the acceptor stem, where the amino acid is attached.

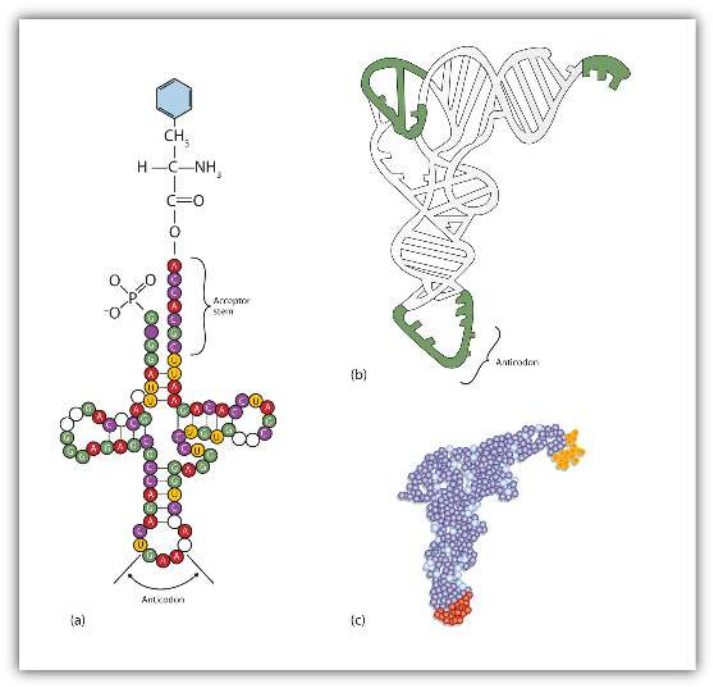

Figure : Transfer RNA (a) In the two-dimensional structure of a yeast tRNA molecule for phenylalanine, the amino acid binds to the acceptor stem located at the 3′ end of the tRNA primary sequence. (The nucleotides that are not specifically identified here are slightly altered analogs of the four common 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.

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26.5: 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.

One of the definitions of a gene is as follows: a segment of deoxyribonucleic acid (DNA) carrying the code for a specific polypeptide. Each molecule of messenger RNA (mRNA) is a transcribed copy of a gene that is used by a cell for synthesizing a polypeptide chain. If a protein contains two or more different polypeptide chains, each chain is coded by a different gene. 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*.

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*.

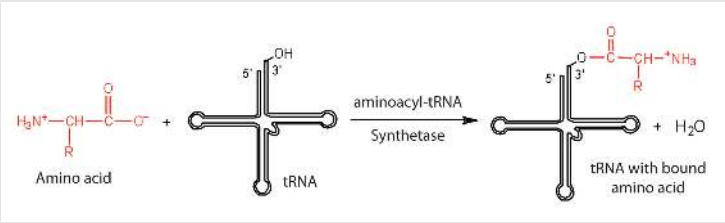
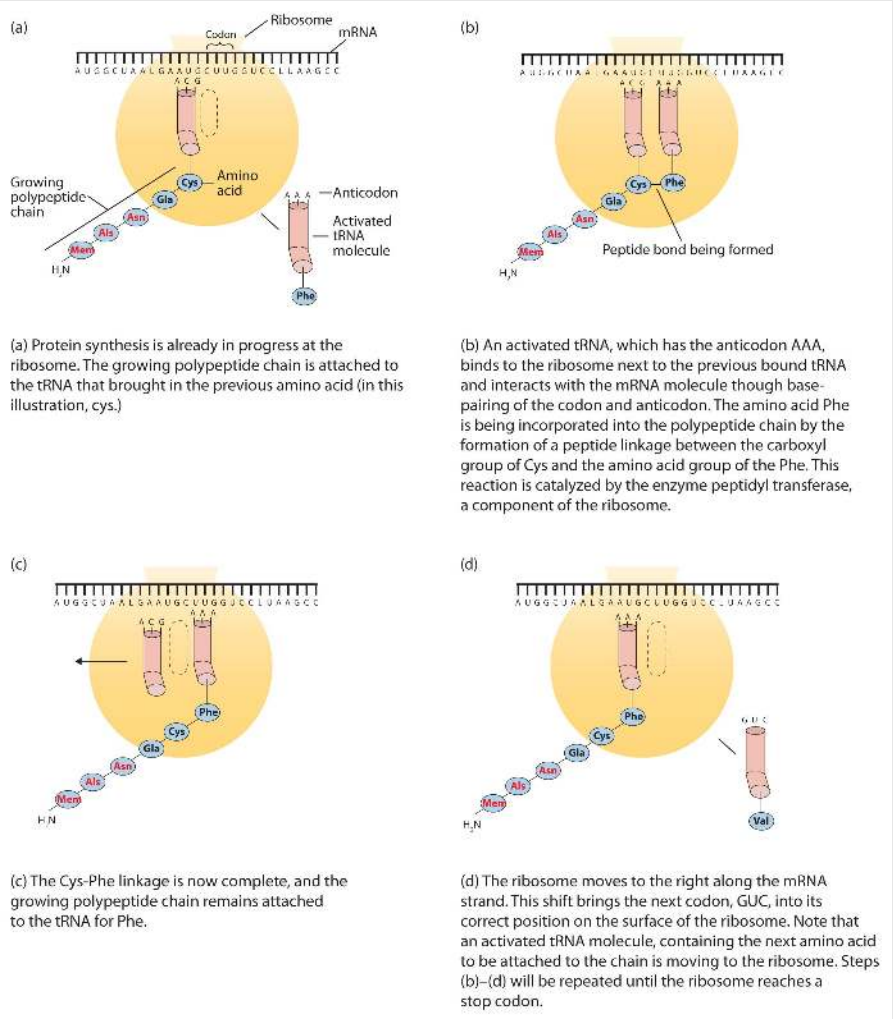


Figure: Binding of an Amino Acid to Its tRNA

Before an amino acid can be incorporated into a polypeptide chain, it must be attached to its unique tRNA. Each tRNA molecule has an **anticodon** for the amino acid it carries. An anticodon is a sequence of 3 bases, and is complementary to the codon for an amino acid. 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. Wherever the codon AAG appears in mRNA, a UUC

anticodon on a tRNA temporarily binds to the codon. 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 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: The Elongation Steps in Protein Synthesis

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.

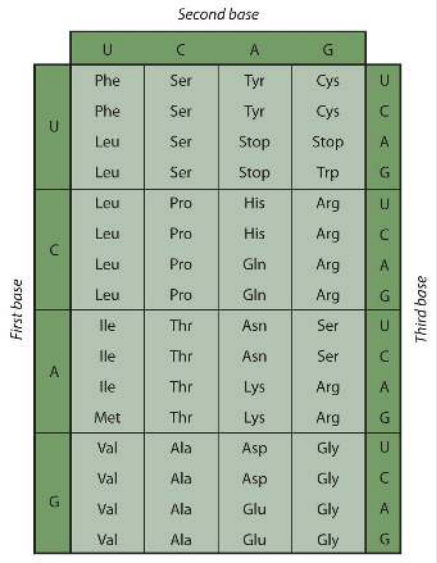


Figure: **The Genetic Code**

Example

A portion of an mRNA molecule has the sequence 5′-AUGCCACGAGUUGAC-3′. What amino acid sequence does this code for?

Solution

Use the Genetic Code Figure above 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

A portion of an RNA molecule has the sequence 5′-AUGCUGAAUUGCGUAGGA-3′. What amino acid sequence does this code for?

Further experimentation threw much light on the nature of the genetic code, as follows:

1. The code is virtually universal; animal, plant, and bacterial cells use the same codons to specify each amino acid (with a few exceptions).
2. The code is “degenerate”; in all but two cases (methionine and tryptophan), more than one triplet codes for a given amino acid.
3. The first two bases of each codon are most significant; the third base often varies. This suggests that a change in the third base by a mutation may still permit the correct incorporation of a given amino acid into a protein. The third base is sometimes called the “wobble” base.
4. The code is continuous and nonoverlapping; there are *no* nucleotides between codons, and adjacent codons do not overlap.
5. The three termination codons are read by special proteins called release factors, which signal the end of the translation process.
6. The codon AUG codes for methionine and is also the initiation codon. Thus methionine is the first amino acid in each newly synthesized polypeptide. This first amino acid is usually removed enzymatically before the polypeptide chain is completed; the vast majority of polypeptides do not begin with methionine.

Concept Review Exercises

1. What are the roles of mRNA and tRNA in protein synthesis?
2. What is the initiation codon?
3. What are the termination codons and how are they recognized?

Answers

1. 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.
2. AUG
3. UAA, UAG, and UGA; they are recognized by special proteins called release factors, which signal the end of the translation process.

Key Takeaways

- In translation, the information in mRNA directs the order of amino acids in protein synthesis.
- A set of three nucleotides (codon) codes for a specific amino acid.

Exercises

1. 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′

2. Write the codon on mRNA that would pair with each tRNA anticodon.

    a. 5′-UUG-3′
    b. 5′-GAA-3′
    c. 5′-UCC-3′
    d. 5′-CAC-3′

3. The peptide hormone oxytocin contains 9 amino acid units. What is the minimum number of nucleotides needed to code for this peptide?
4. Myoglobin, a protein that stores oxygen in muscle cells, has been purified from a number of organisms. The protein from a sperm whale is composed of 153 amino acid units. What is the minimum number of nucleotides that must be present in the mRNA that codes for this protein?
5. Use Figure 28.5.3to identify the amino acids carried by each tRNA molecule in Exercise 1.
6. Use Figure 28.5.3to identify the amino acids carried by each tRNA molecule in Exercise 2.
7. Use Figure 28.5.3to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGAGCGACUUUGCGGGAUUA-3′.
8. Use Figure 28.5.3to determine the amino acid sequence produced from this mRNA sequence: 5′-AUGGCAAUCCUCAAACGCUGU-3′

Answers

1. a. 3′-AAA-5′
    b. 3′-GUA-5′
    c. 3′-UCG-5′
    d. 3′-GGC-5′
3. 27 nucleotides (3 nucleotides/codon)
5. 1a: phenyalanine; 1b: histidine; 1c: serine; 1d: proline
7. met-ser-asp-phe-ala-gly-leu

Contributors and Attributions

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26.6: DNA Sequencing

We will discuss one method of reading the sequence of DNA. This method, developed by Sanger won him a second Nobel prize. To sequence a single stranded piece of DNA, the complementary strand is synthesized. Four different reaction mixtures are set up. Each contain all 4 radioactive deoxynucleotides (dATP, dCTP, dGTP, dTTP) required for the reaction and DNA polymerase. In addition, dideoxyATP (ddATP) is added to one reaction tube The dATP and ddATP attach randomly to the growing 3' end of the complementary stranded. If ddATP is added no further nucleotides can be added after since its 3' end has an H and not a OH. That's why they call it dideoxy. The new chain is terminated.. If dATP is added, the chain will continue to grow until another A needs to be added. Hence a whole series of discreet fragments of DNA chains will be made, all terminated when ddATP was added. The same scenario occurs for the other 3 tubes, which contain dCTP and ddCTP, dTTP and ddTTP, and dGTP and ddGTP respectively. All the fragments made in each tube will be placed in separate lanes for electrophoresis, where the fragments will separate by size.

Didexoynucleotides

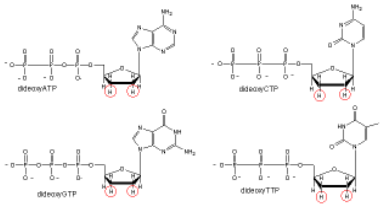


Figure: Didexoynucleotides

$$t = \frac{0.9\lambda}{\sqrt{B_M^2 - B_S^2}\cos\theta}$$

Example

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)

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.

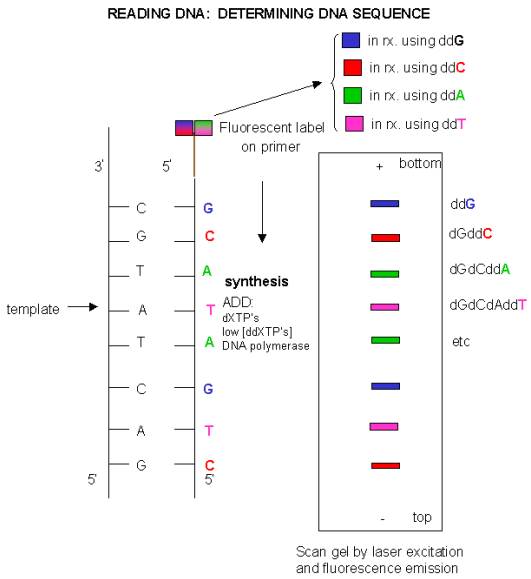
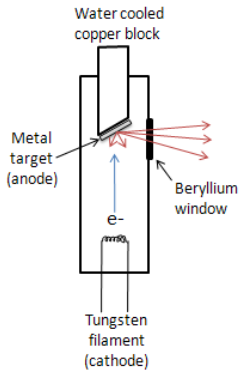


Figure: DNA sequencing using different fluorescent primers for each ddXTP reaction

One recent advance in sequencing allows for real-time determination of a sequence. The four deoxynucleotides are each labeled with a different fluorphore on the 5' phosphate (not the base as above). A tethered DNA polymerase elongates the DNA on a template, releasing the fluorophore into solution (i.e. the fluorophore is not incorporated into the DNA chain). The reaction takes place in a visualization chamber called a zero mode waveguide which is a cylindrical metallic chamber with a width of 70 nm and a volume of 20 zeptoliters (20 x 10-21 L). It sits on a glass support through which laser illumination of the sample is achieved. Given the small volume, non-incorporated fluorescently tagged deoxynucleotides diffuse in and out in the microsecond timescale. When a deoxynucleotide is incorporated into the DNA, its residence time is in the millisecond time scale. This allows for prolonged detection of fluorescence which give a high signal to noise ratio. This method might bring the cost of sequencing the human genome down from the initial billion dollar range to $100.



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26.7: Polymerase Chain Reactions

In the mid 80's a new method was developed to copy (amplify) DNA in a test tube. It doesn't require a plasmid or a virus. It just requires a DNA fragment, some primers (small polynucleotides complementary to sections of DNA on each strand and straddling the section of DNA to be amplified. Just add to this mixture dATP, dCTP, dGTP, dTTP, and a heat stable DNA polymerase from the organism Thermophilus aquaticus (which lives in hot springs), and off you go. The mixture is first heated to a temperature which will cause the DsDNA strands to separate. The temperature is cooled allowing a large stoichimetric excess of the primers to anneal to the ssDNA. The heat stable Taq polymerase (from Thermophilus aquaticus) polymerizes DNA from the primers. The temperature is raised again, allowing dsDNA strand separation. On cooling the primers anneal again to the original and newly synthesized DNA from the last cycle and synthesis of DNA occurs again. This cycle is repeated as shown in the diagram. This chain reaction is called the polymerase chain reaction (PCR). The target DNA synthesized is amplified a million times in 20 cycles, or a billion times in 30 cycles, which can be done in a few hours.

***Figure**: Copying DNA in the test tube - the polymerase chain reaction (PCR)*

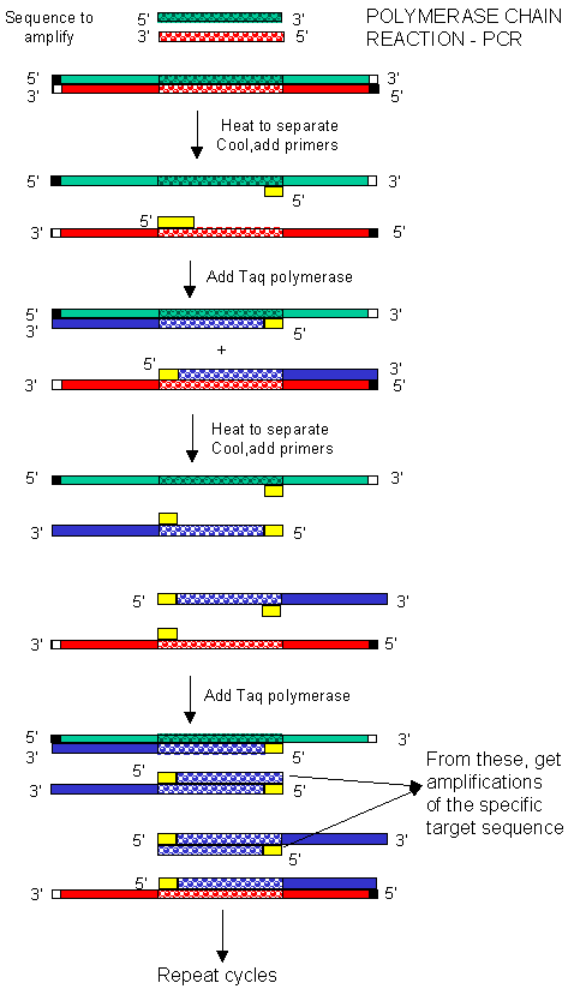
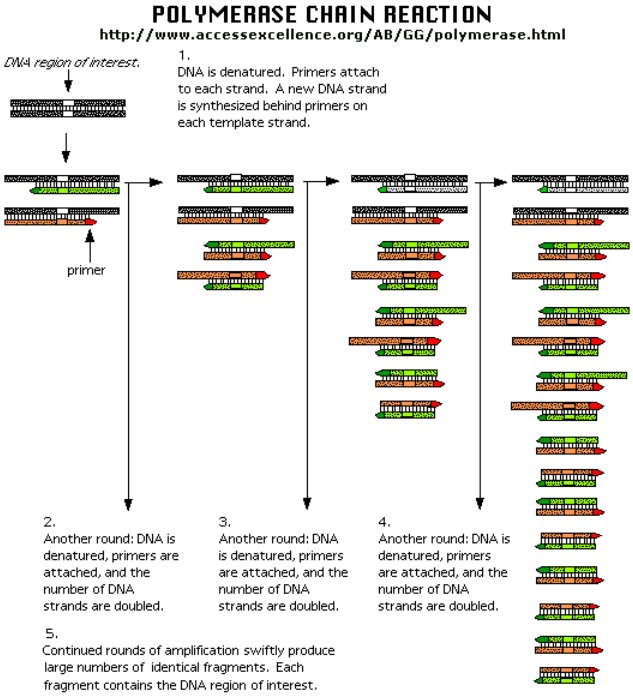


Figure: Another View of PCR



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